A comparison of different community models of Antiretroviral Therapy delivery among stable HIV+ patients in an urban setting, Zambia.

A cluster-randomized non-inferiority trial.

Mohammed Limbada

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Faculty of Infectious & Tropical Diseases

London School of Hygiene & Tropical Medicine

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Declaration

I, Mohammed Limbada, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature: 

Date: 30 November 2021

Abstract

Background

Community models of antiretroviral therapy (ART) delivery also known as differentiated service delivery (DSD) models are a novel innovative strategy to increase sustainable ART coverage for people living with HIV (PLHIV) in resource-limited settings. We compared two different models of ART delivery with the health care facility to gather evidence on the impact of these models' patients' clinical and virological outcomes, operational feasibility, and acceptability to guide policy makers on which models to roll out in the context of universal treatment.

Methods

A three-arm cluster randomized non-inferiority trial was conducted in two urban HPTN 071 trial communities in Zambia comparing three different models of ART delivery: Standard of Care (SoC), Home-Based delivery (HBD) and Adherence Clubs (AC). Adult HIV+ patients defined as "stable" on ART, were eligible for inclusion. The primary endpoint was the proportion of PLHIV with virological suppression (≤1000 copies HIV RNA/ml) at 12 months (+/- 3 months) after study entry across all three arms. Analysis of our outcomes used statistical methods for CRT.

Results

A total of 2,489 participants were enrolled in the study (781 SoC, 852 HBD, and 856 AC). There was a strong evidence ($p<0.001$) that both community models of ART delivery were non-inferior to SoC. The proportion of virological suppression in our three study arms > 95% compares favourably or superiorly with results published from literature. This trial also identified gaps in the evidence base and programmatic priorities for DSD implementation in SSA in the coming years with respect to viral load testing and monitoring and evaluation of DSD models embedded in routine HIV service delivery.

Discussion

Community models of ART delivery were as effective as facility-based care in terms of viral suppression. However, availability of viral load test results remains a challenge to HIV programmes and could undermine gains from universal treatment. Offering PLHIV choices of these different models of ART is feasible and acceptable.

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Table of Contents

Declaration 2

Abstract 3

Acknowledgements 4

Table of Contents 6

List of Figures (Exclusive of figures in research papers) 10

List of Tables (Exclusive of tables within Research papers) 11

List of Abbreviations 12

Chapter 1. Introduction 14

1.1 Background 14

1.2 Rationale for Research 16

1.3 Study aims and objectives 17

1.3.1 Hypothesis 17

1.3.2 Study Aims 17

1.3.3 Specific Objectives 17

1.4 Structure of the PhD thesis 18

1.5 Candidate's Role and Contribution to Research 19

Chapter 2: Literature Review 22

2.1 Global HIV epidemic 22

2.2 Universal treatment 24

2.2.1 The Revolution of antiretroviral therapy 24

2.2.2 From CD4-based initiation to immediate treatment for all HIV-Positive adults 26

2.2.3 Strategies to deliver universal ART for all PLHIV 27

2.2.4 Universal Test-and-Treat Randomized trials 30

2.3 The Impact of Universal ART on the HIV epidemic 34

2.4 Challenges of treating all people with HIV in sub-Saharan Africa. 38

2.5 Barriers/Gaps in the HIV care cascade 38

2.5.1 Barriers to linkage to care 39

2.5.2 Barriers to rapid ART initiation 40

2.5.3 Barriers to retention in care 41

2.6 Differentiated Service Delivery 42

2.6.1 Types of community models of ART delivery 44

2.7 HIV in Zambia 48

Chapter 3: A systematic review of the effectiveness of non- health facility-based care delivery of antiretroviral therapy for people living with HIV in sub-Saharan Africa measured by viral suppression, mortality and retention on ART. 51

3.1 Outline of chapter 51
3.2 Research Paper 1 52
3.3. Supplementary Information 69
Chapter 4: Methodology 78
4.1 Outline of the chapter 78
4.2 Background to the HPTN 071 (PopART) Trial 78
4.3 Background to the nested ComART study: A comparison of different community models of ART delivery amongst stable HIV+ patients in two urban settings in Lusaka, Zambia. 81
4.4 Study Design 83
4.4.1 Overall design of the ComART study 83
4.4.2 Study Setting 85
4.4.3 Study Population 86
4.4.4 Study Randomization 87
4.4.5 Study Endpoints 87
4.4.6 Sample size and study power 88
4.4.7 Description of the study interventions 89
4.5 Study procedures 91
4.5.1 Screening and recruitment 91
4.5.2. Follow-up of study cohorts 92
4.6 Data Management and Analysis 94
4.6.1 Data Collection 94
4.6.2. Data Management and Cleaning 97
4.6.3 Data Analysis 98
4.7 Ethical considerations 98
4.7.1 Informed Consent 98
4.7.2. Confidentiality 99
4.7.3 Participants Risks and Benefits 99
4.7.4 Regulatory review 100
4.8 Funding 100
4.9 Research Methodology Paper 2: A comparison of different community models of antiretroviral therapy delivery with the standard of care among stable HIV+ patients: rationale and design of a non-inferiority cluster randomized trial, nested in the HPTN 071 (PopART) study. 100
Chapter 5. Implementation of the trial 115
5.1 Chapter overview 115
5.2 Overview of the planning 116
5.3 Study Preparations 118

5.3.1 Introducing the study to relevant authorities and key stakeholders 118
5.3.2 Recruitment of Staff 123
5.3.3 Development of the intervention components 125
5.3.4 Management support 127
5.4 Pre-implementation procedures 128
5.4.1 Study sensitization in the selected communities and health care facilities 128
5.4.2 Randomization ceremony 129
5.4.3 Trainings 135
5.4.4 Clinic space and Infrastructure 137
5.4.5 Clinic set up and logistics 137
5.4.6 Laboratory Procedures 138
5.4.7 Preparation of data collection tools 138
5.5 Study Implementation and Procedures 139
5.5.1. Screening for eligibility 139
5.5.2 Obtaining written consent 140
5.5.3 Enrolment 141
5.6 Operations of the intervention models [HBD and AC] and facility based SoC. 141
5.7 Monitoring and evaluation 152
5.8 Study exit 153
5.9 Implementation successes and challenges 153
5.10 Discussion 169
Chapter 6: Acceptability and Preferences of Community Models of ART delivery 173
6.1 Chapter overview 173
6.2. Research paper 3. Acceptability and Preferences of Two Different Community Models of ART Delivery in a High Prevalence Urban Setting in Zambia: Cluster Randomized Trial, Nested in the HPTN 071 (PopART) Study 173
Chapter 7: Primary Results 190
7.1 Research Paper 4: Rates of viral suppression in a cohort of stable HIV+ patients in two community models of ART delivery versus facility-based HIV care in Lusaka, Zambia: A cluster-randomized non-inferiority trial nested within the HPTN 071 (PopART) trial. 190
Abstract 190
Intro 190
Methods 190
Results 190
Discussion 190
7.2. Supplementary information 204
Chapter 8. Discussion 210

8.1 Outline of the chapter 210
8.2 Summary of the key findings 210
8.3 Strengths and Limitations of the study 224
8.4 key lessons learned from this PhD process. 227
8.5 Findings in the context of research 228
8.6 Implications for scaling up DSD models in resource-limited settings. 229
8.7 Recommendations for programming and research 231
8.8 The current status of DSD scale-up in SSA 234
8.9 DSD – The way forward 236
8.10 Conclusion 238
Chapter 9 References 239
Chapter 10 Appendices 255
Appendix I: Ethics Approvals and permissions 255
Appendix II: Participant eligibility and information sheets 264
Appendix III: Study documents 273
Appendix IV: Additional files for research 1 285

List of Figures (Exclusive of figures in research papers)

Figure 2.1: Global estimates of people living with HIV Section……..***Page 23***

Figure 2.2: Implementation of Treat All ART recommendation among adults and adolescents living with HIV (Situation as of mid-2018)……***Page 35***

Figure 2.3: PLHIV accessing treatment globally……***Page 36***

Figure 2.4: Number of people living with HIV accessing antiretroviral therapy, global, 2000–2017 and 2020 target……***Page 37***

Figure 2.5: HIV prevalence in Zambia among adults, by province……***Page 49***

Figure 4.1: PopART/HPTN 071 Trial Schema……..***Page 79***

Figure 4.2: Schematic overview of the PopART intervention package……***Page 80***

Figure 4.3: Overview of study design and randomization scheme……..***Page 84***

Figure 4.4: Steps in recruiting participants……***Page 91***

Figure 4.5: Follow-up schedule for participants enrolled in the intervention arms……***Page 93***

Figure 5.1: Implementation steps of the study ……..***Page 115***

Figure 5.2: Overview and hierarchy of the Primary health care facility in Zambia……..***Page 117***

Figure 5.3: Randomization Scheme ……..***Page 132***

Figure 5.4: Maps of the communities with the zones allocated to the interventions……***Page 133-134***

Figure 5.5(a-j): Pictures of the home and club visits/ operations ……***Page 148-151***

Figure 5.6: Reasons for exclusion during the screening process ……***Page 158***

Figure 5.7: Viral Load continuum……..***Page 163***

List of Tables (Exclusive of tables within Research papers)

Table 2.1: Summary of Community Models of ART delivery for Stable Patients……..***Page 47***

Table 4.1: Total number of zones in the communities served by the CHiP teams ……..***Page 86***

Table 4.2: Study power to show that community ART provision is not inferior to standard-of-care, in terms of patient viral suppression 12 months after either enrolling into community ART or continuing with standard-of-care at the clinic……..***Page 89***

Table 4.3: Broad Overview of the three ART delivery models ……..***Page 90***

Table 4.4: Overview of the study related forms and data collected ……***Page 96-97***

Table 5.1: Summary of the concerns raised by various teams and ways to mitigate them……..***Page 120-122***

Table 5.2: Roles and responsibilities of ComART study staff ……***Page 123-125***

Table 5.3: Clinic operations and responsible parties ……..***Page 129***

Table 5.4: List of 10000 allocations created for each community ……***Page 130***

Table 5.5: Characteristics of the trainings ……..***Page 136***

Table 5.6: Comparison of facility based (SoC) and community models (HBD and AC) for management of patients ……***Page 143***

Table 5.7: Outline of the HBD and AC preparations and operations……***Page 144***

Table 5.8: Summary of the main factors identified enabling or jeopardizing the implementation and sustainability of HBD and AC models ……***Page 144-147***

Table 5.9: Reasons for excluding patients for study recruitment……***Page 156***

Table 5.10: Strategies to increase the identification of potential eligible patients for the study……***Page 160***

Table 8.1: Patient Preferences and satisfaction for DSD models in SSA……..***Page 214***

List of Abbreviations

AC	Adherence Clubs
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral
AZT	Azidothymidine
CAB	Community Advisory Board
CAC	Community Adherence Clubs
CAG	Community Adherence Group
CASG	Community Adherence Support Group
CBDP	Community Based Distribution Points
CD4	Cluster of Differentiation
CDDP	Community Drug Distribution Point
CHIP/s	Community HIV Providers
CHW	Community Health Workers
DAIDS	Division of AIDS
DHMT	District Health Management Team
DSD	Differentiated Service Delivery
EDC	Electronic Data Capture
FGD	Focus Group Discussion
HAART	Highly Active Antiretroviral Therapy
HBD	Home-Based Delivery
HCF	Health Care Facility
HCT	HIV Counselling and Testing
HCW	Health Care Worker
HFBC	Health Facility Based Care
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
LIMS	Laboratory Information Management System
LTFU	Loss-to Follow-up
MMD	Multi-Month Dispensation
MOH,	Ministry of Health

NAC	National AIDS Council
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitors
NRTI	Nucleoside Reverse Transcriptase Inhibitors
OPD	Out-Patient Department
PHO	Provincial Health Office
PLHIV	People Living with HIV
SoC	Standard of Care
SOP	Standard Operating Procedure
SSA	sub- Saharan Africa
UAG	Urban Adherence Group
UNAIDS	United Nations Programme on HIV/AIDS
UTT	Universal Test and Treatment
VL	Viral Load
VS	Viral Suppression
WHO	World health Organization

Chapter 1. Introduction

1.1 Background

The use of antiretroviral drugs (ARVs) in the last decade has transformed survival for People living with HIV (PLHIV) from a life-threatening condition to a chronic health condition. Highly active combination ARV regimen, referred to as antiretroviral therapy (ART) have proven to slow the progression of the disease to AIDS and reduce the risk of transmission for PLHIV[1]. ART has dramatically increased the life expectancy of PLHIV in both high and low income countries[2] and several studies have provided scientific evidence on the benefits of early and effective initiation of ART in reducing morbidity and mortality[3-5]. In 2015, the World Health Organization (WHO) recommendations on the use of antiretroviral drugs (ARVs) had been revised in favour of immediate treatment regardless of CD4 count and disease stage due to patient's benefit [6]. Despite initial concerns about the feasibility of scaling up the "treat-all "strategy in resource-limited settings, early reports have shown comparable treatment benefits to those reported in high-income countries[7-9]. Recent evidence has shown that taking ART daily as prescribed can suppress HIV viral load to undetectable levels and by keeping PLHIV with a suppressed viral load , reduces the risk of onward HIV transmission[10], a concept known as "Undetectable = Untransmittable" or "U=U"[11], and therefore this has prompted the need to initiate and sustain all PLHIV on ART across the globe[5, 9, 12].

Over the last decade, sub-Saharan African countries at the epicentre of the HIV epidemic have achieved remarkable progress in increasing access to ART for PLHIV[9]. National ART programs in this region are striving to achieve the 90-90-90 ambitious targets by 2020 for HIV diagnosis, treatment, and viral suppression (with 95-95-95% respectively by 2030) set by WHO and Joint United nations on HIV/AIDS Programmes (UNAIDS)[13-16]. The rapid expansion of ART programs to reach these targets has resulted in an increase coverage of ART as all PLHIV are now eligible and in need of immediate treatment. Initiation and maintaining nearly 10 million people on ART in resource-limited settings in order to reach UNAIDS targets has created shortfalls in both health system capacity and quality[16].

In most resource-limited settings, HIV service delivery is primarily health care facility-based and significant barriers to treatment access and retention in HIV care in this high burden of HIV includes existing fragile health systems, inadequate human resources, transport costs and long waiting times at the clinic [17-19]. Adherence to treatment and virological suppression are critical factors for survival, prevention of onward transmission and development of drug resistance [20].

It is becoming clear that further successful scale up of ART services and lifelong ART for all PLHIV will neither be feasible, nor sustainable without a change in the current primary facility-based delivery model of ART in resource-limited settings[9]. To overcome these challenges and ensure that all PLHIV have access to sustainable lifelong ART, HIV services must be simplified, with a focus not only on decentralization and task shifting but also on community-based healthcare models to reduce the burden on health systems and PLHIV and improve ART retention [9].

Many countries in resource-limited settings are now scaling up alternative HIV service delivery approaches or differentiated service delivery (DSD) models. These may be important and innovative strategies for maintaining the continuum of care and the 2015 WHO guidelines recommend that ART services can be provided in the community, but operational guidance and further evidence are required for this to happen in practice[6]. As HIV national programs address the various challenges to accessing HIV care, lessons from these innovative models can help shape HIV care and scale up of treatment.

DSD is a client-centred approach to patient care that differs from traditional HIV care in the location and frequency of interactions with the health care system, the cadre of providers involved, and/or the types of services provided (16, 21). These models are centred on the preferences and expectations of PLHIV and aim to increase efficiencies in HIV service delivery in order to achieve program expansion while ensuring that care meets the wide range of patient needs (22). The primary objective of DSD is to streamline and remove barriers to care, resulting in a wide range of possible benefits for both health care providers and PLHIV, such as improved clinical outcomes, increased patient satisfaction, and decreased provider and patient expenses[16].

DSD models generally focus more on stable patients and have been broadly categorized as group or individual models, with HIV service delivery either in a health care facility or in the community [16, 21]. The definition of stable patients varies across different models dependent on the resources available and includes PLHIV who are virally suppressed, adherent to treatment, have no opportunistic infections and do not require frequent clinical consultations[22]. However, over the last few years, these DSD models have also been adaptable to a variety of target populations, including pregnant and breast-feeding women and their children, adolescents and youth, and key populations[23].

Despite the large-scale implementation of DSD models in various formats across multiple resource-limited settings, evidence on the effectiveness of these DSD models versus health facility-based care in terms of viral suppression, ART retention and adherence, mortality, and lost-to-follow-up in PLHIV in resource-limited settings is needed. The majority of available studies and evaluations have been widely inconsistent in their designs, methods, and outcomes, making it difficult to draw conclusions

about whether these models of ART delivery will be feasible in urban resource-limited settings, or whether the outcomes will be as good as the standard quality of care provided by health care facilities[24].Therefore, this thesis will provide us with data on clinical outcomes, operational feasibility and acceptability of DSD models in comparison to the standard of care in a high-burden urban setting to validate their effectiveness and guide policy makers on the best models to roll out in the context of universal treatment.

1.2 Rationale for Research

Although community-based models of ART delivery have demonstrated promising outcomes in terms of retention in care and adherence to treatment, more data from innovative community-based models of care are needed to support long-term retention as ART cohorts in resource-limited settings continue to expand in the context of universal treatment[25]. Very little is known about the effects of community-based models of ART delivery versus health care facility with regards to ART adherence, retention, viral suppression, mortality, LTFU and stigma in PLHIV in resource limited settings.

Several recent systematic reviews on community-based models of ART delivery have shown that there are no significant differences in optimal ART adherence, viral suppression all-cause mortality and LTFU between health care facility and community models of ART delivery for PLHIV in resource limited settings [24, 26, 27]. However, community-based models may in fact be superior when it comes to selected outcomes such as retention in care[27].

Most of this literature has been derived from observational studies and evaluation of pilot programs that focused largely on adherence clubs [26, 28-30]. To date there is limited evidence from randomized trials on the effectiveness of community models of ART delivery when compared to health care facility-based care in terms of viral suppression, retention in care and patient acceptability. Two RCTs that compared home ART delivery to facility-based care in Uganda and Tanzania both showed home delivery models performing at least as well in viral suppression rates as facility-based care and could therefore enable improved and equitable access to HIV treatment in resource limited settings[31, 32].

Despite the significant progress in scaling up ART services over the last 15 years and recently adopting the WHO treat-all policy, Zambia faces a significant shortage of health care workers with staffing deficits at over 70% for doctors, clinical officers, and nurses[17, 33]. The critical shortage of health care workers and inequitable distribution of HCWs across urban and rural areas, high attrition rates and staff burnouts are the major factors contributing to inadequate human resources[34]. In trying to

cope with the demand, there has been decentralization of ART services from hospitals to primary health care facilities and task shifting from doctors to nurses and CHWs [33].

Little is known whether these models of ART delivery will be feasible in urban low-resource high HIV burden settings and whether care will be as good as the standard quality of care provided by health systems, therefore a timely and innovative study is required to rigorously evaluate different models of community ART delivery as the information obtained will be critical for the continued scale up of universal treatment and provide policy makers with evidence on operational feasibility and acceptability and guide policy on the best models to roll out in the context of universal treatment[24]. This study will provide us with data on operational, acceptability and cost effectiveness and guide policy makers on the best models to roll out in the context of UTT. The analysis of these models will be critical for the continued scale up of UTT and also describe the cascade of care in an urban setting with a high HIV prevalence. Information coupled with qualitative data will provide information about the success and challenges of implementing community models of ART delivery in real world settings in resource limited setting.

1.3 Study aims and objectives

1.3.1 Hypothesis

Overall clinical, immunological, and virological outcomes in patients receiving care via community models of ART delivery are not inferior to those receiving care in the clinic (standard of care) in urban resource-limited settings.

1.3.2 Study Aims

The primary aim of this thesis is to determine whether patients receiving or participating in community models of ART delivery have a lower or equal ("non-inferior") risk of virological failure than patients who receiving standard of care in an urban resource setting.

1.3.3 Specific Objectives

1) To compare virological suppression (VS) at 12 months in HIV+ patients receiving care via community ART models with those receiving care in the clinic (standard of care).

2). To compare the two community ART models with the standard of care with respect to:

- Proportion of patients with VS at 18-24 months after entering the models of care
- Retention in the models of ART delivery at 12 and 24 months
- Mortality and Loss-to-follow at 12 and 24 months.

1.4 Structure of the PhD thesis

The aim of this PhD is to compare community ART models with that of the current standard of care in a resource-limited setting with respect to clinical outcomes, acceptability, and feasibility. To that end, a three-arm cluster randomized non-inferiority trial in a prospective cohort of adults enrolled into ART care was conducted at two primary urban health care facilities.

This thesis comprises of eight chapters and of these, four chapters have been prepared as stand-alone manuscripts that have been submitted or are ready for submission to peer-reviewed journals and thus contain unavoidable repetition of information such as setting, definitions among the papers. These chapters are identified by headings in italics in the table of contents. The remaining chapters contain materials not submitted for publication, but which contribute to achieving the objectives of the thesis.

The initial chapter comprises an introduction to the thesis, rationale and its aims and objectives, and outlines the candidate's role in the research, the structure of the thesis, ethical clearance, and funding. It begins by explaining the implications of scaling up universal treatment in resource limited settings and the need for decentralizing ART delivery into the community to sustain lifelong ART for PLHIV.

Chapter 2 comprises an overview of the HIV epidemic and the WHO recommendations towards universal treatment, progress towards treatment coverage and the challenges faced by resource-limited settings as they increase ART coverage. This chapter also focuses on the barriers to the HIV continuum of care and why differentiated models of delivery have become an important innovate strategy to address these challenges.

Chapter 3 is a systematic review research paper on the effectiveness of non-health facility-based care delivery of ART for PLHIV in sub-Saharan Africa measured by viral suppression, mortality, and retention on ART. Several systematic reviews published on community ART models have shown there are no significant differences in optimal ART adherence, viral suppression (VS), loss-to-follow-up (LTFU) and all-cause mortality between patients assigned to non-health facility-based care and health facility-based care. Although these data were from initial studies, we provided an update on much recent data as these models have been rolled out providing more data on clinical outcomes.

Chapter 4 this chapter describes the study design and methodology. It also includes a methodological research paper that looks at several aspects of the study design and why we chose a non-inferiority design cluster versus individual randomization, as well as anticipated challenges, advantages, and disadvantages of this particular study design.

Chapter 5 describes the implementation and duration of the study period. This chapter discusses the planning, development, and implementation of the trial's interventions, assess their fidelity, successes, and challenges before, during and after the implementation. It gives the reader an insight on what it took to implement these models of ART delivery, trainings, recruitment of personal, conducting these home and club visits, challenges with viral load testing and data collection. It includes the processes involved, and implications for programs.

Chapter 6 is a research paper on the acceptability, choices, and preferences that PLHIV have towards community ART models in high HIV prevalence resource-limited settings. It addresses the "client-centred care" which tells us what PLHIV actually want. As national ART programs in resource-limited settings scale up alternative models of ART delivery, it is important to understand acceptability, choices, and preferences of PLHIV to determine which models to prioritize over long term.

In Chapter 7, the fourth research paper discusses the primary aim of this thesis that determines whether patients in community models of ART delivery have a lower or equal risk of virological failure compared to those receiving standard of care in an urban resource setting as well as some of the secondary objectives such as mortality and lost-to-follow-up.

Chapter 8 summarizes the main findings of the PhD thesis, examines the strengths and limitations and highlights recommendations for future research and health policy. This is followed by a brief conclusion.

Appendices contain important documents relevant to this thesis and includes ethical approval, data collection and consent forms.

1.5 Candidate's Role and Contribution to Research

Since joining Zambart in 2014, I have had the opportunity to serve in various roles and contribute substantially to the HPTN 071 (PopART) trial.

I conceptualized this non-inferiority trial and designed it with input from Helen Ayles as my supervisor and oversight from the HPTN 071 protocol chairs (Richard Hayes and Sarah Fidler). Despite the fact that this was an ancillary study subject to the regulatory requirements of the larger HPTN 071 (PopART) experiment, I was responsible for the trial's leadership. Prior to developing the protocol for this study, the studies objectives were identified as components which would contribute to my PhD. With oversight and contributions from my supervisors who were the principal investigators of the main trial and HPTN 071 protocol chair and members, I designed the study (including the data

collection tools), wrote the study protocol, interventions standard operating procedure manuals and applied for ethics and regulatory approvals. Once approvals were obtained, I was responsible for the following:

- Recruitment and management of study staff (study coordinators, research nurses, and pharmacy technicians and data clerks).
- Developing the training packages and conducted trainings for study staff including additional training for the community HIV providers (CHiPs) who were already part of the main trial.
- Collaborating with Zambart data managers on programming data collection tools and database.
- Collaborating with statisticians at London School of Hygiene and Tropical Medicine and Zambart on the randomization process and with help from the study teams at Zambart and healthcare facility staff, conducted the public randomization ceremony.
- Conducted meetings with in-country PEPFAR implementing partners and Zambian Ministry of Health (Provincial and District health management) teams to promote the study and work closely with all the teams to ensure patient safety, logistical supplies and data collection tools were in place.
- Ensured that all logistics for the interventions were procured and delivered to the sites with the Zambart procurement team.

Following study activation, I led the initial process of screening and enrolment of study participants in close collaboration with the study staff and health care facility staff in the respective communities.

I was in weekly contact with the study staff, health care staff and CHiPs supervisors about the interventions progress and offered them support and guidance when encountering challenges. I was also responsible for working closely with the implementing partners and Ministry of Health teams to ensure that patient had their routine laboratory monitoring and results available; drug logistics in the facility pharmacy were available; and patient routine clinical data was entered in the SmartCare database. I was also responsible for the "real-time" monitoring of the field and clinic data collected by the CHiPs and study staff which was sent to me on a weekly basis. I also prepared the study progress monthly report which was sent to the protocol team prior to a monthly conference call. I performed the necessary data cleaning, following up on missing laboratory results and carried out all statistical analysis, with advice from my supervisors, David Macleod, and Sian Floyd (statisticians on PopART).

For the systematic review, I worked with Geiske Zjitre (Medical Doctor at Imperial) on the first draft with guidance from Sarah Fidler (Protocol Chair for PopART and clinician at Imperial College). We performed a database search and retrieved all publications for inclusion in the review process. Together with GZ, we

independently screened titles and abstracts and the full text reviews of eligible articles were done by both of us independently. All conflicts were resolved through discussion with both of us and Sarah Fidler (my supervisor) who was the third reviewer. Data was extracted in duplicate by both reviewers from articles considered eligible and forest plots was done by David Macleod (Statistician at LSHTM). We also conducted the quality analysis. I drafted the systematic review manuscript following comments from the co-authors.

For the qualitative work that is presented in some of the papers as well as the thesis, I worked with a social scientist (Bwalya Chiti) from Zambart. He was responsible for developing the in-depth interviews, key informant interviews and focus group discussions for the qualitative data collected for this PhD.

With regards to the papers for publications included in the body of this thesis. I wrote the initial drafts and incorporated feedback from my co-authors and supervisors. I was also responsible for submitting the papers for publications and responded to reviewers' comments. I disseminated results of this work through poster presentations at the AIDS conference in 2018, International AIDS society (IAS) in 2019 and Conferences on retrovirus and opportunistic infections (CROI) in 2019. The primary trial findings were presented as a poster presentation at the AIDS 2020 conference. In addition to international conferences, I presented preliminary findings of the study at local meetings and to the Ministry of health technical working groups.

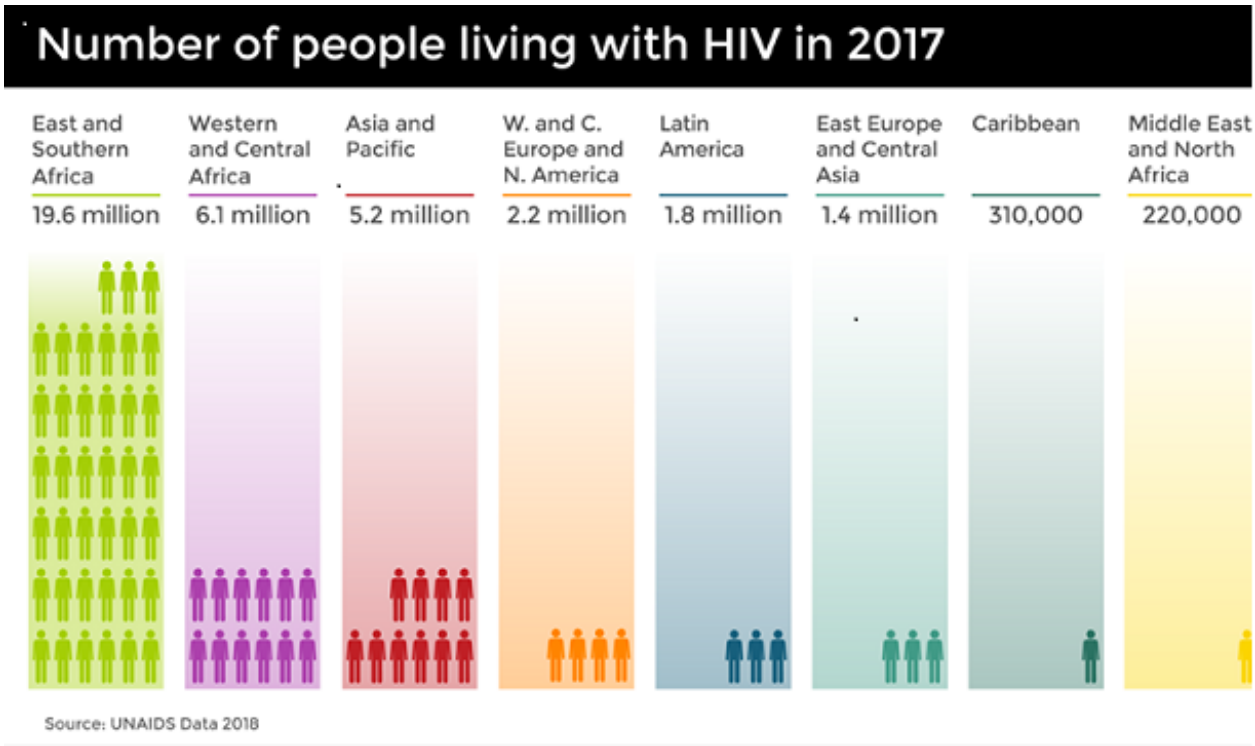
Chapter 2: Literature Review

2.1 Global HIV epidemic

HIV, or the human immunodeficiency virus that causes AIDS (acquired immunodeficiency syndrome), has been one of humanity's deadliest and most persistent epidemics, and despite tremendous advances in combating new HIV cases and AIDS fatalities, the HIV pandemic persists [11]. The first case of AIDS was reported in 1981 and soon after, the retrovirus HIV was isolated leading to decades of intense research on the virus itself, pathogenesis, and development of approaches to test, treat and prevent new infections [35, 36]. The virus is primarily spread through unprotected sexual intercourse (including anal and oral), sharing needles, contaminated blood transfusions, or perinatally during pregnancy, childbirth, or lactation [11]. On a worldwide basis, heterosexual transmission represents the most common means of HIV acquisition [37]. HIV attacks the CD4 cells of the immune system that is vital to fighting off infection and destruction of these cells increases the risk and impact of other infections and diseases leaving people with untreated HIV vulnerable to a chronic, potential life-threatening condition (AIDS) and death [11]. There is currently no effective cure or vaccine for HIV, but today effective anti-HIV drugs allow people living with HIV (PLHIV) to live long and healthy lives. Adherence to highly active combination ARV regimens, commonly referred to as HAART has transformed HIV from an infectious disease to a chronic disease [11, 25]. Taking ART on a daily basis as prescribed can reduce the amount of virus in the blood to undetectable levels by routine tests, and those who achieve and maintain undetectable viral loads are unable to sexually transmit the virus to others, a concept known as Undetectable=Untransmittable (U=U)[11].

Since the start of the HIV epidemic, 74.9 million [58.3 – 98.1 million] people have become infected with HIV and 32.0 million [23.6 – 43.8 million] people have died from AIDS-related illnesses [38]. Today, HIV is still a global epidemic and in 2018, 37.9 million [32-7 -43.8 million] people were living with HIV (PLHIV) globally with an estimated 1.7 million new infections and 770,000 AIDS related deaths [38]. As the world commits to reaching the UNAIDS 90-90-90 targets by 2020 to end the AIDS epidemic by 2030, there has been substantial progress in scaling up antiretroviral treatment (ART) programs globally. By 2018, more than two thirds (79%) of all PLHIV knew their status with 23.3 million (62%) PLHIV accessing ART [38] [Fig.2.1].

Fig 2.1: Global estimates of people living with HIV



Source: UNAIDS 2018. www.avert.org

HIV has disproportionally affected Africa, particularly sub-Saharan Africa which has the largest burden of the disease and continues to be the epicentre of the epidemic. An estimated 68% of PLHIV are living in this region particularly in low- and middle-income countries. Among this group, East and Southern African countries are heavily affected by the pandemic. This region accounts for approximately 6.2% of the world's population but is home to over 50% (20.6 million) of the total number of PLHIV globally with 800,000 new infections in 2018 [39]. In countries like South Africa, Botswana, Eswatini and Lesotho, the HIV prevalence levels in the adult population are as high as 20-25%, followed by Zimbabwe, Zambia and Malawi where prevalence levels range from 9-13% [40]. In 2018, South Africa accounted for more than a quarter of the regions new HIV infections and other countries within the same region accounted for more than 50% of new infections [38, 40].

The region has seen rapid declines in new HIV infections by 28% and AIDS-related deaths by 44% since 2010 [41] due to the scale up and widespread coverage of ART. However, progress towards controlling the epidemic is fragile, and varies considerably within the region [40, 41]. The HIV epidemic in this region is mainly driven by heterosexual sex with a concomitant epidemic in children through vertical transmission [42]. As such young women (15-24 years) are disproportionally affected as they account for approximately 26% of new infections in this region [41, 42]. Other key population groups such as men who have sex with men, sex workers, prisoners and people who inject drugs are also vulnerable to the infection [40].

2.2 Universal treatment

HIV cannot replicate on its own, and to do so, must infect the CD4 cells of the immune system which play a major role in protecting the body from infection. The virus uses the CD4 cells machinery to multiply and spread throughout the body. This process is called the HIV life cycle which involves multiple stages. As the virus multiplies, it destroys the CD4 cells hindering the body ability to recognize and fight off infections and if not controlled by treatment, the loss of CD4 cells lead to development of opportunistic infections and eventually AIDS [43, 44]. Although there is no cure for HIV, antiretroviral therapy (ART) is used to treat HIV infection and these drugs are capable of blocking HIV at different stages of the virus's life cycle. These drugs help PLHIV live longer and healthier and reduce the risk of HIV transmission. ART is recommended for all PLHIV as it prevents the virus from replicating and reducing the amount of the virus in the body (viral load) to undetectable levels. PLHIV with undetectable viral loads are not at risk of spreading HIV to uninfected partners during unprotected sex [43].

2.2.1 The Revolution of antiretroviral therapy

Over the past 30 years, the outcome of HIV infection has been revolutionized by a major step forward in the development of effective antiretroviral drugs that have transformed HIV from a fatal infection into a chronic, controllable disease [36, 37]. In 1987, AZT, also known as Zidovudine, became the first drug approved for the treatment of AIDS. AZT belongs to a class of drugs called nucleoside reverse transcriptase inhibitors (NRTIs), which have been shown to reduce mortality and opportunistic infections in AIDS patients [36, 45, 46]. However, the development of virus resistance to AZT has led to the development of new drugs based on insights into the viral replication cycle and methods of targeting it [36]. In the early 1990s, additional NRTIs were approved for HIV treatment and this paved the way for the discovery and development of newer generations of antiretroviral drugs and these drugs now exist in a variety of categories based on enzymatic and/ or cellular targets [37, 45]. NRTIs were targeted against the viral reverse transcriptase enzyme but newer drugs were developed that targeted against protease, and most recently against integrase inhibitors [37]. However, the limitations of single-drug treatment for HIV became apparent quickly as the virus has the ability to replicate rapidly.

During replication, the virus is susceptible to errors and these errors, or mutations causes small changes in the virus that can confer resistance to an antiretroviral drug and evolves rapidly [45]. This impelled further investigations to determine whether combining drugs would prevent the virus to become resistance to all the drugs simultaneously and in the early 1990s, researchers further noted that two-drug therapy (AZT in combination with another NRTI) was more effective than AZT alone in immune restoration or preventing deaths, raising hopes on the use of a combination therapy to treat HIV/AIDS [45]. Although the use of dual therapy was superior to monotherapy for PLHIV, it was of limited duration and in 1996, a major breakthrough was made with the introduction of a combination therapy of several drugs to durably supress HIV replication to minimal levels and create a high genetic barrier against the development of drug resistance [36, 45]. The success of triple-drug therapy, also known as highly active antiretroviral therapy, or HAART, was due in part to the addition of a protease inhibitor alongside two NRTIs, and studies showed that use of HAART significantly reduced morbidity and mortality [36, 45]. Whilst HAART was lifesaving provided patients adhered to these prescribed drugs, these drug regimens were far from perfect as the pill burden was complex and side effects burdensome making it difficult for people infected with HIV to adhere to the regimens long-term [45]. To address the complexity of the drug regimens, toxicities and development of resistance, several other drugs were developed to target the various steps in the HIV replication cycle and in the mid-1990s drugs such as non-nucleoside reverse transcriptase inhibitors (NNRTIs) drugs and later in the 2000s, integrase inhibitors were developed and approved to treat HIV. In 2013, a second generation integrase inhibitor was developed and was found to have a high barrier to the development of HIV drug resistance [45].

Currently there are more than 30 antiretroviral drugs available, including fixed-dose combination allowing people to adhere to their drugs regimens by taking a single pill once a day and clinical research today continues to improve therapeutic options available aimed at controlling viral replication[36]. Drugs such as NNRTIs are less expensive and easier to manufacture than protease and integrase inhibitors, allowing ART to be scaled up in resource-constrained settings. The successful development of combination therapies has been key in transforming HIV from an infectious to a chronic disease [2, 25, 45] with near normal life-span expectancy in almost all developed and resource-limited countries.

2.2.2 From CD4-based initiation to immediate treatment for all HIV-Positive adults

HIV infected individuals require ART to prevent disease progression to AIDS, mortality, and on-going transmission. The optimal timing of when to initiate ART had been a subject of on-going research over the last couple of years but there has now been convincing evidence for the benefits of early initiation [3, 47]. During the late 1990s, antiretroviral drugs available were few, expensive and associated with significant drug toxicities. Most of the drug combinations available at that time were less robust and carried a high risk of developing drug resistance, there were fewer treatment options and decision on when to initiate treatment needed to balance benefits against the risks [48]. The treatment threshold for asymptomatic HIV-infected persons was reduced to 200 cells/mm, with the prevailing view that disease progression and mortality were lower above this threshold. This transition was mostly owing to extreme caution regarding drug toxicity and the development of drug resistance at a time when alternative treatment options were limited [48, 49].

With time, the availability of further treatment options that were much affordable and less toxic, evidence for starting ART at a higher CD4 thresholds emerged and between 2006 and 2009, WHO raised the CD4 threshold for ART initiation to 350 cells/mm³ based on evidence of moderate quality that ART initiated at this threshold reduced disease progression, mortality and serious adverse events [50, 51]. In 2013, WHO guidelines raised the CD4 threshold for ART initiation to 500cells/mm³ [52], based on moderate-quality evidence from three RCTs and 21 observational studies showing that initiation ART below CD4 threshold of 500cells/mm³ compared with later initiation (200 or 350 cells/mm³) reduced the risk of disease progression and/or death as well as opportunistic infections [5, 52, 53]. By 2015, WHO subsequently updated their guidelines recommending all PLHIV to start ART irrespective of CD4 cell count [6, 48]. This final step was inspired by the result of three randomized controlled trials, START, TEMPRANO and HIV Prevention Trial Network (HPTN) 052 [5, 49, 54-56] that provided concrete scientific evidence that immediate and effective ART in all PLHIV have superior clinical outcomes to deferring ART based on CD4 cell count threshold [54, 55] and less likely to transmit HIV to uninfected sexual partners[5, 57].

The TEMPRANO trial showed that initiation of ART at a CD4 count >500cells/mm^3 reduced the risk of AIDS related illness and deaths by 44% compared to deferring treatment and the START trial showed a reduction of AIDS-related illness and death by 57% in the intervention arm that received immediate ART regardless of CD4 count versus those randomized to ART initiation at a CD4 threshold of <350cells/mm^3 [3, 54].

In addition to reducing morbidity and mortality, ART irrespective of CD4 cell count has the potential to prevent further transmission of HIV demonstrated by the HPTN 052, a large randomized clinical trial which demonstrated a 96% reduction in linked HIV transmission from HIV-positive to un-infected partners when the former was virally suppressed on ART that was started outside of contemporary CD4 guided thresholds [5, 6]. These trials provided the common conclusion that PLHIV globally should be initiated on lifelong-ART irrespective of their CD4 cell count or disease stage to suppress viral replication for individual benefit and prevent ongoing HIV transmission to non-HIV infected partners.

2.2.3 Strategies to deliver universal ART for all PLHIV

The benefits of ART are now well known. Not only does it improve the health of PLHIV, but it is also an effective strategy to prevent transmission of HIV from an infected individual to their sexual partners or to their babies during pregnancy, delivery, and breastfeeding. High levels of HIV viral load in blood and genital secretions is a critical driver of HIV transmission [58]. ART works by controlling the replication of the virus reducing the HIV viral load to low levels that cannot be detected by standard blood tests. This is called 'undetectable' viral load or viral suppression [59, 60]. The current standard practice for the clinical management of HIV is to ensure long-term viral suppression through the use of ART for patient health benefit and decreasing risk of transmission. Viral suppression can only be achieved and maintained when adhering to ART correctly and consistently and therefore imperative that PLHIV on ART are accessing regular treatment support to monitor viral load and adherence support from a healthcare professional.

The concept of using treatment for HIV-infected individuals to achieve viral suppression and reduce the risk of transmission to uninfected sexual partners known as "Treatment for Prevention" (TasP) arose following a landmark study in 2011 [61]. The HIV Prevention Trials Network (HPTN) 052, a randomized clinical trial which examined this concept, showed at final analysis a 96% reduction in linked HIV transmissions amongst serodiscordant couples when evaluating the effects of early versus deferred ART [57, 62]. Similarly, the results of the PARTNER study showed that ART and undetectable viral loads (<200copies/ml in this study) can prevent sexual transmission of HIV in heterosexual and same-sex male partners [63]. Evidence on the effectiveness of TasP both on public health interventions and patient-specific strategy led the WHO guidelines to recommend 'test and treat' or 'treat all' strategy - a push towards alerting as many people as possible to know their HIV status through testing, and starting people infected with HIV on ART irrespective of their clinical or immunological status [6].

The reason for this push was that if a large number of PLHIV are diagnosed and on treatment successfully, then not only can it positively affect the health and well-being of PLHIV, but also a reduction in the average amount of virus circulating in the community resulting in the occurrence of fewer transmission, in fact the chances of transmitting HIV sexually would be almost zero. This is referred to as a drop in community viral load on a population level [61, 64, 65]. Diminishing the rate of new HIV infections brought about by these strategies was a key cornerstone of the Joint United Nations Programme on HIV and AIDS (UNAIDS) targets to end the AIDS epidemic as a major public health program by 2020 [14]. These ambitious targets were coined "90-90-90" that is ensuring 90% of all PLHIV know their status, 90% of all HIV+ infected person who knew their status are on treatment, and 90% of those on ART virally suppressed) by 2020, with 95-95-95% respectively reaching these targets by 2030 [14, 15, 66].

For treatment as prevention programs to succeed to reach the UNAIDS target, there is need to maximize the HIV care cascade. This cascade evaluates the HIV continuum of care from the time of diagnosis, engaging and retaining in care, and ultimately achieving viral suppression and has been a framework in which to evaluate potential gaps in HIV programs [58, 67]. The overall effectiveness of HIV programs especially in sub-Saharan African countries is severely undermined by attrition of patients across the HIV care cascade. Stigma, discrimination, lack of knowledge of HIV status and the negative perceptions of PLHIV, of HIV services and ART have been shown to be the major barriers in the care cascade [62, 68]. People who do not access testing and treatment services immediately after infection are more likely to spread HIV even if they go on to access treatment [52]. Therefore, in order to improve individual health outcomes and potentially prevent further transmission to others, each step of the care cascade need to be maximized to enhance HIV diagnosis, linkage to and retention in care, ART adherence and ultimately viral suppression [69].

Although national HIV programs globally adopted the WHO guidelines to scale-up rollout of ART and some reductions in the incidence of new HIV infections became apparent, sub-Saharan Africa continued to experience severe generalized epidemics [70]. HIV incidence and prevalence continued to remain at unacceptable high levels and despite ART having an impact on AIDS-related mortality, the total number of HIV-infected individuals continued to rise [70, 71]. This imposed a huge challenge towards curbing the epidemic as the incidence of new HIV infections continued to rise, there will be a continuous increase in the number of PLHIV who will require ART in the future and sustaining ART services for all those who need them will become extremely difficult especially in high HIV burden resource-limited settings [71, 72].

This led researchers to examine the effectiveness of TasP on a larger population level in high HIV prevalence settings to determine if expansion of ART coverage in a real-world uncontrolled setting could still produce a significant decline in HIV incidence [61]. Provision of ART on a wider scale was now being recognised as one of the key preventive intervention for HIV control following the clinical effectiveness TasP which was based on evidence that HIV transmission was strongly correlated with viral load, and transmission risk is very low with undetectable viral load [5, 10, 71, 73, 74].

Disappointingly, there have been very few HIV prevention tools that have been shown to be effective in randomized controlled trials in resource-limited settings. Of over more than 30 interventions that had been tested in rigorously conducted RCTs of HIV prevention, only 5 trials showed significant evidence of protection [72, 75]. Three trials on male circumcision[76-78] has been shown to reduce the risk of men acquiring infection by 50-60%, although not enough to eliminate HIV, even under the most optimistic conditions[75, 79] and furthermore implementation of male circumcision on a wider-scale has been slow. In high HIV burden settings, a study of sexually transmitted infection (STI) for HIV prevention in Mwanza, Tanzania was shown to be relatively less effective in high HIV burden settings[72] and the RV144 vaccine trial in Thailand was of borderline significance and showed a modest effect [72, 80].

As the availability of treatment expanded globally and with limited array of proven HIV prevention tools, using treatment as an intervention to prevent infection was proposed and mathematical modelling was used to evaluate this argument[75, 81]. This model proposed “universal test-and-treatment,” or UTT, as a potential HIV prevention strategy that could be effective in high-prevalence settings [71, 72, 75, 82-85]. UTT entails providing HIV counselling and testing (HCT) to the entire population, as well as prompt ART to all HIV-positive people, regardless of CD4 cell level or disease stage. This model suggested that in high prevalence setting, an intervention such as UTT could reduce the incidence to below 1 per 1000 person-years at risk that is approximately more than 95% reduction and potentially lead to the elimination of HIV as a public health problem over a period of 15-20 years and also reduce HIV-related morbidity and mortality [72, 75, 82].

Following the models projection for UTT as a potential prevention strategy, there was a sparked interest in rolling out “test -and-treat “type of interventions to meet the ambitious UNAIDS 90-90-90 targets by 2020 and eventually 95-95-95 targets by 2030, with the goal of significantly reducing HIV incidence and prevalence by then [14]. In order to fully achieve the potential impact of UTT on a wider scale (population-level), there is need to maximize coverage of HIV testing, effective linkage to and retention in care, rapid access to and initiation of ART, and adherence to ART to achieve viral suppression [86-88]. This led to numerous research questions on the feasibility, effectiveness, and

costs of UTT on a large scale in resource limited settings and how best do we implement UTT or what coverage can be achieved in practice [72, 86].

Although the WHO 2015 guidelines recommended immediate ART for all PLHIV regardless of CD4 cell count, this removed one barrier to meeting the second 90% target. However, there are numerous obstacles and challenges to ensuring UTT and this includes scaling up HIV testing services in a community so that everyone knows their status, linking all HIV-infected individuals to care and initiating ART as soon as possible, keeping all PLHIV on ART in care, and achieving viral suppression [71]. As the momentum to determine the feasibility, acceptability, scalability, and affordability of UTT on a larger scale grew, different investigators over the last ten years designed and implemented five community-based randomized trials in Southern and East Africa, where there is the most urgent need for effective HIV control [72, 86, 89]. In addition to measuring the impact of UTT on HIV incidence, these studies were also expected to provide strong evidence for policy formulation and practice for optimal scale-up approaches [86, 87].

2.2.4 Universal Test-and-Treat Randomized trials

The five large-scale UTT randomized studies that were conducted in East and Southern Africa included: the ANRS 12249 TasP (ANRS TasP) trial in South Africa [88, 90, 91], SEARCH (Sustainable East Africa Research in Community Health) trial in Uganda and Kenya [92], the Botswana Combination Prevention Project (BCCP)/Ya Tsie trial in Botswana [93], M*ax*ART study in Eswatini (previously known as Swaziland) [94] and the HPTN 071 Population Effects of Antiretroviral Therapy to Reduce HIV Transmission (PopART) trial in South Africa and Zambia [91, 95]. All of the aforementioned UTT trial teams came together as a consortium (UT3C) to better understand if and how population-level HIV testing and treatment could reduce HIV incidence and mortality in order to meet the UNAIDS 90-90-90 goal for epidemic control [86, 89]. The consortium shared study protocols, intervention packages, themes explored, and highlighted and interpreted the similarities and differences across the trials.

All the five UTT trials evaluated the impact of UTT on population-level HIV incidence as their primary endpoint, and evaluated multiple interventions that integrate HIV testing, prevention, and treatment, as well as their long-term benefits and sustainability. The trials were conducted across a broad range of settings from rural (ANRS TasP and SEARCH), peri-urban (PopART) to both rural and peri-urban (BCCP and M*ax*ART). Although all five UTT studies were randomized trials, they differed somewhat in terms of their design, with four adopting a community-based randomized design and one a stepped-wedge clinic randomized design [88]. The trial also had difference in their study arms with four trials having two arms and one trial with three arms [86, 88]. The baseline prevalence of HIV amongst adults in the population where the 5 trials were conducted ranged from 4-30% and over a million community

members participated across these studies [86, 89]. Whilst the trials were ongoing, the HIV policy landscape had been evolving and several changes with regards to ART initiation for PLHIV following WHO ART recommendations were taking place. The UNAIDS launched the 90-90-90 targets, for countries to reach for 90% for people to know to their status, start ART and viral suppression. In 2013, the WHO guidelines recommended ART initiation for HIV -infected individuals with CD4 count <500 cells/mm³ and those with advanced stages of the disease and in 2015, expanded eligibility to all PLHIV irrespective of CD4 count or disease stage [6].

As the countries in which the trials were being conducted adopted the WHO guidelines for ART eligibility, the UTT trials also promptly modified their interventions and strategies. In all the trials, the control arm (communities) immediately followed the national guidelines for initiating ART at a CD4 threshold of 500 cells/mm³ (2013 WHO guidelines) and universal ART (2015 WHO guidelines). The only study that did not immediately switch to universal treatment was the TasP trial as guidelines in South Africa did not shift towards universal treatment until the very end of the study [86, 89]. In addition, other parameters such as simplification of ART delivery procedures, targeting key populations etc. were altered in the trials to adapt to the operational challenges. The five trials were able to adapt extremely well to the study settings political, economic and public health environment, therefore generating rigorous scientific evidence of the effectiveness of UTT on a large-scale in resource limited settings [86].

The ANSR 12249 TasP trial in rural South Africa was a two-arm cluster-randomized trial designed to assess the effectiveness of TasP on HIV incidence in KwaZulu Natal [61, 90]. Clusters or communities were randomized to either immediate ART initiation (intervention) or ART initiation according to national guidelines (control arm) after HIV diagnosis. The study found no reduction in the HIV incidence between the intervention and control arms [61, 96]. When compared to the control arm, home-based HIV testing was well-accepted and met the first 90 target, linkage to care, ART initiation, and viral suppression only witnessed moderate increases, falling significantly short of the second and third 90 goals [61, 74]. Linkage to care was a weak link in the cascade, possibly associated with HIV-related stigma in their setting [97]. Although this trial only compared the impact of immediate treatment vs treatment according to national guidelines, it did not address the critical barrier in the long delay between HIV diagnosis and ART initiation in this setting. This highlighted the critical importance of achieving high rates of linkage to care after HIV diagnosis for multiple heterogeneous groups [61, 86, 98].

Other UTT trials examined the impact examined the impact of the treatment cascade such as universal testing, linkage to care and immediate ART vs the current standard of care [95]. The SEARCH study, a cluster-randomized trial in Kenya and Uganda was designed to evaluate whether universal HIV treatment and annual testing delivered through community-based, multi-disease, patient-centred approach would result in a reduction in HIV incidence [99]. In the study's intervention arm, HIV incidence decreased by 32% from the first to the third year, paralleling a significant increase in viral suppression among HIV+ individuals from 42% at baseline to 79% in the third year. The cumulative HIV incidence, however, did not differ between the intervention and control arms [86, 92, 100]. Despite not seeing a significant difference in HIV incidence between the two arms, the intervention arms rapidly achieved and surpassed the UNAIDS 90-90-90 targets in rural Kenya and Uganda, improving community health (HIV mortality, Tuberculosis (TB) and hypertension control)[92]. In both countries where the trial was conducted, the national guidelines had changed to universal treatment a year after the SEARCH trial began and therefore could have diminished the effect of the intervention as originally hypothesized [100]. In addition, the communities where the trial was conducted were small and rural with low levels of education, migration and employment and the results may not be generalized to other rural or urban communities with different demographic characteristics.

The Botswana Combination Prevention Project (BCCP): the *Ya Tsie* study used a pair-matched community randomized trial in 30 communities in Botswana [61]. This study explored the impact of a combination prevention which included scale up of HIV testing (home-based and mobile HCT), point-of-care CD4 testing, linkage to care, and ART at higher CD4 counts and enhanced voluntary medical male circumcision (VMMC), on HIV incidence at population level and compared to standard of care in rural and peri urban communities [101]. At the start of the study, intervention communities expanded ART eligibility to cover individuals with either CD4 count of >350-500 cells/mm^3 or CD4 count >500 cells/mm^3 and HIV-1 RNA ≥ 10,000 copies/mL. Midway through the study in 2016, in-country guidelines began offering universal ART which was implemented in all the intervention and control communities [61]. The trial observed that compared with the control community, the HIV incidence rate in the intervention community was reduced by 30%, but it was of little statistical significance [61, 101, 102].

The MaxART study evaluated the feasibility, acceptability, clinical outcomes, affordability, and scalability of providing ART to all HIV-infected citizens in Swaziland's public health system [103]. The study's main purpose was to evaluate whether early ART initiation for all adults infected with HIV can improve retention and viral suppression at population-level in the government health system. This was the only universal test-and-treat study to be undertaken in the public health sector to evaluate retention and viral suppression rather than HIV incidence and one of the first to focus on crucial

implementation problems and evaluations in resource-limited settings [103]. The study was a three-year stepped-wedged randomized design open to enrolment for all adult (≥ 18 years) across 14 health care facilities over three years (2014-2017). The sites were grouped to transition from the control (standard of care using national eligibility guidelines) to the intervention stage. All the sites began in the standard of care stage and then went through a four-month transition period before entering the intervention stage. On the first day of the transition phase, ART was implemented regardless of CD4 count (Early Access to ART for All) [104]. As of October 2016, national guidelines in Swaziland expanded ART eligibility to all PLHIV irrespective of CD4 count or disease stage and the study design was equally revised to coincide with the national roll-out of test and treat. The study found that Early Access to ART for All has a substantial effect on retention and viral suppression and 12-month retention and post ART initiation viral suppression rates in the intervention arm providing UTT were 86% and 79% respectively, compared to 80% and 4% in the control (standard of care) arm [104]. The performance of the health systems in providing ART to PLHIV improved following adoption of UTT and the results of this "real-world" health system trial strongly supported the expansion of UTT in resource-limited setting because it was found to be acceptable, feasible and affordable[104, 105].

The recently completed HPTN 071 (PopART) trial, Population Effect of Antiretroviral Therapy to Reduce HIV Transmission, was the largest community randomized trial evaluating the impact of a combination prevention package that included UTT in reducing HIV incidence at a population level [95]. This was a 3-arm community randomized trial that ran from 2013 through 2018 across urban and peri-urban communities in Zambia and South Africa. A total of 21 communities (population of approximately 1 million) were randomly assigned to either one of the three arms: 1. Combination prevention intervention with universal ART; 2. Combination prevention intervention with ART according to national guidelines and 3. Standard of care (control arm) [105]. The prevention strategy (interventions) included annual rounds of home-based HIV testing by community HIV providers (CHiPs) who supported linkage to care, ART adherence, and other HIV services such as voluntary medical male circumcision advocacy and condom distribution. Midway through the study, national guidelines for ART initiation changed to universal ART, and communities that were randomized to initiating ART at CD4 thresholds changed to universal ART, at which time arm 1 was identical to arm 2. The control arm continued to provide standard of care including universal ART consistent with national guidelines. The study's intervention communities achieved the UNAIDS 90-90-90 targets and high rates of viral suppression (~ 70%). The final findings of this trial revealed, surprisingly, that HIV incidence was lower by 30% in the communities that provided the combination prevention package and ART according to national guidelines (arm 2) than in the standard of care control communities. There was no evidence of such an effect in the communities that provided universal ART and

combination prevention package (arm 1) [105]. This lack of effect in the full intervention arm where UTT was delivered was inconsistent with data on viral suppression [105, 106]. This finding of HIV incidence in the arms that provided universal ART did not differ significantly from the control is yet unexplained and requires significant ongoing work to understand better. Several explanations for this lack of effect on HIV incidence included: 1. Use of written informed consent for starting ART outside national guidelines at the start of the trial could have discouraged individuals initiating ART though this was not supported by data which had similar coverage of ART uptake and viral suppression in both intervention arms; 2. Wide scale ART in universal ART communities may have led to reduction in primary prevention efforts or sexual disinhibition but this was not supported by data on participant-reported risk behaviours; possibility that there may have been other factors such as mobility and migration that could have resulted in HIV exposure but analysis of data showed that differential migration across the study communities was not apparent [105]. Given that the interventions in the two arms were similar for the majority of the primary analysis period, it is possible that the difference in observed effects was due to chance, and that their combined difference with the control arm (20% reduction in HIV incidence) in a post hoc analysis reflects the trial's key finding [105].

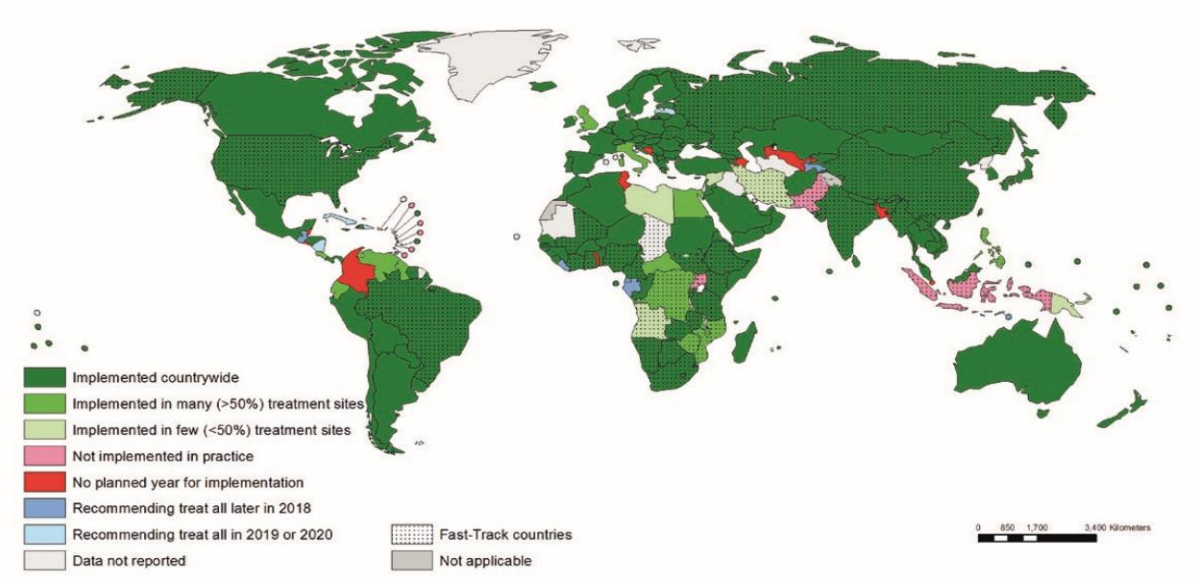
The five trials have collectively signaled a way forward to rapidly achieving the UNAIDS 90-90-90 goals and have provided solid evidence that UTT is feasible in resource-limited settings in sub-Saharan Africa. All the trials agree that optimizing the HIV care cascade is the key to a successful UTT strategy. Compared with the current standard of care offered in SSA, UTT with universal testing, active linkage, and access to ART care can rapidly achieve viral suppression and ultimately reduce HIV incidence and mortality [89] Despite the four trials achieving approximately 30% reduction in HIV incidence, a shortfall from what the modelling studies suggested, the full potential of UTT is likely to be greater with widespread implementation and addition of other prevention modalities such as pre-exposure prophylaxis [89] to achieve HIV epidemic control.

2.3 The Impact of Universal ART on the HIV epidemic

The worldwide response to the HIV epidemic has been unprecedented. Although ART was available in resource-rich countries since 1995, it was only after another 10 years to reach resource-limited settings hardest hit by the epidemic, such as sub-Saharan Africa [107]. In the early stages of the epidemic, the use of ART for PLHIV began as an emergency response for PLHIV with advanced disease stage, who were at a higher risk of dying. WHO treatment guidelines in 2002 recommended ART initiation for those who were asymptomatic with a CD4 count below 200 cells/mm^3 or those with

advanced stages of the disease [108]. This was because it was widely assumed that drug exposure exceeding this threshold would result in significant drug toxicity and the development of drug resistance in the face of restricted therapeutic options. However, these guidelines laid the foundation of ART delivery within a public health framework, including resource-limited settings not just for individual case management but to support public health approach in delivery and scale up of ART [48, 109]. As further treatment options became available and affordable in parallel with evidence supporting overall benefits of starting treatment at higher CD4 threshold, WHO expanded HIV treatment guidelines in 2010 recommending ART initiation at CD4 threshold of 350 cells/mm³ and again to 500 cells/mm³ in 2013 [48]. With improvements in ART options and increasing evidence showing that individuals on effective ART have superior clinical outcomes and less likely to transmit HIV to others (START, TEMPRANO and HPTN 052 trials), this led the WHO to subsequently update its guidelines in 2015, strongly recommending that all PLHIV should start ART irrespective of CD4 cell count or disease stage [6]. This was aimed to end the HIV epidemic and meet the UNAIDS targets of 90-90-90% by 2020, with 95-95-95% by 2030 [13, 15]. This has resulted in an increase coverage of ART as all PLHIV are now eligible and in need of immediate treatment as countries started adopting the WHO 2015 guidelines. By the middle of 2018, 84% of low-and middle- income countries adopted the WHO "treat all" guidelines, covering 98% of all PLHIV globally [Fig.2.2] [110, 111].

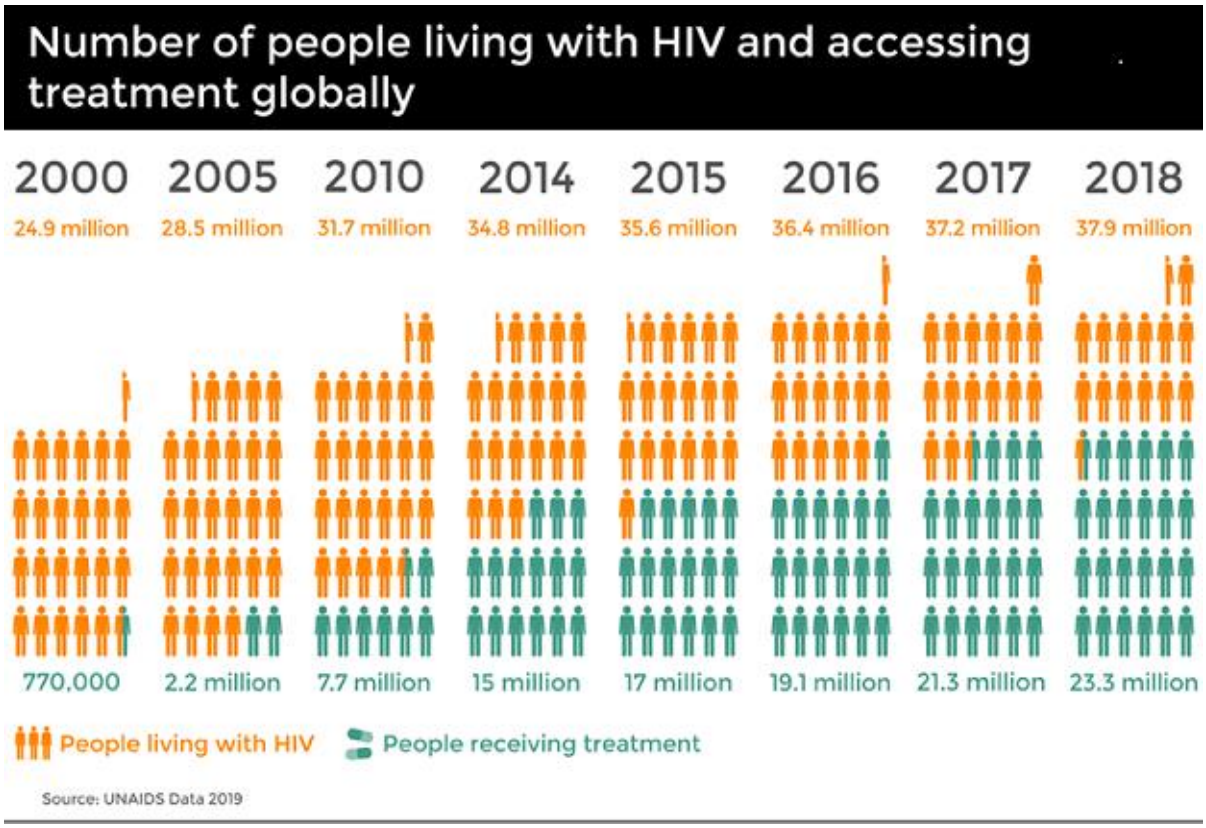
Fig. 2.2. Implementation of Treat All ART recommendation among adults and adolescents living with HIV (Situation as of mid-2018).



Source: Global AIDS Monitoring (UNAIDS/WHO/UNICEF) and WHO HIV Country Intelligence Tool, 2018. https://apps.who.int/iris/bitstream/handle/10665/275468/WHO-CDS-HIV-18.21-eng.pdf?ua=1

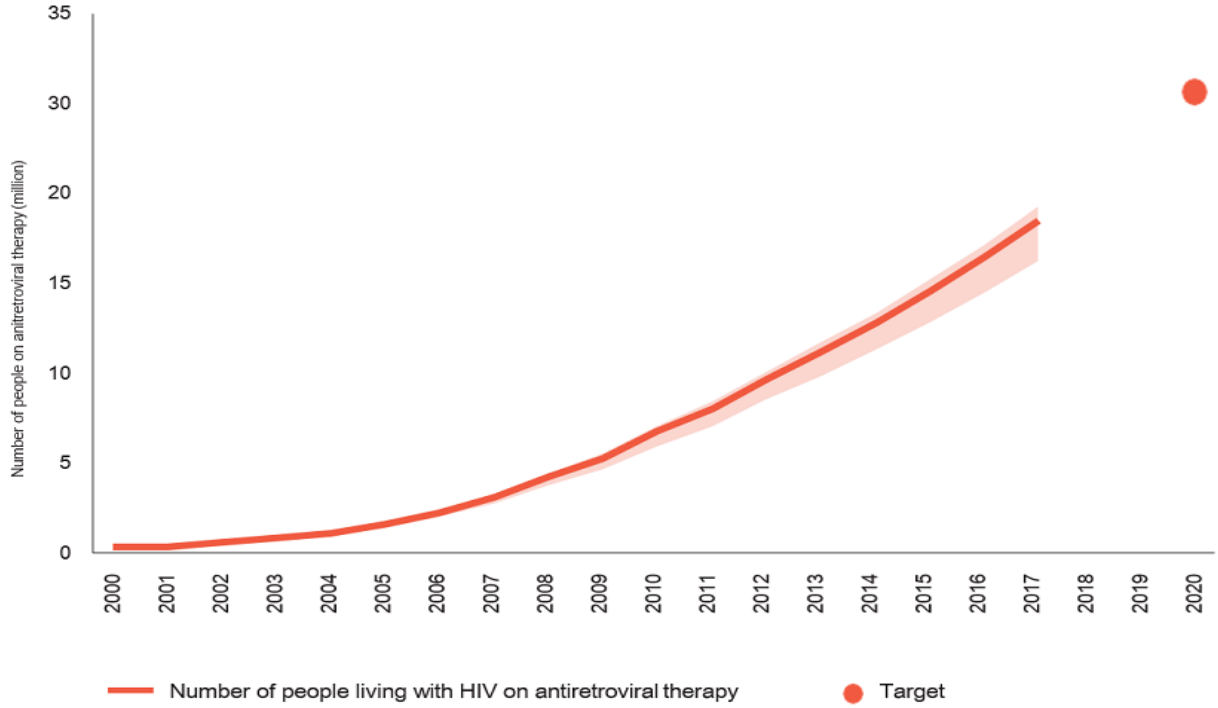
The adoption of WHO recommendations for universal ART has resulted in an increase coverage of ART globally, including sub-Saharan African region most affected by the epidemic. In 2018, 62% [23.3 million] PLHIV globally were accessing treatment and in 2019, 24.5 million PLHIV were on ART [40, 112], a major improvement since 2010 when ART initiation was based on CD4 guidelines and only 7.7 million PLHIV were on ART [Fig.2.3]. however, despite this achievements, the treatment scale up is still below the UNAIDS global target of treating 30 million HIV infected individuals by 2020 [Fig.2.4] [41]. With increased ART coverage for PLHIV, the number of new HIV infections and AIDS-related deaths has decreased. Although the annual number of new infections among adults has been stable in recent years, approximately 1.7 million people became newly infected with HIV in 2018, a modest reduction from 1.8 million in 2017 [40, 112]. Although new HIV infections globally have declined by 16% compared to the peak in 1997 [2.9 million], this is of major concern as the decline is not enough to reach the target of less than 500,000 new infection by 2020 [40]. The number of AIDS-related deaths have also shown a reduction by more than 55% since 2004 and 2010 when the number of HIV-related deaths peaked at 1.7 million and 1.4 million respectively[40].

Fig 2.3. PLHIV accessing treatment globally



Source: www.avert.org /global-HIV-and-aids-statistic

Fig 2.4. Number of people living with HIV accessing antiretroviral therapy, global, 2000–2017 and 2020 target.



Source: UNAIDS. Global AIDS update 2018: miles to go. Geneva: Joint United Nations Programme on HIV/AIDS (unaids); 2018.

East and South Africa, the region hardest hit by the HIV pandemic and home to the largest number of PLHIV globally have made huge strides to meet the UNAIDS targets. Following the WHO guidelines in expanding HIV treatment guidelines initially at CD4 thresholds since 2010 and finally extending treatment to all PLHIV irrespective of CD4 count or disease stage, has led to substantial gains in ART coverage for PLHIV in this region [107]. Through the combined efforts of countries ART programs, international donor funding, community stakeholders and PLHIV, the number of PLHIV on ART has rose rapidly across the region over recent years. This accomplishment has resulted in rapid reduction in the incidence of new HIV infections and AIDS-related deaths in areas with high ART coverage, albeit progress is fragile and varies greatly across the region [41, 107]. Among the region's estimated 20.6 million PLHIV, an estimated 67% [13.8 million] PLHIV were on treatment in 2018 (up from 53% in 2015). The gap to reaching the second UNAIDS 90 target of ART initiation among PLHIV stood at 1.1 million and additional 3 million PLHIV still need to access treatment [38, 113].

2.4 Challenges of treating all people with HIV in sub-Saharan Africa.

There is now sufficient evidence that following the current WHO guidelines on universal treatment will change the face of the HIV epidemic through substantial gains in ART coverage and concomitant improvements in life expectance and reduced mortality [107]. However, this needs to be widely and successfully carried out especially, in high HIV burden countries in sub-Saharan Africa. Despite substantial improvements in the trends of new HIV infections and deaths since the scale up of HIV treatment in SSA, the current statistics are sobering. According to the latest UNAIDS data, there are still an estimated 470,000 AIDS-related deaths per annum amongst the 25.6 million PLHIV in sub-Saharan Africa [112], and an estimated 16.4 million [64%] of PLHIV [13.8 million in East and Southern Africa and 2.6 million in Western and central Africa] are on treatment [112], leaving treatment coverage still far below the UNAIDS 90-90-90 target. In addition to covering all HIV-infected people receiving treatment, the current annual rate of 1.28 million new infections in the region alone is an overwhelming realization that millions of new HIV infections will need diagnosis and treatment. Therefore, the public health systems in resource-limited settings need to be prepared to face the challenges that implementation of universal ART on a large scale will bring. Despite universal ART removing one barrier to achieving the second UNAIDS 90 target to treat all PLHIV, the need to scale up HIV testing in a population so that everyone knows their status; to ensure that PLHIV are linked to care and initiated on ART rapidly and ensuring all PLHIV on treatment are retained in care and virally suppressed will be challenging [71]. The HIV care cascade or continuum of care describes the sequential steps involved in HIV care, from initial diagnosis to engagement in care, antiretroviral medication treatment, and ultimately the goal of viral suppression [114, 115]. Globally, HIV programs have adapted this cascade as a tool to evaluate programmatic performances achieving the essential steps in the cascade and identify gaps and opportunities necessary to maximize individual health and prevention benefits of ART on a large scale [115, 116]. To achieve the UNAIDS 90-90-90 targets, each step of the cascade should be maximized by PLHIV for successful implementation of universal ART.

2.5 Barriers/Gaps in the HIV care cascade

As the scale up of universal ART has resulted in an increase coverage of ART as all PLHIV are now eligible and in need of treatment [6, 52], this poses a challenge for resource-limited settings in SSA as increasing coverage of ART services must minimize barriers to the continuum of care. The potential benefits of ART depend on successfully going through all stages of the HIV care continuum, including diagnosis, linkage to HIV care services, and ultimately treatment initiation. Following treatment initiation, retention in care and lifelong adherence to antiretroviral therapy (ART) are critical for optimal individual and public health outcomes, as failure to do so could result in treatment

interruption, resulting in increased morbidity and mortality due to suboptimal viral suppression and an increased risk of drug resistance and HIV transmission [117, 118]. There is growing evidence that Individuals who test positive are not effectively linked to HIV care, resulting in delayed treatment, ongoing transmission and increased risk of morbidity[117]. Despite the global progress, persistent challenges with linkage to care have impeded efforts to achieve the second and third 90 [111]. In 2017, of all PLHIV globally, 21% of PLHIV were not receiving ART and in the eastern and southern Africa, of the 81% PLHIV who were aware of their status, 15% of those who knew their status were not receiving treatment [14].

2.5.1 Barriers to linkage to care

Approximately 30%-60% of individuals who test positive are linked to care in resource-limited settings according to several recent studies [117-119]. Although definition of linkage to care varies, it is commonly defined as patients who receives clinical care following HIV diagnosis [120]. Evidence currently available has highlighted delays in linking PLHIV to care resulted in delayed ART initiation and subsequently increased morbidity and mortality [121, 122]. Various studies have shown delays in linkage to care in SSA where PLHIV start treatment very late and in the advanced stage of the disease [122-124]. Two important clinical trials conducted in sub-Saharan Africa have recently shown significant delays in linking patients to HIV care after they have been diagnosed with HIV despite getting support services for linking them to care in regions disproportionately burdened by the HIV epidemic. The ANRS 12249 [TasP] in KwaZulu-Natal (South Africa) showed that only 36.9% linked to care by 3 months after referral. This is despite high uptake of community HIV testing [96, 97, 125]. The HPTN 071 (PopART) trial which evaluated the effects of a combination HIV prevention package including UTT on population level HIV incidence using a cadre of lay trained counsellors (Community HIV care Providers [CHiPs]) to deliver the interventions showed an estimate time from CHiP referral to linkage to care (first attendance at clinic), by 3, 6 and 12 months to be 45, 57 and 71% respectively after first referral to care in Zambia and slightly more rapid linkage in South Africa at 48, 60 and 79% [125, 126]. Similarly studies have also shown that despite increasing rates and improvements in HIV testing services and expansion of outreach programs, there is still a challenge to link individuals who test HIV-positive [127]. A study conducted in Northern Tanzania reported only 14% of individuals linking to care within the first 4 months of diagnosis [128]. These rates of linkage to care from various regions in sub-Saharan Africa are indicative of a broader issue confronting national HIV treatment and implementation programs[127].

Several factors have been known to facilitate or mitigate linkage to care from the point of diagnosis to ART initiation and these include a combination of individual/patient, health care provider and health system factors. Several studies that have explored the barriers and facilitators to linkage to care in resource limited settings in sub-Saharan Africa have identified fear of stigma for accessing HIV care services, disclosure of status, negative attitudes of HCW, fear of drug adverse effects, being asymptomatic at the time of diagnosis, complexity of navigation to care registration and readiness to accept treatment as some of the barriers to timely linkage into HIV care [111, 125, 129-131]. Integration of HIV testing and care services, good healthcare provider relationships and minimal clinic waiting times were identified as factors facilitating timely linkage to care [127, 130].

2.5.2 Barriers to rapid ART initiation

The benefits of commencing ART promptly or on the same day as diagnosis have been discussed previously. Prior to the 2015 WHO guidelines advocating ART irrespective of CD4 count, multiple clinical trials and programmatic data demonstrated delays in treatment uptake by PLHIV in different settings[125]. The HPTN 052 experiment, which was done prior to the test and treat recommendations, revealed that despite counselling PLHIV on the significance of urgent treatment and providing access to ART, 17% had not started treatment after one year[57, 125]. Other studies in sub-Saharan Africa had identified multiple barriers to ART initiation prior to the test and treat guidelines and these included stigma related concerns, confidentiality, privacy whilst accessing treatment, negative HCW attitudes, distance to health care facility, poor knowledge of drug regimens and fear of side effects[132-134]. Being asymptomatic at the time of HIV diagnosis was also considered a barrier to starting ART because patients felt they were too healthy to start ART, their CD4 level was not low enough, and/or they feared drug adverse effects. Various studies have established the fact that some PLHIV required time to begin ART despite being adequately informed and encouraged [125, 133, 135]. There is now emerging data from various settings on the hurdles and facilitators to ART initiation among healthy clients eligible for ART under the new Test and Treat policy [132]. A recent qualitative study conducted in Mozambique to examine the barriers and facilitators for ART uptake in the context of universal test and treatment amongst healthy patients found that the already established or "well-known" barriers to care and treatment uptake remain a problem for newly diagnosed patients alongside new barriers, such as being in good health makes it difficult for patients to accept a positive status or initiate treatment [132]. The barriers included: (1) feeling well; (2) denial of HIV+ status; (3) lack or poor knowledge about ART; (4) fear of side effects; and (5) disclosure. Other important barriers included reluctance to start ART for life, and the concept of feeling "healthy" was linked to resisting ART commencement [132].

The HPTN 071 trial equally showed similar findings where despite observing a steep reduction in the time taken to start ART after community HIV testing, approximately 30% of patients had not begun ART by 12 months after testing [125]. The reasons included were similar to finding from other studies described above. One of the facilitators to ART initiation mentioned include new models of ART services that can enable adaptation of counselling to client's individual needs, efficient patient flow and integrated HIV/ primary care services [132].

2.5.3 Barriers to retention in care

According to the WHO, retention in care is defined " from the moment of initial engagement in care, when a person with HIV is linked successfully to services, to assessment for eligibility, initiation on ART and retention in lifelong ART care"[136, 137]. This definition varies and there is no gold standard in measuring retention in care [138, 139]. Retention in HIV care is also defined as the ability to adhere to the HIV care package that includes regular clinical follow-up and pharmacy appointments, scheduled laboratory tests and other monitoring activities according to the standard of care guidelines [140, 141]. Others have defined it as "being alive and on ART or being transferred out to other health care facilities to continue treatment"[139] or "patients known to be alive and receiving ART at the end of the follow-up period"[139].

The ability of PLHIV to remain in care and on treatment is crucial to attaining good health outcomes and limiting HIV transmission[142, 143]. For PLHIV, the ability to remain in care and on treatment is crucial to attaining good health outcomes and limiting HIV transmission[142]. Although treatment efforts in Sub-Saharan Africa have resulted in more than 21 million PLHIV obtaining ART over the last decade, high levels of attrition have greatly hampered the effectiveness of these programs[143]. The high attrition rates are a serious concern since treatment interruptions result in increased viral loads, which increases the risk of morbidity, mortality, drug resistance and ongoing transmission [144]. Retaining PLHIV on lifelong ART especially in resource limited settings such as East and Southern Africa is challenging. Since 2008, there has been a growing number of published literature that has identified poor retention in HIV care prior and after ART initiation[145]. Systematic reviews of studies conducted between 2007 and 2010 in sub-Saharan African HIV treatment cohorts estimated overall retention at 24 months averaging 70-77% and 65-72% at 36 months[146]. A recent systematic review that further updated and expanded previous reviews to estimate retention rates amongst those on ART from low and middle income countries between 2008 and 2013 showed that overall retention at 12, 24 and 36 months was estimated to be 83%, 74% and 68% respectively[145]. These findings show that one in every three patients was LTFU within 3 years of starting ART [145, 147] and determining the proportions of patients who stop taking ART is challenging as that cannot be easily determined from routine clinical data as LTFU may include patients who have died or self-transferred to another HIV

treatment centre [147-149]. Whilst there have been some variations in the estimating program retention in sub-Saharan Africa, it is obvious that retention in care is a significant challenge to the effectiveness of ART programs.

Despite the availability of free ART services in resource limited settings, several barriers have been identified as to why patients disengage from HIV care, and these tend to vary by settings. Social barriers such as stigma and discrimination, lack of social support or personal support were barriers to remain in care and adhere to treatment[150]. PLHIV feared being seen at the clinic by people they know when accessing HIV services, including collecting drugs, involuntary disclosure when accessing these services and lack of privacy forced patients to travel further to another health care facility outside their community to seek care [125]. Structural barriers include poverty, long distance to clinics, transportation costs and constraints. Poverty is likely to affect adherence to care as funds are needed to travel to the clinics for appointments and patients may feel the need to direct their resources elsewhere. Associated with poverty such as inadequate housing, unemployment and forced migration may result in patients missing their clinic visits and treatment interruptions[151]. Transportation costs and geographical distance to the clinics are also barriers to ART care although this is more prevalent in rural areas compared to urban areas [152, 153]. Clinic- related barriers include long waiting times for clinical reviews and drug collection, overcrowding, negative attitudes of health care providers and lack of human resources[151].

The current situation, in which an increasing number of PLHIV must be initiated on treatment and maintained on treatment for life, cannot be sustained unless innovative strategies to facilitate ART expansion and minimize barriers to the HIV care cascade are developed. Over the last couple of years, the scale up of ART has led to innovative HIV-care models that complement the current conventional facility-based care by adapting to the needs of the communities, patients, and health care systems. These include differentiated service delivery (DSD) models.

2.6 Differentiated Service Delivery

Decentralizing ART services outside of healthcare facilities and into the community has the potential to improve the HIV continuum of care by overcoming the aforementioned constraints. Models for decentralizing ART services through community ART delivery may be important to encourage maintenance on ART, and innovative strategies for maintaining the continuum of care in the context of universal treatment to meet the ambitious joint United Nations Program on HIV/AIDS (UNAIDS) 90-90-90 targets to end the epidemic by 2030. The WHO 2015 guidelines recommended that provision of ART services can be maintained in the community but operational guidance and further evidence is

needed for this to happen in practice[154]. A framework for "Differentiated Care" was developed and describes it as follows:

"***Differentiated care is a client-centred approach that simplifies and adapts HIV services across the cascade to reflect the preferences and expectations of various groups of PLHIV while reducing unnecessary burdens on the health system. By providing differentiated care, the health system can refocus resources to those most in need….."[22].***

The principle of this framework was to provide guidance on how to address some of the barriers to treatment access and retention in HIV care by optimizing models of ART drug and care delivery [22, 24, 52]. This is an approach designed to streamline care along the HIV cascade in ways that are intended to better serve the needs of PLHIV, reduce unnecessary burdens/costs on the health care system, and improve client outcomes [155, 156]. With this approach, patients with complex needs ds receive increased care, while those who are stable or have a less advanced disease receive adequate treatment in the environment that is most appropriate for them[122]. These DSD models of care are divided into 4 categories: "health care worker-managed group models; client-managed group models; facility-based individual models; and out-of-facility individual models"[22]. All these models focus on stable patients and the definition of stable patients varies across different models dependent on resources available. The definition of "stable patient" includes PLHIV who are on treatment for more than 6 months, adherent to treatment, have no opportunistic infections and do not require frequent clinical consultations[24]. However, this definition varies amongst ART delivery models and is dependent on resources such as viral load monitoring[22].

At the time DSD guidelines were published by WHO, there was little evidence around how differentiated models of ART delivery should be applied to non-stable patients or members of the key populations, pregnant women, and adolescents. Currently there is growing appreciation that non-stable patients and key populations (e.g., men who have sex with men, young men) may also benefit from these models of care as they are more likely not to go to health care facilities to pick up their medications and would access their care better if were brought closer to their homes.

Community models of ART delivery methods are one example of decentralizing HIV services from health care facilities to the community in order to meet the growing number of stable PLHIV on ART. These models have been developed in various settings and have the potential to improve the HIV care continuum by decongesting clinics and strengthening community participation through the integration of community-based activities and health care institutions [24, 154, 157, 158].

2.6.1 Types of community models of ART delivery

The last few years has seen several models of differentiated care being implemented in high-prevalence resource limited settings in East and South African regions. These models are aimed at improving retention and LTFU through task shifting and decentralization from primary health care facilities into the communities [159]. These models of ART delivery focus on PLHIV who are clinically stable allowing them to receive care within the communities through on-going adherence support and delivery of pre-packed drugs by community health workers (CHWs), thus reducing the frequency of clinical visits. Examples include:

A. Client-Managed Group Models

An example of this model is the Community Adherence Group (CAG) model which was originally developed by Médecins Sans Frontiéres (MSF) in Tete, Mozambique [159-161]. This model is targeted towards stable patients who receive their ART refills in a group and managed by the group themselves where each member in the group takes turn collecting ARVs for all members [Table 1]. Each group is composed of approximately 6 PLWH and meet up either monthly or three monthly depending on the settings and resources available. Each member has a clinical review either 6 monthly or yearly with routine laboratory testing [22, 160]. Results from this pilot study in Mozambique found high rates of retention among CAG members at 97.7%, 96.0%, 93.4% and 91.8% at 12, 24, 36 and 48 months respectively[161, 162], with a mortality rate of 2.1/100 per client and LTFU rate of 0.1/100 per client year[22, 161] as well as high levels of acceptance by patients and HCWs as CAGs reduced the cost and time burden on patients and strengthened adherence support[100, 160, 161, 163-165]. Data from this pilot enabled the CAG model to be incorporated into Mozambique's National HIV care Strategy and by the end of 2013, more than 17, 000 patients were receiving ART in CAG models[25, 163]. Similarly, several resource-limited high HIV burden countries incorporated CAG models into their national guidelines[166, 167]. Based on this CAG model, Zimbabwe began a national roll-out of Community ART Refill Groups (CARGs) and found that this model was overwhelmingly perceived as beneficial both by patients and HCWs and was successfully implemented on a national scale reducing the workload of HCW distributing ART[160]. Additional data from three smaller cohorts in Lesotho, Eswatini and Haiti also showed encouraging results. In Lesotho, stable patients who joined a CAG had a 12 month retention rate of 98.7 percent, compared to 90.2 percent for those who did not join a CAG[167, 168].

In Eswatini, 12 months retention was 81% in CAGs [169] and in Haiti, retention for a cohort of CAG patients was 88.4% [170]. In Zambia, CAGs were favoured by both patients and HCWs since they were able to decongest clinics and minimize the workload despite various problems with health care systems, such as drug stockouts and failure to conduct laboratory testing as planned[168, 171].

B. Health Care Worker-Managed Groups

An example of this model includes Adherence Clubs (AC) which could be either facility-based or community based. This model of care was designed to provide peer support and facilitate patient self-management to groups of stable patients on ART [163, 172]. The purpose of this club was to decongest health care facilities by decentralizing ART medication pick-ups and adherence in the facility health care or in the community. During the club sessions, essential tasks such as symptom screening, adherence counselling and dispensation of pre-packed medications, are provided by a trained peer educator or community health worker who serves as the club facilitator[122] [Table 2.1]. Club members are seen once or twice yearly for their clinical review and laboratory tests[122]. Patients are referred back to the clinic for assessment if they report symptoms suggestive of illness, drug adverse effects or have weight loss [173]. The club facilitator leads short group discussion on range of health topics. In addition to these clubs being held within the premises of the health care facilities, they have also been implemented within the community settings and held at venues such as schools, churches, and community centres.

Since 2012, Médecins Sans Frontiéres (MSF) piloted an extension of adherence clubs into the community and by 2013, collaborated with the Provincial government of Western Cape in implementing 776 clubs representing 19% of all ART patients in care in the Cape metropolitan area. The implementation of these community-based adherence clubs (CACs) at a large, public sector facility in peri-urban Cape Town had more than 2000 stable patients down referred from primary health care facilities to CACs[25] and overall retention was 97% and 94% at 6 and 12 months respectively. These findings bolstered the case for continuing to expand community-based ART delivery approaches in high-prevalence resource settings [163, 164]. These models have shown potential benefits associated with retention in care, reduced LTFU and mortality and improved viral suppression. Three large observational cohort studies have also demonstrated that, as compared to health care facilities, adherence clubs promote retention in care and virus suppression [161, 173-175]. In addition to decongesting the clinics, adherence clubs have shown reduction in time spent accessing care at the clinic and transportation costs associated with frequent clinical visits [29, 163, 175-177]. In addition to studies that have focused on patient outcomes and benefits in adherence clubs, a recent qualitative study assessing the acceptability and barriers of rolling out adherence clubs in the community has the potential to benefit both patients and the health care systems such as decongestion and alleviating staff shortages and workload. In addition to the above benefits mentioned, clubs also reduced defaulter rates, improved treatment adherence and reduced stigma levels[176]. These models of care have now been recommended by the WHO[52] as they have as they have been shown to provide at

least comparable outcomes to health care facility based care for stable PLHIV in resource limited settings[27, 174].

C. Out-of-facility individual models

Out-of-facility models vary according to the services delivered and by whom and where in the community these services are provided. These are divided into home delivery, mobile outreach and community drug distribution points (CDDP)[22]. In these models' stable patients are given the option to pick up their drug refills at a designated place in the community or have their drugs delivered to them in their homes by a trained community lay worker[122]. During these visits, patients receive their adherence support, and a symptom screen is conducted prior to dispensation of pre-packed drugs. Patients are seen at the clinic once or twice a year for their clinical review and routine laboratory monitoring [Table 2.1].

Three cluster randomized trials from Kenya, Uganda and Tanzania have reported outcomes from home-ART delivery models. In Uganda, CHW delivered pre-packed medications at home, provided adherence support, and referred sick patients to the clinic. There was no difference in virological failure rates between home delivery and facility care[31], and mortality rates were comparable in both groups. Similarly, in Kenya, CHWs were recruited among PLHIV and trained to deliver ART and provide adherence support to patients in their homes. There were no significant differences between the intervention and standard of care with respect to virological failure, mean CD4 count and development of opportunistic infections. Patients in the home delivery models made half as many clinic visits as those in the clinics [22, 178, 179]. A randomized pragmatic trial in Tanzania recently found that a home delivery model performed at least as well as the standard of care in terms of the critical health indicator of virological failure[32], and that this type of model was popular with patients because it made ART care more convenient and saved them time.

Community drug distribution points (CDDP) have also been found to reduce the frequency of clinical visits by stable PLHIV on treatment resulting in a decrease in HCW workload [163, 180]. This allows the health care facility to focus management of complex clinical cases. Distribution of ART in the community at fixed points also reduced patients transportation costs, time and absence from work due to frequent clinical visits[180]. Evidence from Uganda, Democratic Republic of Congo and South Africa have shown promising outcomes with this model. Results of a pilot model in Kinshasa, DRC showed retention rates at 89% at 12 months and was recognized as good practice in the country's national strategic plan[181]. In Uganda, stable clients initiating ART from 2004 to 2009 in the CDDP model had 69% retention in care and 17% mortality [182]. In South Africa, CDDP included fixed community points and private pharmacies and patients using this model had a lower retention at 12

months as compared to the facility (81.5% vs 87.2%) and comparable sustained viral suppression [183]. Mobile outreach ART delivery has also shown to have promising outcomes although there is limited published evidence regarding this method of distributing ART refills outside the health care facility. In Swaziland, 12 months retention was 77% for this model of care [26, 183].

Table 2.1. Summary of Community Models of ART delivery for Stable Patients [ŧ]

Where	**Client-Managed Groups**	**Health Care Worker-Managed Groups**	**Out-of-facility individual models**	
Type	Community Adherence Groups (CAGs)	Adherence Clubs	Home -Delivery	Community ART distribution points
Setting	Rural/ urban	Urban	Rural /urban	Urban/rural
Who	***Provider*** – PLHIV ***Clients*** – group of 5-8 stable PLHIV	***Provider*** – HCW or lay worker ***Clients –*** group of 15-30 stable PLHIV	***Provide***r – trained lay worker ***Clients*** – stable PLHIV	***Provider*** – community nurse/ pharmacist/ lay worker ***Clients*** – stable patients
Where	Patient's home or community venue	Facility premises Community venues	Patient's home	Community venue closer to patients' home
What	Dispensation of pre-packed medications, Adherence support Symptom screen	Dispensation of pre-packed medications, Adherence support Symptom screen Group education and Health promotion	Dispensation of pre-packed medications Adherence support Symptom screening	Dispensation of pre-packed medications Adherence support Symptom screening
When	Monthly 2-3 monthly	Every 2-3 months	Every 3 months	Every 2-3 months
How	Pre-packed medication at HCF One member picks up medications for group members during the day of clinical visit	Pre-packed medications at HCF and picked up by club facilitator who dispenses during club meetings	Pre-packed medications at HCF Lay worker dispenses during home visits	Pre-packed medications at HCF Space for drug storage Medications at community level
M&E	CAG register Attendance monitoring form Symptom checklist	Club registers Attendance monitoring form Symptom checklist	Home attendance registers Symptom checklist	CDDP registers Attendance monitoring form Symptom checklist

[ŧ] modified from ICAP Approach to Differentiated Service Delivery. Cquin.icap.columbia.edu. 2019. Available from: https://cquin.icap.columbia.edu/resources/icap-approach-to-differentiated-service-delivery/

Over the last few years, the large-scale rollout of universal ART has resulted in dramatic reforms in health care delivery in order to address shortages in capacity and quality of care through the large-scale adoption of various DSD models throughout SSA countries. Although some ART delivery approaches have showed encouraging results, there is currently a dearth of data to support their claimed benefits in routine deployment. Despite several systematic reviews reporting no significant differences in optimal ART adherence, viral suppression, LTFU and all-cause mortality, very few studies or evaluations have compared these alternative models of care to conventional facility-based care, making it difficult to draw firm conclusions about the effects of community models versus health care

facility-based care with regards outcomes[16]. Little is known whether these models of ART delivery will be feasible in urban low-resource high HIV burden settings and whether care will be as good as the standard quality of care provided by health systems, therefore a timely and innovative study is required to rigorously evaluate different models of community ART delivery as the information obtained will be critical for the continued scale up of universal treatment and provide policy makers with evidence on operational feasibility and acceptability and guide policy on the best models to roll out in the context of universal treatment[24].

2.7 HIV in Zambia

Zambia, a landlocked country in southern Africa has a total population of approximately 18 million[184] with 45.3% of the population in urban areas. The country has a young population with 36.7% of the people between 15-35 years[185] and characterized by continuing urban drift. High levels of poverty and unemployment rates, high burden of diseases, infrastructural challenges, geographical and social barriers are some of the major constraints facing the country and have significant impact on the health service delivery[186]. Zambia is one of the countries hardest hit by the HIV/AIDS epidemic, with an estimated HIV prevalence of 11.3 percent among adults and 1.2 million PLHIV[186], most in urban areas. Despite the decreasing rates of new infections over the last decade, the prevalence of HIV amongst adults has not much changed much since 2010 when the prevalence was 13%[38]. The majority of HIV transmission is driven by heterosexual sex and women; particularly adolescent girls and young women are disproportionally affected by the epidemic. By 2018, women made up 58.3% of PLHIV, and new HIV infections among young women (15-24 years) were more than twice as common as new HIV infections among young males (13000 new infections among young women, compared to 5600 among young men[39]. The incidence of HIV in the country is mainly driven by structural and biomedical factors, such as multiple and simultaneous sexual partners, low and inconsistent condom use; low male medical circumcision; migration and mobility; mother-to-child transmission and marginalization groups (prisoners, sex workers, etc.). These key drivers are further compounded by social factors that continue to increase the risk and drive new infections through high-risk sexual behaviour such as stigma and discrimination, transactional sex and denial and marginalization of key populations and vulnerable groups, polygamy, gender-based violence, poverty, religious and cultural beliefs against condom use and alcohol abuse[187].

HIV is a national health priority and as a result there has been substantial progress over the last decade in the fight against the epidemic through scaling-up of intervention aimed at prevention, treatment, and care. This includes scaling up of PMTCT, HIV testing services (HTC), free antiretroviral therapy and

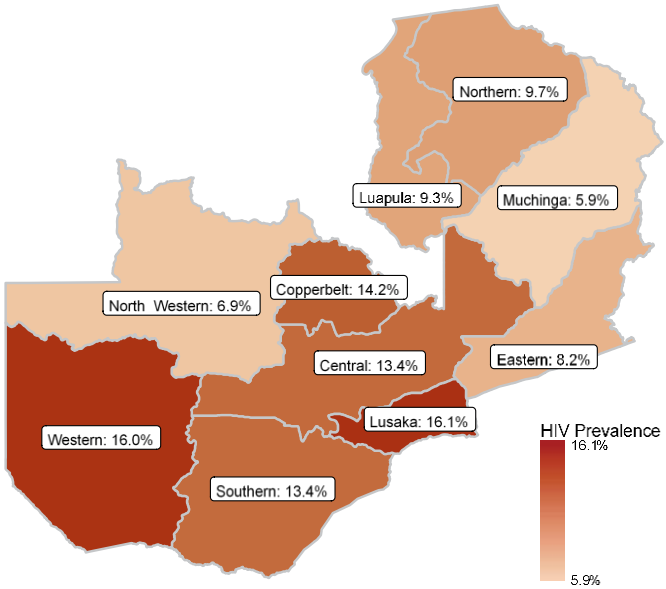
care and public awareness. These interventions resulted in the country's progress towards the UNAIDS targets of 90-90-90. In 2019, 87% of people living with HIV knew their status and 89% on treatment and 75% were virally suppressed[39].

In 2018, the HIV incidence was 2.97% and estimated 1.2 million people were living with HIV[188]. By 2017, the country adopted the WHO guidelines on universal treatment resulting in an increase coverage of ART, a progress towards achieving the UNAIDS 90-90-90 targets. In 2018, 87% of PLHIV knew their HIV status and 78% of PLHIV on treatment[39]. Despite the progress, the HIV burden is still high and affects women, particularly adolescent girls, and young women, disproportionately. Of the 1.2 million adults living with HIV in Zambia, 58.3% [700,000] were women. In 2017, it was estimated that 23,000 new HIV infections occurred among women (>15years), compared to 17,000 among men. According to the Zambia Population-based HIV Impact Assessment (ZAMPHIA), the HIV prevalence among women aged 15-59 years was 14.6% in 2017, compared to 9.3% for males of the same age, with 83% of adult women living with HIV on treatment, compared to 69% of adult men[39].

The HIV epidemic in Zambia is geographically heterogeneous, with prevalence rates higher in urban areas (15.6%) than in rural areas (7.4%). There are also variations among provinces with HIV prevalence highest in Lusaka (16.1%) and western provinces (16%) with Muchinga province having the lowest prevalence rate of 5.9% [Fig.2.5][187].

Fig 2.5. HIV Prevalence among adults, by province in Zambia

Province	HIV Prevalence	95% CI
Central	13.4	11.1-15.8
Copperbelt	14.2	12.7-15.8
Eastern	8.2	6.1-10.4
Luapula	9.3	6.8-11.8
Lusaka	16.1	14.5-17.8
Muchinga	5.9	4.2-7.7
Northern	9.7	7.5-11.9
North Western	6.9	5.6-8.2
Southern	13.4	11.7-15.1
Western	16.0	11.7-20.4



Source: ZAMPHIA, 2016

The Zambian Government through the Ministry of Health has been providing ART in public health care facilities since 2003 and over the years has continued to develop strategies with the President Emergency Plan for AIDS Relief (PEPFAR) partners to ensure wider access and quality of care for PLHIV. Following the adoption of the WHO 2015 guidelines for universal ART, there has been an increased demand for ART coverage and scale-up of ART services in-country has placed a huge strain on the health system in trying to cope with the demand[189]. DSD models have been identified by the Zambian Ministry of Health as a means of widening access to treatment in the context of universal ART and, by way of the National AIDS Council, a number of local implementing partners and researchers have all been engaged to trial different DSD models in order to collect information that will be needed to standardize DSD models across Zambia.

Based on the above DSD models that showed promising outcomes, I further conducted a thorough systematic review in the next chapter (Chapter 3) of the evidence on DSD models before carrying out a trial in our specific urban setting in Zambia.

Chapter 3: A systematic review of the effectiveness of non-health facility-based care delivery of antiretroviral therapy for people living with HIV in sub-Saharan Africa measured by viral suppression, mortality and retention on ART.

3.1 Outline of chapter

When the PhD was started in 2016, non-health facility-based care (nHFBC) was being increasingly recognized as a safe and effective alternative to the current standard model of health facility-based care (HFBC) in sub-Saharan Africa. Decentralizing ART services outside of the health care facilities into the community held the promise of improving the continuum of care by overcoming barriers in providing facility-based care including distance between rural health clinics and communities, overburdened clinics resulting in long waiting times and lack of human resources. Various models of non-health facility-based care (nHFBC) have been piloted and implemented in high burden low resource settings and are now being increasingly recognised as safe and effective alternatives to the current standard model of health facility-based care in East and Southern Africa. These include healthcare worker-managed groups (adherence clubs); client managed group models (community adherence groups (CAGs)); and out-of-facility individual models (community-based distribution points (CBDPs) and home-based delivery). Models of ART delivery outside the health care facility needs to be safe and sustainable and they must achieve non-inferior clinical outcomes as a condition for scaling up nHFBC in resource-limited settings. Several systematic reviews published recently have shown that community programs increase both affordability and accessibility to ART and have shown that there are no significant differences in optimal ART adherence, virological suppression (VS), all-cause mortality and loss-to follow-up (LTFU) between patients assigned to nHFBC and HFBC. To help fill this gap, we undertook a systematic of current literature exploring the effectiveness of nHFBC interventions versus HFBC and we report here the results of our search for viral suppression, mortality, retention and Lost-to-follow up (LTFU). As several models have been rolled out in recent years providing more data on clinical outcomes, we therefore chose to only focus on programmatic data and trials from 2010 onwards. This systematic review was published in BMC Public Health on 10th June 2021 and the manuscript is presented below.

3.2 Research Paper 1

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

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SECTION A – Student Details

Student ID Number	lsh 1602448	**Title**	Dr
First Name(s)	Mohammed		
Surname/Family Name	Limbada		
Thesis Title	A comparison of different community models of Antiretroviral Therapy delivery among stable HIV+ patients in an urban setting, Zambia		
Primary Supervisor	Prof Helen Ayles		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	BMC - Public Health		
When was the work published?	10th June 2021		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	ML and GZ concieved the manuscript idea and undertook literature search. ML and GZ reveiwed the full text journals and agreed the final inclusion of the papers with SF. ML and GZ did the data extraction and wrote the first draft of the manuscript. DM assisted ML and GZ with the statistical analysis. The final draft of the mansucript was reviewed by all authors.

SECTION E

Student Signature	[redacted]
Date	

Supervisor Signature	[redacted]
Date	21

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BMC Public Health

RESEARCH ARTICLE Open Access

A systematic review of the effectiveness of non- health facility based care delivery of antiretroviral therapy for people living with HIV in sub-Saharan Africa measured by viral suppression, mortality and retention on ART

Mohammed Limbada[1*†], Geiske Zijlstra[2†], David Macleod[3], Helen Ayles[1,3] and Sarah Fidler[4]

Abstract

Background: Alternative models for sustainable antiretroviral treatment (ART) delivery are necessary to meet the increasing demand to maintain population-wide ART for all people living with HIV (PLHIV) in sub-Saharan Africa. We undertook a review of published literature comparing health facility-based care (HFBC) with non-health facility based care (nHFBC) models of ART delivery in terms of health outcomes; viral suppression, loss to follow-up, retention and mortality.

Methods: We conducted a systematic search of Medline, Embase and Global Health databases from 2010 onwards. UNAIDS reports, WHO guidelines and abstracts from conferences were reviewed. All studies measuring at least one of the following outcomes, viral load suppression, loss-to-follow-up (LTFU) and mortality were included. Data were extracted, and a descriptive analysis was performed. Risk of bias assessment was done for all studies. Pooled estimates of the risk difference (for viral suppression) and hazard ratio (for mortality) were made using random-effects meta-analysis.

Results: Of 3082 non-duplicate records, 193 were eligible for full text screening of which 21 published papers met the criteria for inclusion. The pooled risk difference of viral load suppression amongst 4 RCTs showed no evidence of a difference in viral suppression (VS) between nHFBC and HFBC with an overall estimated risk difference of 1% [95% CI -1, 4%]. The pooled hazard ratio of mortality amongst 2 RCTs and 4 observational cohort studies showed no evidence of a difference in mortality between nHFBC and HFBC with an overall estimated hazard ratio of 1.01 [95% CI 0.88, 1.16]. Fifteen studies contained data on LTFU and 13 studies on retention. Although no formal quantitative analysis was performed on these outcomes due to the very different definitions between papers, it was observed that the outcomes appeared similar between HFBC and nHFBC.

* Correspondence: mohammed@zambart.org.zm
†Mohammed Limbada and Geiske Zijlstra contributed equally to this work.
[1]Zambart House, PO Box 50697, UNZA-Ridgeway Campus, Lusaka, Zambia
Full list of author information is available at the end of the article

Conclusions: Review of current literature demonstrates comparable outcomes for nHFBC compared to HFBC ART delivery programmes in terms of viral suppression, retention and mortality.

PROSPERO number: CRD42018088194.

Keywords: Human immunodeficiency virus, Antiretroviral therapy, Sub-Saharan Africa, Community-based delivery

Background

There are an estimated 37.9 million people living with human immunodeficiency virus (HIV) globally and 32 million people have died from AIDS-related illnesses since the start of the epidemic [1]. The HIV epidemic has disproportionately affected Africa, particularly sub-Saharan Africa (SSA) which has the largest burden of the disease. Although the region accounts for approximately 6.2% of the world's total population, it is home to over 50% (20.6 million) of the total number of PLHIV globally, with over 800,000 new infections recorded in 2018 [2].

Antiretroviral therapy (ART) controls viral replication to below the limit of detection and in doing so, improves survival [3, 4] and limits the risk of onward viral transmission [5, 6], but requires daily lifelong adherence to oral medication. Stopping ART invariably leads to rapid viral recrudescence and reversal of its beneficial effects [7]. In order to significantly reduce the number of new HIV infections globally, UNAIDS in 2014 set coverage targets by 2020 for the three key indicators; knowledge of HIV status for 90% of people living with HIV (PLHIV), ART access for at least 90% of all PLHIV and viral suppression for at least 90% of all of those living with HIV on ART; the "90–90-90 targets" with the aspiration to end the HIV epidemic by 2030 [8]. Following the World Health Organization (WHO) 2015 recommendation of lifelong ART for all PLHIV regardless of CD4 count and clinical staging [9], there has been substantial progress in scaling up ART programs; and by mid-2018, 84% of low- and middle-income countries had adopted these guidelines [10, 11] to provide universal treatment to all PLHIV. Despite the high HIV burden, SSA has made tremendous progress in treatment coverage and by 2018, 85% of PLHIV were aware of their status and 67% (13.8 million) were on treatment [12, 13].

Maintaining this unprecedented scale-up of ART services poses a challenge in high HIV burden resource limited settings, especially in SSA where healthcare facilities are overburdened with long waiting times, inadequate and overburdened human resources, transportation costs, congestion and long waiting times at the health facility-based care (HFBC) [14, 15], leading to poor retention in care and adherence. Recent data from sub-Saharan Africa (SSA) shows 5- year retention on ART is close to 60% [16–21].

Decentralizing ART provision services outside of the HFBC into the communities holds the promise of improving the continuum of care and facilitating access to treatment. Various models of non-health facility-based care (nHFBC) [22] have been piloted and implemented in high burden low resource settings and are now being increasingly recognised as safe and effective alternatives to the current standard model of health facility-based care in SSA [23, 24]. These include; healthcare worker-managed groups (adherence clubs); client managed group models (community adherence groups (CAGs)); and out-of-facility individual models (community-based distribution points (CBDPs) and home-based delivery). Adherence clubs consists of a group of 15–30 stable PLHIV who meet up at a venue within or outside the HFBC space, once every 2–3 months where they receive their adherence support and pre-packed medications by a trained lay worker or healthcare worker. Club members are seen once or twice-yearly at the clinic for routine clinical review and laboratory tests [25–29]. CAGs, originally developed by Médecins Sans Frontiéres (MSF) in Tete, Mozambique, also target stable patients who receive ART refills and adherence support in a group, where each member of the group takes turns collecting ART for all group members. Each group is composed of approximately six patients who meet up every 2–3 months, and each member has their routine clinical visit once or twice-yearly [26, 30–32]. Out-of-facility models vary according to the services delivered, by whom and where in the community these services are provided. In home-based delivery, clients receive their adherence support and pre-packed medications once every 3 m in their homes by a trained lay worker [33, 34]. CBDPs allow patients to pick up their drug refills at a designated place in the community [26, 27, 35, 36].

These models of care are best directed towards stable adult patients, defined as those with suppressed HIV viral loads on ART for more than 6 m. It allows them to receive treatment and sometimes medical care within their communities with ongoing adherence support where needed, and may sometimes involve community health workers (CHWs) dispensing pre-packedART, thus reducing the frequency of clinic visits.

Ideal nHFBC models of ART delivery must be sustainable and safe. They must confer similar successful clinical outcomes in order to effectively contribute to the decrease of HIV transmission and extension of life expectancy. Feasibility of these models need to be stringently evaluated and compared with concurrent HFBC in order to determine the safe sustainable delivery of ART to UNAIDS targets. Several systematic reviews published recently have shown that community programs increase both affordability and accessibility to ART [24] and have shown that there are no significant differences in optimal ART adherence, virological suppression (VS), all-cause mortality and loss-to follow-up (LTFU) between patients assigned to nHFBC and HFBC [23, 37]. This review looks at programmatic data and trials from 2010 onwards in order to provide an update on large amounts of recently published data, as several models have been rolled out providing more data on clinical outcomes.

We undertook a review of published literature comparing HFBC with nHFBC models of ART delivery in terms of health outcomes; viral suppression, loss to follow-up, retention and mortality among PLHIV. We included all descriptions of novel programmatic delivery of ART in nHFBC settings, and compared where available specific outcomes between HFBC and nHFBC, including VS, mortality, retention and LTFU.

Methods

Search strategy

A systematic electronic search of peer-reviewed literature was conducted most recently on the 21 August 2019 in the following databases: Medline, Embase and Global Health. The search strategy was created with the support of a medical librarian; key terms were identified to combine ART AND nHFBC AND SSA. The search strategy is outlined in full in Additional file 1: Appendix 1. The review was prospectively registered with online database PROSPERO (ID=CRD42018088194). In addition to the databases, two key UNAIDS reports and all WHO guidelines, and their references, from 2010 onwards were reviewed.

Eligibility criteria

Articles were considered for inclusion if they described the effectiveness of one of four nHFBC methods of delivery of ART in sub-Saharan African settings: adherence clubs, CAGs, CBDPs and home-based delivery. Adherence clubs were included irrespective of whether they were physically located within the healthcare facility or in the community as they are run independently and are considered novel care pathways outside the routine HFBC pathway. Appointment spacing, and fast track refills that take place within the facility were excluded as this was considered to be part of standard HFBC pathway. Studies had to measure a clinical outcome, either; retention in care, LTFU in accordance with WHO and national guidelines definitions, transfer to alternative care, viral load (VL), viral suppression (VS), CD4 count or mortality. The definition of LTFU varied by study and year, but papers were considered eligible if they defined LTFU in accordance with standard WHO and guideline practices [38]. While some studies reported patient outcomes within the LTFU cohort, such as death or transfer to other services, this was not essential for inclusion. The definitions of viral suppression were varied between studies as laboratory assays changed, but for this analysis we included all papers that reported to < 1000 copies HIV RNA/mL.

For inclusion, studies were not required to have a comparator current standard of care control group. It was not necessary for studies to be delivering ART in isolation of other interventions, such as counselling. There was no restriction on study population age, history of infection or line of ART.

Original research articles were included, and systematic reviews were excluded. Where data from the same cohort was published multiple times, the most recently available publication was included. The search was conducted in English only due to available expertise, time and budgetary restrictions. A publication date limit of 1st January 2010 until 31st August 2019 was applied to the searches in all databases as the aim was to review the current published literature and update previously published review articles [24].

Data extraction and quality appraisal

All database search results were imported into EndNote software (EndNote X8.2) for duplicate removal, and then into Covidence systematic review software, which was used for screening [39]. The screening of titles and abstracts and the full text reviews of eligible articles were done in duplicate by two independent reviewers (GZ, ML). All conflicts were resolved through discussion between both reviewers, and a third reviewer (SF). Where full texts of abstracts were not available, these were accessed via the British Library. Additional articles were identified by examining references of articles included for full text review (Fig. 1). Articles considered eligible for inclusion were read in full by GZ & ML, and approved by reviewer SF.

Data was extracted in duplicate by two reviewers (GZ, ML), including: first author, year of publication, country of origin, study design, sample size, the community model used to deliver ART, outcomes, length of follow up and who was responsible for ART provision. All discrepancies in data extracted were solved through discussion between both reviewers. Results of this data

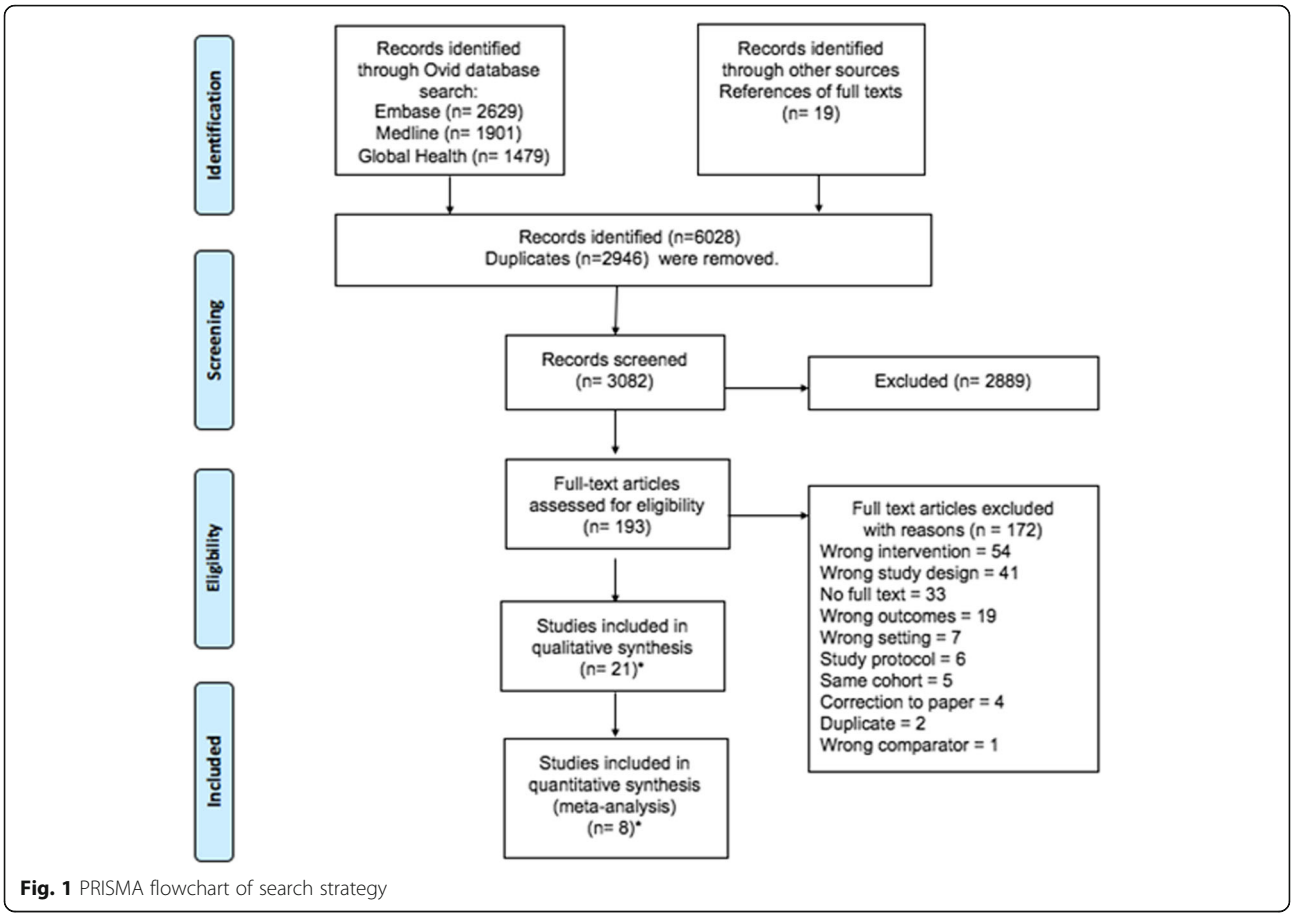

Fig. 1 PRISMA flowchart of search strategy

extraction were summarized in Table 1. Quality analysis was done by reviewers GZ and ML using the Cochrane tool for risk of bias for all randomised control trials (RCTs) and using the Newcastle-Ottawa scale [58, 59] for cohort studies, which can be found summarised in Appendices 2 and 3.

Quantitative and qualitative analysis

Results were extracted for VS (thresholds defined in the articles ranged from ≤1000–400 copies HIV RNA/mL), mortality and LTFU/retention in care. Studies with variable definitions of VS were still considered eligible for quantitative comparison. Pooled estimates of the comparison between nHFBC and HFBC were calculated for both VS and mortality using random-effects meta-analysis. When comparing VS, the pooled risk difference was the reported statistic, and for mortality the pooled hazard ratio was reported. Due to the large variations in the definitions of LTFU and retention in care between papers, only a descriptive analysis was carried out in accordance with the Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline [60]. For quality assessment, RCTs were risk assessed using the Cochrane Risk of Bias tool [59] which can be found in full in Additional file 2: Appendix 2. Quality assessment of cohort studies was done using the Newcastle-Ottawa Scale (Additional file 3: Appendix 3) [58].

Results

Our search identified 3082 non-duplicate records, of which 2889 were excluded after abstract and title screening against our search criteria. One hundred ninety-three records were eligible for full text screening, of which 21 published papers were eligible for inclusion in our analysis (Fig. 1).

Of the 21 articles included, results were presented from a total of six randomized control trials (RCTs) [37, 40–44], 15 observational cohort studies [32, 36, 37, 45–56] and one cross-sectional study [57] (one article presented the results from both an RCT and a cohort study). These studies were conducted in SSA, including: South Africa, Uganda, Tanzania, Mozambique, Kenya, Zimbabwe, Eswatini and Democratic republic of Congo. The number of participants included in the studies ranged from 129 to 129,936, and the design and methodology of the included studies are detailed in Table 1. Our included articles represented nHFBC models that provided service delivery either as individual or group

Table 1 Characteristics of the studies and their Design, nHFBC model and key findings

Study	Setting	Non-facility based model	Comparator	Sample Size	Length of follow-up	Outcomes and key findings
RANDOMIZED CONTROL TRIALS						
Fox 2019 [37]	South Africa	Adherence clubs	Health care facility	*N* = 596 AC *n* = 275 HCF *n* = 294	18 months	***Viral Suppression*** – comparable 12 months viral suppression between the intervention (80%) and control (79.6%) arms (aRD: 3.8%; 95% CI: −6.9 to14.4%). ***Retention*** – AC's had a higher 1-year retention (89.5% vs 81.6%, aRD:8.3%; 95% CI: 1.1 to 15.6%)
Hanrahan 2019 [40]	South Africa	Community Adherence clubs	Health care facility clubs (Standard of care)	*N* = 775	24 months	***Loss from the club*** – proportion of patients who dropped out of clubs in both community and facility clubs or were transitioned to standard of care. Overall, 47% [95%CI 44–51%] of patients were returned to health care facility. Among community-based club participants, the cumulative proportion lost from club-based care was 52% (95% CI: 47–57%), compared to 43% (95% CI: 38–48%, $p = 0.002$) among clinic-based club participants. ***Virological failure*** **-** Documented viral rebound was higher among participants assigned to facility-based clubs (21, 95% CI 13–27%) than those assigned to community-clubs (13, 95% CI 8–18%, $p = 0.051$). But this was not significant. ***All-cause mortality*** **–** no mortality observed in both arms **Loss from ART care** -during follow up, 77 (10%) overall. No significance between the two arms. Among community club participants, the proportion lost from any ART care was 12% (95% CI 9–16%), compared to 7% (95% CI 5–10%, $p = 0.024$) among facility- club participants, corresponding to a difference of 5% (95% CI 1–9%, $p = 0.018$). In a univariate Cox proportional hazards model, the risk of loss to any ART care was non-significantly increased among participants assigned to community clubs as compared with those assigned to facility clubs (HR 1.69, 95% CI 0.98–2.91, $p = 0.057$).
Geldsetzer 2018 [41]	Tanzania	Home ART delivery	Health care facility	*N* = 2172 HD *n* = 1163 HCF *n* = 1009	326 days	***Virological failure*** – 10.9% (95/872) in the control arm and 9.7% (91/943) in the intervention arm were failing at the end of the study period. Risk ratio demonstrated non-inferiority of the HBC to HCF (RR 0.89 [1-sided 95% CI 0.00–1.18]) ***Lost to follow-up*** – 18.9% in HBD versus 13.6% in HCF. No *P* value or CI reported. **Mortality** – 0.09% in HBD versus 0.2% in HCF. No P value or CI reported.
Woodd 2014 [42]	Uganda	Home ART delivery	Health care facility	*N* = 1453 HD n = 859 HCF *n* = 594	28 months	Home delivery of ART and support leads to similar survival rates as clinic-based care. ***Mortality*** **–** One hundred and ninety-seven participants died over a median follow-up time of 28 months (IQR 15–35) giving an overall mortality rate of 6.36 deaths per 100 person-years [95% confidence interval (CI) 5.53–7.32]. 110 (25%) deaths in participants with baseline CD4 < 50 cells and 87 (9%) in those with higher baseline CD4.Among participants with baseline $CD4^+$ count < 50 cells/μl, mortality rates were similar for the home and facility-based arms; adjusted mortality rate ratio 0.80 [95% confidence interval (CI) 0.53–1.18] compared with 1.22 (95% CI 0.78–1.89) for those who presented with higher $CD4^+$ cell count. In CD4 counts < 50 cells – crude mortality RR 0.81 and In CD4 counts higher - crude mortality RR 0.55 ***Lost to follow up*** – 1.8% among those with CD4 < 50 and 2.6% among those with CD4 at least 50.
Amuron 2011 [43]	Uganda	Home deliveries	Health care facility	HD n = 594 HCF *n* = 859	42 months	***Mortality*** – in the facility there were 117 deaths (mortality rate 6.3 per 100 persons per yrs.) whereas in HBD, 80 deaths (mortality rate 6.5 per 100 person yrs.). The one, two and three year survival probabilities (95% CI) were 0.89 (0.87–0.91), 0.86 (0.84–0.88) and 0.85 (0.83–0.87) respectively
Selke 2010 [44]	Kenya	Home ART delivery	Health care facility	HD *n* = 96 HCF *n* = 112	28 months	Home delivery of ART and support resulted in similar clinical outcomes as clinic care but with half the number of clinic visits. Task-shifting and mobile technologies can deliver safe and effective community-based care to PLHIV. ***LTFU*** – 4.5% in the HCF and 5.2% in Home delivery [95% CI: 0.24 to 3.03; $p = 1.0$] ***Mortality*** – 0 in both arms ***Viral rebound*** **–** no significant difference between the two groups (10.5% in HBD and 13.5% in HCF, 95%CI: 0.54 to 3.31, $p = 0.65$)

Table 1 Characteristics of the studies and their Design, nHFBC model and key findings *(Continued)*

Study	Setting	Non-facility based model	Comparator	Sample Size	Length of follow-up	Outcomes and key findings
OBSERVATIONAL COHORT STUDIES						
Fox 2019 [37]	South Africa	Decentralized medication delivery (DMD)	Health care facility	*N* = 578 DMD *n* = 232 HCF *n* = 346	18 months	
Tun 2019 [45]	Tanzania	Community Based ART distribution (CBPDs)	Health care facility	CBPD *n* = 309 HCF *n* = 308	6 months	**Retention** in the CBDP – 82.8% vs 82.1% in the HCF at 6 months **LTFU** – 53 in the intervention and 55 in the HCF arms
Pasipamire 2018 [46]	Swaziland	1. Community Adherence groups (CAGs) 2. Facility Based clubs 3. Treatment outreach	No comparator	***N* = 918** CAGs *n* = 531 FBC *n* = 289 Outreach *n* = 98	12 months	**Retention in the models** – The overall care model retention was 90.9 and 82.2% at 6 and 12 months. Retention in the care models differed significantly by model type, being lowest in CAGs at all time points ($p < 0.001$). Only 70.4% of patients were retained in CAGs at 12 months compared with 86.3% in comprehensive outreach and 90.4% in clubs. Retention in care model was significantly higher in eligible patients compared with non-eligible patients (85.0 and 76.4% at 12 months, $p = 0.017$. **Retention to ART –** over 90% from all three models and no difference noted ($p = 0.52$).Patients in CAGs had a higher risk of disengaging from the care model (aHR 3.15, 95%CI: 2.01–4.95, $P < 0.001$) compared with treatment clubs. Note: disengagement defined as LTFU, Death, return to clinical care)
Myer 2017 [47]	South Africa	Adherence clubs [post-partum women]	Health care facility	*N* = 110 AC n = 77 HCF *n* = 33	6 months post-partum follow-up	**Viral suppression -** overall no difference in viral suppression between the two groups. **86% of women remained in the evaluation through 6 months postpartum; in this group, there were no differences in VL < 1000 copies/mL at six months postpartum between women choosing HCFs (88%) vs. adherence clubs (92%; $p = 0.483$.**
Vogt 2017 [48]	Democratic Republic of Congo (DRC)	Community based refill centers	No comparator	*N* = 2259	24 months	Attrition increased steadily after decentralizing services such as drug pick up points. Low attrition throughout follow-up ***LTFU*** – 9.0% at 24 months ***Mortality –*** 0.3% at 24 months overall attrition was 5.66/100 person years (95% CI: 4.97 to 6.45)
Tsondai 2017 [49]	South Africa	Adherence clubs	No comparator	*N* = 3216	24 months	Stable patients on ART can safely be offered differentiated care as they overall had good outcomes. Adherence clubs scaled up at large scale had had high levels of retention and viral suppression. ***Retention*** – Retention was 95.2% (95% CI: 94.0–96.4) at 12 months and 89.3% (95% CI: 87.1–91.4) at 24 months after AC enrolment. ***Viral suppression -*** Of the 88.1% who had a viral load assessment, 97.2% (95%CI, 96.5–97.8) were virally suppressed < 400 copies/ml ***LTFU*** – 4.2% (135). Cumulative incidence of LTFU was 2.6% (95% CI, 2.1–3.2) at 12 months, rising to 6.9% (95%CI, 5.7 to 8.1) at 24 months after AC enrolment. ***Mortality*** – 0.1% (95% CI, – 0.01 to 0.2) at 12 months and 0.2% (95%CI, – 0.01 to 0.4)
Decroo 2017 [50]	Mozambique	Community ART groups (CAGs)	Health care facility	CAGs *n* = 901 HCF *n* = 1505	24 months	***LTFU*** – overall 12% [11.2% in HCF and 0.8% in CAGs]. CAG members had a greater than fivefold reduction in risk of dying or being LTFU (adjusted HR: 0.18, 95% CI 0.11 to 0.29). **Retention -** 12-month and 24-month retention in care from the time of eligibility were 89.5 and 82.3% respectively among patients in individual care and 99.1 and 97.5% among those in CAGs ($p < 0.0001$).
Auld 2016 [51]	Mozambique	Community support ART groups (CASG)	Health care facility	*N* = 306, 335 CASG *n* = 6766 HCF *n* = 299,569	4 years	***Mortality*** – similar rates in both groups [0.3% among CASG at 2 yrs. and 1.4% at 4 yrs.] CASG patients were associated with a 35% lower LTFU rates [AHR 0.65; 95% CI:0.46, 0.91] but similar mortality.
Grimsrud 2016 [52]	South Africa	Adherence clubs	Health care facility	*N* = 8150 AC *n* = 2113 HCF *n* =	12 months	**Viral suppression** – high rates of VLS among those who had a VL result, but no comparison made between the two cohorts. ***LTFU –*** clubs were associated with a decreases risk of LTFU compared to facility in all crude and adjusted models. Clubs

Table 1 Characteristics of the studies and their Design, nHFBC model and key findings *(Continued)*

Study	Setting	Non-facility based model	Comparator	Sample Size	Length of follow-up	Outcomes and key findings
				6037		were associated with a 67% reduction in LTFU compared with facility (aHR 0.33, [95% CI, 0.27–0.40]).
Okoboi 2016 [53]	Uganda	Community based distribution points (CBDP)	Health care facility	CDDP *n* = 476 HCF *n* = 752	5 years	Overall retention rates were above 80% in both HCF and CBDP ***Retention rates*** – 83.9% in the facility and 82.9% retained in the community distribution model of delivery ($p = 0.670$)
Jobarteh 2016 [54]	Mozambique	Community ART support groups (CASG)	Health care facility (non-CASG)	CAGs *n* = 6760 HCF *n* = 123,178	12 months	**LTFU** – LTFU among CASG and non-CASG members was 7.2 and 15.9%, respectively. Compared with CASG participants, non-CASG participants had significantly higher LTFU (hazard ratio [HR]: 2.36; 95% confidence interval [CI]: 1.54–3.17; $p = .04$] ***Mortality*** **-**no significant mortality differences between CASG and non-CASG members (1.4% vs 1.2%) (HR:0.98; 95%CI, 0.14 to 1.82; $p = 0.96$)
Okoboi 2015 [36]	Uganda	Community distribution points (CDDP)	No comparator	CDDP *n* = 3340	5 years	Community-based ART distribution systems are capable of overcoming barriers to ART retention and result in good rates of virologic suppression. ***Viral suppression-*** of the 870 patients who had a VL measured, 87% were suppressed **Mortality-** mortality rate was low (3.22 per 100 person-years) ***LTFU-*** 1.59 per 100 person-years ***Retention***- more than 69% of patients who initiated ART from 2004 to 2009 were retained in care after more than 5 years of treatment.
Decroo 2014 [32]	Mozambique	Community ART groups (CAGs)	No comparator	CAGs *n* = 6158	4 years	Long-term retention in CAG was exceptionally high [91.8% at 4 years of follow-up (95% CI, 90.1 to 93.2)]. ***LTFU*** – event rate was 0.1% per 100-person yrs. ***Mortality*** – event rate was 2.1 per 100-person yrs. ***Retention*** among CAG members at 1 year on ARTwas 97.7% (95% CI 97.4–98.2); at 2 years, 96.0% (95% CI 95.3–96.6); at 3 years, 93.4% (95% CI 92.3–94.3); and at 4 years, 91.8% (95% CI 90.1–93.2). Overall, the attrition rate was 2.2 per 100 person-years among the 5729 adult members.
Study	**Setting**	**Non-facility based model**	**Comparator**	**Sample size**	**Length of follow-up**	**Key outcomes**
Luque-Fernandez 2013 [55]	South Africa	Community Adherence clubs	Health care facility	ACs *n* = 502 HCF *n* = 2372	3 years	Outcomes less frequent in patients participating in the clubs. ***Viral rebound*** – 214 patients had viral failure at study end in the HCF (90.4 event rates per 1000 person yrs. [95%CI: 79.1–103.4). In the clubs 14 had viral rebound 31.8 event rates per 1000 person yrs. ***Retention*** - 97% of club patients remained in care compared with 85% of other patients. In adjusted analyses club participation reduced loss-to-care by 57% (hazard ratio [HR] 0.43, 95% CI = 0.21–0.91). ***Mortality + LTFU*** **-** 12.8% of patients were LTF or had died (323 LTF and 40 deaths). Both outcomes were less frequent for patients participating in the clubs (29.8 vs 116.8 per 1000 person-yrs. for LTFU/death, crude rate ratio [RR = 0.25, 95% CI 0.14–0.41]
Kipp 2012 [56]	Uganda	Home based ART delivery	Health care facility	HBD *n* = 185 HCF *n* = 200	24 months	ART outcomes such as viral suppression in community models were equivalent to those receiving care in the facility. ***Viral suppression –*** patients in the home delivery model were 2.47 times more likely to achieve viral suppression compared to those in the facility based [95% CI for OR 1.02–6.04 $p = 0.046$]. ***Mortality*** – 32(17%) in Home delivery vs 23 (12%) in HCF. This had limitations as the LTFU in both groups includes unknown number of deaths. Crude mortality was higher in the HBD cohort compared to the HCF cohort, though this difference was not statistically significant (17.3% vs. 11.5%, $p = 0.10$). ***Retention –*** 70% in home model vs 71% in facility
CROSS-SECTIONAL STUDY						
Chimukangarta 2017 [57]	Zimbabwe	Outreach ART delivery	No comparator	*N* = 143	18 months	***Viral suppression-*** over the course of the study period, 94% were virally suppressed

models outside the healthcare facility including facility or adherence clubs, home-based delivery, community adherence groups or distribution points and outreach ART delivery (Table 1). ART delivery was done by a range of community healthcare workers, volunteers and nurses.

The six randomised control trials were appraised using the Cochrane tool for risk of bias. Sequence generation

and allocation concealment were well conducted, and risk of bias was low amongst the studies. Blinding of participants and personnel was not possible in any of the studies due to the nature of the intervention, but there was variability amongst blinding of outcome assessors as in some cases the assessors were also involved in project management. The data collected however were generally objective measures obtained from medical records, which is at minimal risk of bias, even for assessors who were informed of patient allocation. Not all RCTs had published study protocols, which increases the risk of selective outcome reporting, but all did report numbers of attrition and mortality, minimising risk from incomplete outcome data.

Virological suppression (VS) and viral load (VL)

From our included studies, 10 out of 21 reported VS or HIV viral load rebound as an outcome measure. Of these, three articles [36, 49, 57] did not compare to a facility-based cohort and were therefore excluded from the pooled analysis. Three articles [37, 41, 44] were RCTs that compared outcomes to a facility-based cohort, one of which [37] included results from two separate RCTs published in the same article. The remaining four studies were all observational cohort studies [47, 52, 55, 56] comparing VS among participants receiving community-based care with those receiving facility-based care. The pooled risk difference of virological suppression amongst RCTs are shown in Fig. 2, and including the observational studies are shown in Additional file 4: Appendix 4. There was a remarkably consistent effect (I^2 = 0.04%) found across the four randomized trials, very marginally in favour of community care, with an overall estimated risk difference of 1% [95%CI -1, 4%). There was no statistically significant evidence (p = 0.24) of a difference in viral suppression between the two groups. The definition of viral suppression varied between studies, with Geldsetzer et al. using < 1000 copies/ml, Fox at al using < 400 copies/ml, and Selke not defining it. The viral load or suppression reported at baseline in these RCTs also varied. Geldsetzer reported the percentage of people with VL < 1000 copies/ml or CD4 < 350 cells/μl (which was 17.4% in control and 15.4% in intervention group),. Fox reported the median viral load (copies/ml) and interquartile range. For the adherence club (AC) control and intervention groups, these were 50 (20–124) for both and in the Decentralized Medication Delivery (DMD) control and intervention groups these were 42 (20–100) and 124 (35–124) respectively. Selke reported the proportion with detectable viral load at baseline, which was 8.5% in the intervention and 12.6 in the control group. These were all studies assessed as high quality, and apart from not being blinded, all had an overall low risk of bias. Three of the four observational studies showed results broadly consistent with the randomised trial results (although slightly more favourable towards nHFBC, with risk differences ranging from 4 to 6%). One study by Grimsrud et al. had results showing much greater viral suppression in nHFBC (estimated risk difference of 39%), although in that paper the patients receiving nHFBC were those who were classed as "stable on ART" and the comparison group were not (adjusted results for VS were not presented in the paper) [52].

Mortality

Nine papers were identified that reported mortality, four of which were RCTs. Only two RCTs [42, 43] did a formal comparison between trial arms on mortality. The two RCTs included in the pooled analysis were rated as fair quality, and reported the results stratified by whether baseline CD4 count was less than or greater than 50, increasing the accuracy of the intervention comparison. The other two RCTs reporting extremely low rates of mortality (Selke et al. reported no deaths in HFBC and one in nHFBC and Geldsetzer et al. reported two in HFBC and one in nHFBC). Of the five observational cohort studies, four reported a formal comparison of mortality. The hazard ratios across all studies ranged

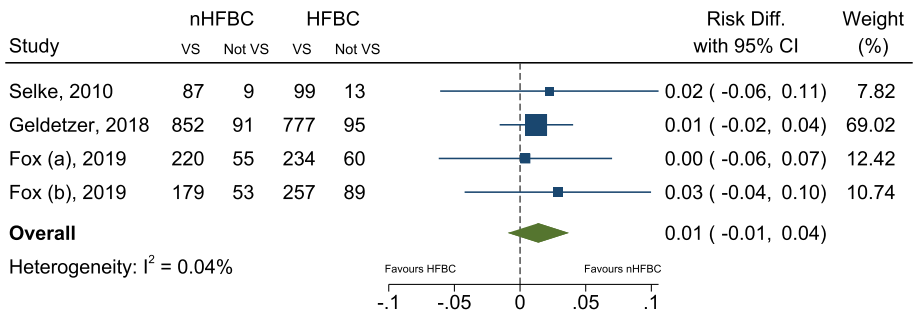

Fig. 2 Forest plot for estimated pooled risk difference comparing viral suppression among those receiving health facility-based care (HFBC) and non-health facility-based care (nHFBC), including results only from randomized controlled trials. Legend to the figure: Dashed line represents zero risk difference. VS (virally suppressed)

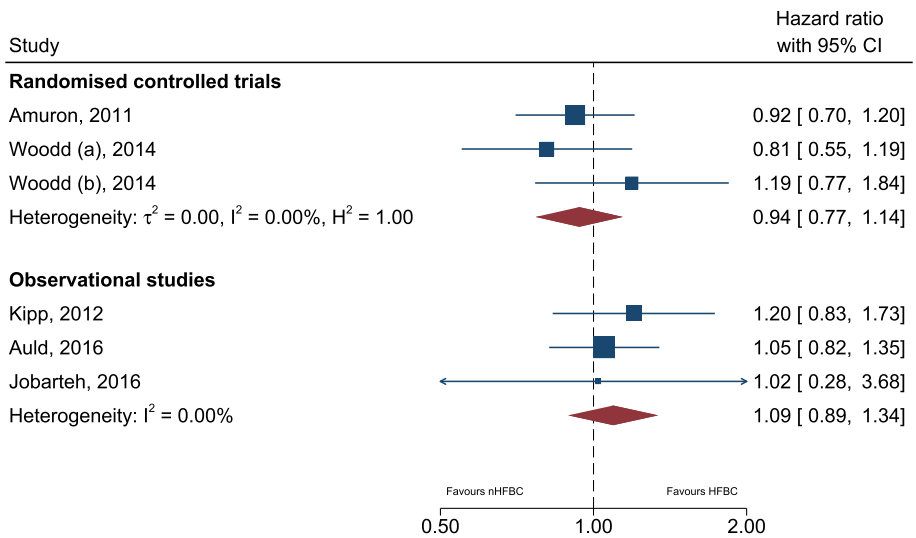

Fig. 3 Forest plot for estimated pooled hazard ratio comparing mortality among those receiving health facility-based care (HFBC) and non-health facility based care (nHFBC). Legend to the figure: dashed line represents hazard ratio of 1. *Wood (**A**) is among participants with a baseline CD4 count < 50, while Woodd (**B**) is among participants with a CD4 count of 50 +

from 0.8 up to 1.2, but with all confidence intervals crossing the null of HR = 1 (Fig. 3). This resulted in a pooled estimate equal to 1.01 (95% CI 0.88–1.16), providing no evidence ($p = 0.92$) of a difference in the mortality rate among those not in facility-based care compared to those in facility-based care.

Due to the large amount of heterogeneity, results were described for LTFU and retention in care without formal methods of statistical comparison. Instead, data was tabulated comparing reported outcomes. A page referencing guide for the SWiM guideline for these outcomes can be found in Additional file 5: Appendix 5.

Loss to follow-up

A total of 15 studies reported LTFU as an outcome, of which four were from RCTs and 11 from observational cohort studies and are summarized in Table 1 and Additional file 6: Appendix 6. In most studies LTFU was defined as no longer having contact with the care services, but there was a large degree of variability in the time frame. This commonly ranged from 60 days to 6 months, however multiple studies defined LTFU as no visit or contact with the service during the study period, which was up to 5 y. Additionally, there were varying degrees of investigation into outcomes of the LTFU populations, with some studies documenting mortality and transfer to alternative services, and some not documenting any.

In the studies included, there were four RCTs that included LTFU as an outcome where LTFU was defined as outlined in Additional file 6: Appendix 6 and varied between studies [34, 40, 42, 44]. A cluster RCT undertaken in South Africa comparing adherence clubs with healthcare facility clubs over a 24 months period showed 105 patients were LTFU with no significant difference between the two study arms [40]. Their definition varied from those used in other studies as it was a measure of loss from their intervention, which goes beyond missing visits, but also includes patients who developed any of the exclusion criteria, such as comorbidity or viral rebound. A RCT in Tanzania [41] compared home delivery to HFBC, and defined LTFU as not having a VL measurement after enrolment into the model of care over the entirety of the 12-month study period. They demonstrated non-inferiority in the rates of LTFU. In the other two randomised trials by Selke et al. and Woodd et al., LTFU was defined as not having had contact with the care services during the study period, which was 28 months in both studies. Selke et al. [44] compared home delivery model to healthcare facility in Kenya and showed comparable LTFU outcomes (4.5% in HFBC versus 5.2% in home delivery) and similarly, Wood et al. compared home delivery to HFBC in Uganda and demonstrated similar rates of LTFU, which were 2.36% in the facility and 2.33% in the community [42].

Eleven observational studies reported LTFU with varying definitions. Six of these studies did a comparison between nHFBC and HFBC and showed nHFBC had comparable or better LTFU outcomes compared to HFBC [45, 50–52, 54, 55] (Additional file 6: Appendix 6: Table 4). Among these, LTFU was defined as being late for their scheduled pharmacy pick-up date by either 60, 90 or 180 days late with the exception of Tun et al. who defined LTFU as combined mortality, transfer out and withdrawal [45]. Grimsrud et al. showed community

adherence clubs were associated with a reduction in the risk of LTFU compared with the clinic with a two-third reduction in the hazard of LTFU [52] (Additional file 6: Appendix 6). Luque-Fernandez et al. compared adherence clubs to healthcare facility and demonstrated that a combined outcome of time to either death or LTFU was less frequent in club participation than in the facility (crude RR 0.25 95%CI: 0.14, 0.41) [55]. Similarly, in Mozambique, patients who participated in community adherence support groups were associated with a lower LTFU rates as compared to those who did not participate in these groups. Auld et al. showed participating in CAGs was associated with a 35% lower LTFU rates (AHR 0.65; 95%CI: 0.46, 0.91) [51]. Another study comparing CAG to non-CAG showed higher LTFU rates amongst non-CAG members (HR 2.36 95%ci: 1.54, 3.17) [54]. In the same country, a comparison between CAGs and HFBC showed that CAG members had a greater than 5-fold reduction in the risk of combined LTFU and mortality (adjusted HR 0.18 95%CI: 0.11, 0.29) [50]. A total of five studies had no comparison to HFBC [32, 36, 46, 48, 49] and despite varying definitions of LTFU, a study in South Africa showed a cumulative incidence of LTFU at 2.6 and 12.2% at 12 and 24 months respectively [48, 49] (Additional file 6: Appendix 6: Table 5).

The definition of LTFU varied amongst included studies, including a missed scheduled visit, being late for drug pick-ups or withdrawal from a model, which could include death or patients transition to alternative health care facility. For studies that defined LTFU as having missed a scheduled visit or model withdrawal, only three indicated patients transition to HFBC [40, 41, 45].

Retention

A total of 13 studies in our review, two of which were published in the same paper [37], reported retention as an outcome, nine of which provided a comparison to health facility based care (Additional file 6: Appendix 6 Table 4). Three RCTs compared retention between nHFBC and HFBC [37, 41, 44], which showed that the community models had comparable rates to those in the facility. Fox et al. defined retention as those not LTFU, died or transferred to alternative care, and reported 81.6% participants retained in facility and 89.5% participants retained in the community with a risk difference of 7.8% [37]. Selke et al. defined it as those still in care at the end of the follow up period, reporting rates of 91.1% in facility compared to 90.6% in the community [44]. Similarly, Geldsetzer et al. defined attrition as those no longer in care, the inverse rates of which are reported as retention of 86.4% in the facility and 81.1% in the community [41].

Equally, most observational studies demonstrated similar retention outcomes between nHFBC and HFBC [45, 53, 56] or better retention outcomes in nHFBC [50, 54]. Only one study showed better HFBC retention rates [37]. Definitions of retention in care used were similar across all studies, however there was large variation in follow up period, ranging from six months to five years. Among the four studies that did not provide a comparison to HFBC, retention rates for nHFBC generally exceeded 90%, including a study with follow up of four years. A study from 2015 by Okoboi et al. was the exception, reporting a retention rate of 69% in patients on treatment for more than five years [36].

Discussion

We reviewed articles describing the current evidence of community ART programs taking place in SSA between 2010 and 2019 on the following key outcomes; Viral load suppression, mortality, LTFU and retention. From our review, all the articles that described nHFBC ART programs found evidence that decentralizing HIV services into the community for PLHIV has promising outcomes and is a safe alternative to facility based care programs in resource limited high burden HIV settings for stable PLHIV on ART. Adherence clubs that were physically located within the health-care facility were also considered as nHFBC as they ran independently and thus considered as outside the standard HCF provision. The studies suggest that levels of VS and mortality are similar in both nHFBC and HFBC groups. Similarly, with regards to LTFU and retention, articles included in our review showed comparable or slightly better LTFU and retention outcomes amongst nHFBC models when compared to HFBC. However, whilst we identified 21 articles that described one or more outcomes of nHFBC models in SSA countries, only two-thirds of the articles compared these models to the HFBC, limiting the strength of conclusions that can be drawn.

In all included articles, the primary clinical care provider for these nHFBC models was poorly described, but provision of the core packages such as ART dispensation, adherence support and referrals of sick patients to the clinics was often shared by community or trained lay workers. nHFBC models have shown that decentralizing HIV services into the community may potentially overcome major structural and financial barriers faced by PLHIV to ART initiation and retention [27]. These models are capable of achieving a range of potential additional benefits to healthcare providers and PLHIV on ART, including patient satisfaction, reduced costs, convenient and efficient service delivery and better clinical outcomes and promote healthy behaviors such as decrease alcohol abuse [23]. As the numbers of PLHIV accessing treatment increases following the 2015 WHO ART guidelines [9], nHFBC models have shown the potential to be able to deliver a package of essential ART

services beyond the clinic, freeing up the capacity within the HFBC workforce to be able to focus on more complex cases [24].

Our findings suggest that nHFBC programs can achieve favorable outcomes for stable PLHIV on ART in resource limited settings, which is in line with a previously published systematic review by Decroo et al. that looked at community-based intervention programs [24]. This review has updated and summarized the evidence that has been published since Decroo et al's review in 2013, and proposes that community-based intervention programs can make treatment readily accessible and affordable as well as help support adherence and sustain retention of patients on ART over the long term [24]. In Uganda, Kenya and Tanzania, lay workers or community health workers delivered ART to patients homes [41, 44, 61] whereas in Tete, Mozambique, CAGs were used to deliver ART within the community [50]. Similarly, in South Africa, adherence clubs piloted by MSF equally showed promising results [55].

With respect to other relevant outcomes, studies comparing CD4 count outcomes between HFBC and nHFBC models showed patients in nHFBC models can achieve similar outcomes in terms of CD4 gains [44, 52]. Decroo et al. also included studies analyzing costs of the interventions, and found that provider costs were either similar or lower in nHFBC models, and considerably more cost-effective for patients [24]. Our review did not include cost-analysis as there have been very few studies that have informed on the costs or cost-effectiveness of these nHFBC models. Studies that have reported on costs have found that provider outcomes were similar for HFBC and nHFBC [62, 63]. One study found that community-based intervention programs were much more cost-effective than estimates for facility based care [64]. However, a recent study in Tanzania showed that although patient satisfaction with a home-based program was high and was likely to save patients substantial amount of time, other envisaged benefits of decongesting the healthcare facility and reductions in patients' health expenditures were minimal [41]. Clearly more research using economic outcomes in different contexts to compare the costs, effectiveness and sustainability of the models are needed. Available data suggests that these models, even if equivalent or significantly non-inferior to the HFBC, may be more cost-effective. Patient transportation costs and use of personnel, operational and utility costs are likely to be lower. This in addition to improved retention rates are more likely to make nHFBC models more cost-effective and sustainable in the long run [23].

At the time of writing, Long et al. published a rapid review of differentiated service delivery models for ART in SSA and noted despite the widespread expectations that these models will be cost-saving, they found little data to support this contention [65]. When evaluating programmatic costs of such nHCFB models of ART delivery, an additional cost that is difficult to measure is the potential costs associated with onward HIV transmission amongst those who interrupt ART with consequent viral rebound.

nHFBC models also have the potential to have an impact on the relationship between healthcare providers and patients and can thus strengthen social and peer support [66]. These models have the opportunity to transform the current siloes to a more integrated approach that will enable HIV care to be combined with care for other conditions, including non-communicable diseases that are becoming more prevalent in resource limited settings [23].

Our study had several limitations and despite searching several databases, yielded a small number of studies that looked at ART delivery for final inclusion. We also noted there is paucity of data from other regions in Africa such as West and Central Africa where the HIV burden is high. nHFBC delivery models are recent strategies and at present resource constraints make this a challenge in many sub-Saharan African settings. The heterogeneity of these nHFBC models in our review ranged from the diversity of the models, be definition and the evaluation methods. Of the 21 articles that were included for inclusion only 15 articles compared outcomes with HFBC, making data available for analysis limited, and its inclusion in the meta-analysis imperfect. Instead of comparing outcomes from every individual nHFBC model to HFBC model separately, the results were pooled, and all community-based programs were evaluated against the standard of care causing clinical heterogeneity. Another limitations in this review include the heterogeneity of the articles that met our inclusion criteria which could have manifested in several ways. Our topic was diverse and the methods of evaluating nHFBC outcomes ranged from facility-site, observational cohorts to randomized trials. With regards to studies reporting on mortality in our review, two observational studies did a comparison between patients who chose nHFBC or not [51, 54] and one study did a comparison in two different settings [56] which could have resulted in bias due to the fact that whether participants received nHFBC or HFBC was not allocated at random. The reported effect estimates were adjusted for potential confounders to mitigate this. Although some residual confounding may remain, the effect observed in the observational cohorts is consistent with that seen in the randomized studies. Assessing outcomes such as LTFU in our review was also a limitation. The lack of a standard definition for LTFU across studies included in our review made it difficult to assess the trends and differences in LFTU to accurately measure the effectiveness of

these programs and obstructed comparibility between HFBC and nHFBC models. LTFU is an important indicator to accurately measure effectiveness of ART programs and therefore there is need for a standard definition in order to understand the changes within and the differences between ART programs especially in settings where ascertainment of mortality is weak. Lastly, unsuccessful pilot studies are less likely to be published, introducing publication bias. Studies included in this review introduce bias in measured outcomes in that those included with available data may differ in terms of stability, ability to access care and treatment or being able to make a choice. The value of such nHFBC models for people currently not retained in care is not included in this systematic review. Other limitations include the diversity of the set-up of these nHFBC models and the study design, resulting in observation bias, and confounding bias when a comparison was made. In this review, stable patients were offered the chance or were able to choose themselves and both avenues introduce significant selection bias, as both these groups are likely to contain individuals more dedicated to their health, evident from their superior clinical outcomes or willingness to participate actively in their care.

Although our findings have shown that nHFBC models can complement HFBC service delivery with regards to clinical outcomes and enhance patients ability to manage HIV, there is need for more in depth information on patients acceptability towards these models of care as well as the negative and positive effects related to stigma and ART delivery in the communities [35].

All the articles in our review, with exception of one [42], focused on stable adult PLHIV on ART, which typically included being on ART for more than 6–12 months and either virally suppressed or immunologically stable. However, there is a need to understand the impact of nHFBC models on key populations who are frequently excluded, such as youth and men who have sex with men, who may benefit the most as they may avoid clinics for other reasons such as domestic violence. There is no data regarding nHFBC models towards key populations and further pilot studies on nHFBC models should be targeted towards key populations to determine the feasibility and key clinical outcomes. In additon to the models included in this review, there is a growing trend towards supporting ART distribution from drop-in centres, and therefore a need to assess their effectiveness. However, at the time of evalaution, there were no RCTs that included this approach to explore their outcomes. There is currently scarce or no data regarding patient satisfaction and improvement in quality of life from these models and therefore further research is needed to determine patient satisfaction and quality of life from these models. Feasibility of implementing these models equally need to be explored as most of these models are implemented by in-country implementing partners with additional funding and resources, and need to understand how these models can be placed into the context of existing healthcare sytem without external funding.

Conclusions

This systematic review further demonstrates non-inferiority of nHFBC amongst stable PLWH on ART in high HIV burden, resource limited settings in sub-Saharan Africa for key outcome measures of VS, death or LTFU compared with current standard HFBC models.

Abbreviations

AC: Adherence clubs; ART: Antiretroviral treatment; CAG: Community adherence group; CBDP: Community-based distribution group; CHW: Community health worker; DMD: Decentrlaized medication delivery; HFBC: Health facility based care; HIV: Human immunodeficiency virus; LTFU: Loss to follow up; MSF: Médecins Sans Frontiéres; nHFBC: Non-facility based care; PLHIV: People living with HIV; RCT: Randomised control trial; SSA: Sub-Saharan Africa; VL: Viral load; VS: Viral suppression

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-021-11053-8.

Additional file 1: Appendix 1. Search strategy in full for all databases, including Medline, Embase and Global Health

Additional file 2: Appendix 2: Table 2. Quality Assessment of Randomised Control Trials using Cochrane Tool for Risk of Bias

Additional file 3: Appendix 3: Table 3. Quality Assessment of Included Cohort Studies using the Newcastle-Ottawa Scale

Additional file 4: Appendix 4: Figure 4. Forest plot for estimated pooled risk difference comparing viral suppression among those receiving health facility based care (HFBC) and non-health facility based care (nHFBC), including results from randomized controlled trials and observational studies. Information on file format. Brief description of file content.

Additional file 5: Appendix 5. Synthesis Without Meta-analysis (SWiM) reporting items

Additional file 6: Appendix 6: Table 4. Loss to Follow-Up and Retention outcomes of nHFBC and HFBC comparison. **Table 5.** Loss to Follow-Up and Retention outcomes without nHFBC and HFBC comparison.

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Authors' contributions

Conceptualization, SF and HA; Investigation, ML and GZ; Quantitative analysis, DM; Writing – Original Draft, ML and GZ; Writing – Review and Editing, ML, GZ, DM, SF; Supervision, SF and HA. All authors have read and approved the manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

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Not Applicable.

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors have no competing interests to declare.

Author details
[1]Zambart House, PO Box 50697, UNZA-Ridgeway Campus, Lusaka, Zambia. [2]Imperial College London, London, UK. [3]MRC Tropical Epidemiology Group, London School of Hygiene and Tropical Medicine, London, UK. [4]Imperial College and Imperial college NIHR BRC, London, UK.

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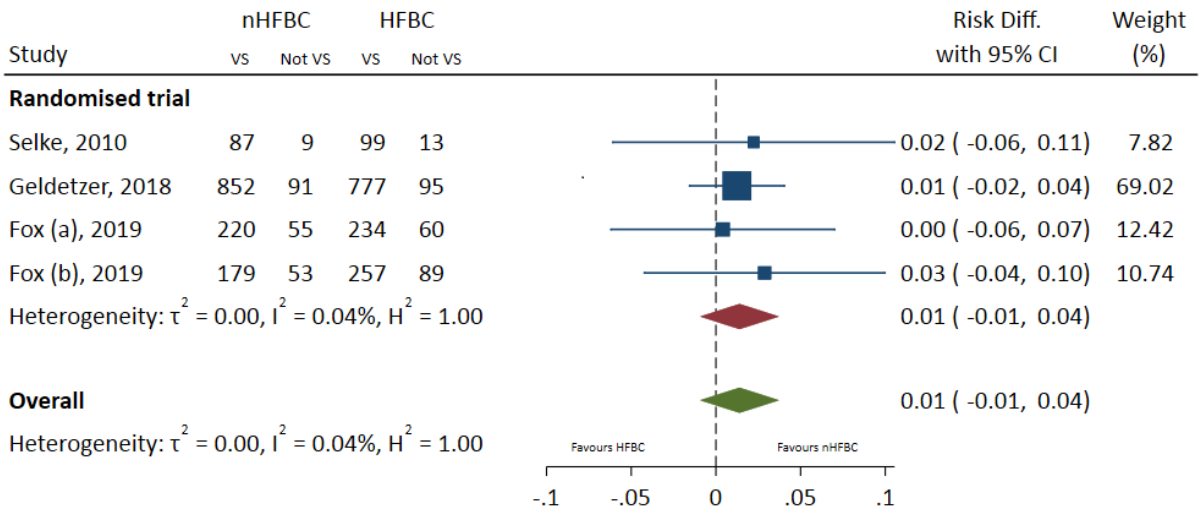
References
1. UNAIDS. Global HIV & AIDS statistics – 2020 fact sheet. [cited 2020Jan12]. Available from: https://www.unaids.org/en/resources/fact-sheet.
2. UNAIDS. Fact sheet - Latest statistics on the status of the AIDS epidemic. 2018.[Available from: https://www.unaids.org/en/regionscountries/countries/zambia. Accessed 4 Jan 2019.
3. INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med. 2015;373(9):795–807. https://doi.org/10.1056/NEJMoa1506816.
4. Group TTAS. A trial of early Antiretrovirals and isoniazid preventive therapy in Africa. N Engl J Med. 2015;373(9):808–22.
5. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Antiretroviral therapy for the prevention of HIV-1 transmission. N Engl J Med. 2016;375(9):830–9. https://doi.org/10.1056/NEJMoa1600693.
6. Rodger AJ, Cambiano V, Bruun T, et al. PARTNER Study Group. Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. JAMA. 2016;316(2):171–81. https://doi.org/10.1001/jama.2016.5148.
7. Eisinger RW, Dieffenbach CW, Fauci AS. HIV viral load and transmissibility of HIV infection: undetectable equals Untransmittable. JAMA. 2019;321(5):451–2. https://doi.org/10.1001/jama.2018.21167.
8. UNAIDS. UNAIDS fast-track: ending the AIDS epidemic by 2030. Geneva; 2014.
9. WHO. Guidelines on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva. 2015.
10. Tymejczyk O, Brazier E, Yiannoutsos CT, Vinikoor M, van Lettow M, Nalugoda F, et al. Changes in rapid HIV treatment initiation after national "treat all" policy adoption in 6 sub-Saharan African countries: regression discontinuity analysis. PLoS Med. 2019;16(6):e1002822. https://doi.org/10.1371/journal.pmed.1002822.
11. World Health Organization. WHO HIV policy adoption and implementation status in countries: fact sheet. Geneva: World Health Organization; 2018.
12. UNAIDS. UNAIDS data 2019.
13. UNAIDS. Global AIDS update 2018: miles to go. Geneva: Joint united Nations Preogramme on HIV/AIDS (unaids); 2018.
14. Sanjana P, Torpey K, Schwarzwalder A, Simumba C, Kasonde P, Nyirenda L, et al. Task-shifting HIV counselling and testing services in Zambia: the role of lay counsellors. Hum Resour Health. 2009;7(1):44. https://doi.org/10.1186/1478-4491-7-44.
15. Hirschhorn LR, Oguda L, Fullem A, Dreesch N, Wilson P. Estimating health workforce needs for antiretroviral therapy in resource-limited settings. Hum Resour Health. 2006;4(1):1. https://doi.org/10.1186/1478-4491-4-1.
16. Fox MP, Rosen S. Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007–2009: systematic review. Tropical Med Int Health. 2010;15(s1):1–15. https://doi.org/10.1111/j.1365-3156.2010.02508.x.
17. Fox MP, Rosen S. Retention of Adult Patients on Antiretroviral Therapy in Low- and Middle-Income Countries: Systematic Review and Meta-analysis 2008–2013. JAIDS. 2015;69(1):98–108.
18. Rosen S, Fox MP. Retention in HIV care between testing and treatment in sub-Saharan Africa: a systematic review. PLoS Med. 2011;8(7):e1001056. https://doi.org/10.1371/journal.pmed.1001056.
19. Mugglin C, Estill J, Wandeler G, Bender N, Egger M, Gsponer T, et al. Loss to programme between HIV diagnosis and initiation of antiretroviral therapy in sub-Saharan Africa: systematic review and meta-analysis. Trop Med Int Health. 2012;17(12):1509–20. https://doi.org/10.1111/j.1365-3156.2012.03089.x.
20. Kranzer K, Govindasamy D, Ford N, Johnston V, Lawn SD. Quantifying and addressing losses along the continuum of care for people living with HIV infection in sub-Saharan Africa: a systematic review. J Int AIDS Soc. 2012;15(2):17383. https://doi.org/10.7448/IAS.15.2.17383.
21. Fox MP, Shearer K, Maskew M, Meyer-Rath G, Clouse K, Sanne I. Attrition through multiple stages of pre-treatment and ART HIV Care in South Africa. PLoS One. 2014;9(10):e110252. https://doi.org/10.1371/journal.pone.0110252.
22. Joint United Nations Programme on HIV/AIDS. 90–90-90:an ambitious treatment target to help end the AIDS epidemic. Geneva: UNAIDS; 2014.
23. Nachega JB, Adetokunboh O, Uthman OA, Knowlton AW, Altice FL, Schechter M, et al. Community-based interventions to improve and sustain antiretroviral therapy adherence, retention in HIV care and clinical outcomes in low- and middle-income countries for achieving the UNAIDS 90-90-90 targets. Curr HIV/AIDS Rep. 2016;13(5):241–55. https://doi.org/10.1007/s11904-016-0325-9.
24. Decroo T, Rasschaert F, Telfer B, Remartinez D, Laga M, Ford N. Community-based antiretroviral therapy programs can overcome barriers to retention of patients and decongest health services in sub-Saharan Africa: a systematic review. Int Health. 2013;5(3):169–79. https://doi.org/10.1093/inthealth/iht016.
25. ICAP Approach to Differentiated Service Delivery [Internet]. Cquin.icap.columbia.edu. 2019 [cited 16 Sep 2019]. Available from: https://cquin.icap.columbia.edu/resources/icap-approach-to-differentiated-service-delivery/ [.
26. International AIDS Society (IAS). DIFFERENTIATED CARE FOR HIV: A Decision Framework for Antiretroviral Therapy Delivery: International AIDS Society; 2016.
27. Bemelmans M, Baert S, Goemaere E, Wilkinson L, Vandendyck M, Cutsem G, et al. Community-supported models of care for people on HIV treatment in sub-Saharan Africa. Tropical Med Int Health. 2014;19(8):968–77. https://doi.org/10.1111/tmi.12332.
28. Wilkinson LS. ART adherence clubs: A long-term retention strategy for clinically stable patients receiving antiretroviral therapy. 2013. 2013;14(2):3.
29. Grimsrud A, Sharp J, Kalombo C, Bekker L-G, Myer L. Implementation of community-based adherence clubs for stable antiretroviral therapy patients in Cape Town, South Africa. 2015.
30. Grimsrud A, Bygrave H, Doherty M, Ehrenkranz P, Ellman T, Ferris R, et al. Reimagining HIV service delivery: the role of differentiated care from prevention to suppression. J Int AIDS Soc. 2016;19(1):21484. https://doi.org/10.7448/IAS.19.1.21484.
31. Bochner AF, Meacham E, Mhungu N, Manyanga P, Petracca F, Muserere C, et al. The rollout of community ART refill groups in Zimbabwe: a qualitative evaluation. J Int AIDS Soc. 2019;22(8):e25393. https://doi.org/10.1002/jia2.25393.
32. Decroo T, Koole O, Remartinez D, dos Santos N, Dezembro S, Jofrisse M, et al. Four-year retention and risk factors for attrition among members of community ART groups in Tete, Mozambique. Trop Med Int Health. 2014;19(5):514–21. https://doi.org/10.1111/tmi.12278.
33. Community-Based Anti Retroviral Therapy Delivery - Experiences Of Médecins Sans Frontières. (2015). [online] Geneva: Joint United Nations Programme on HIV/AIDS (UNAIDS). Available at: http://www.differentiatedcare.org/Portals/0/adam/Content/smn7ayyQgkeloTiU1t39YA/File/20150420_MSF_UNAIDS_JC2707-1.pdf [Accessed 24 Jan. 2018].
34. Geldsetzer P, Francis JM, Ulenga N, Sando D, Lema IA, Mboggo E, et al. The impact of community health worker-led home delivery of antiretroviral therapy on virological suppression: a non-inferiority cluster-randomized health systems trial in Dar Es Salaam, Tanzania. BMC Health Serv Res. 2017;17(1):160. https://doi.org/10.1186/s12913-017-2032-7.
35. Davis N, Kanagat N, Sharer M, Eagan S, Pearson J, Amanyeiwe UU. Review of differentiated approaches to antiretroviral therapy distribution. AIDS Care. 2018;30(8):1010–6. https://doi.org/10.1080/09540121.2018.1441970.

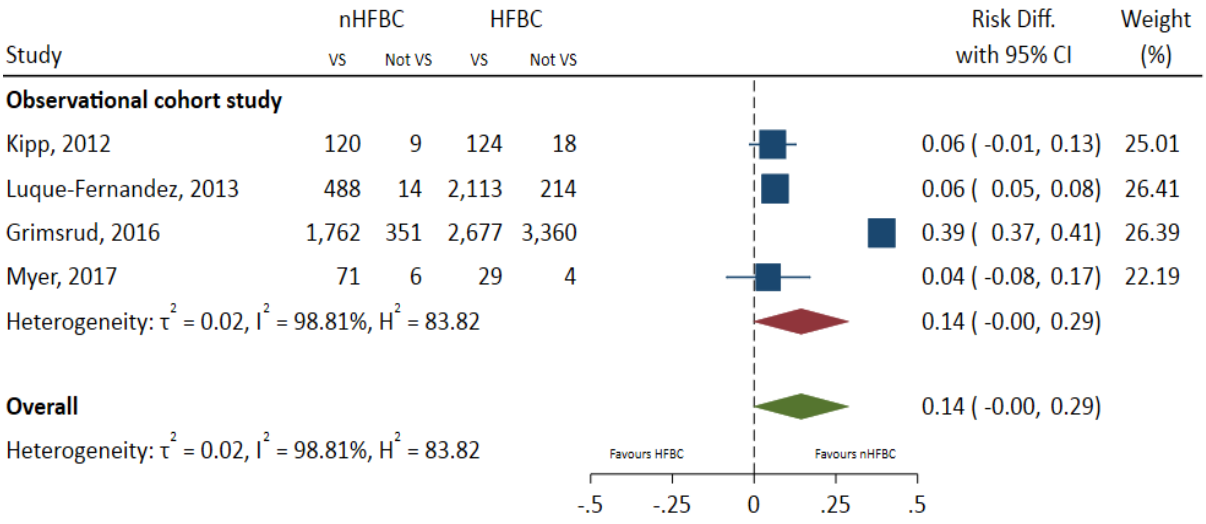
36. Okoboi S, Ding E, Persuad S, Wangisi J, Birungi J, Shurgold S, et al. Community-based ART distribution system can effectively facilitate long-term program retention and low-rates of death and virologic failure in rural Uganda. AIDS Res Ther. 2015;12(1):1–9.
37. Fox MP, Pascoe S, Huber AN, Murphy J, Phokojoe M, Gorgens M, et al. Adherence clubs and decentralized medication delivery to support patient retention and sustained viral suppression in care: results from a cluster-randomized evaluation of differentiated ART delivery models in South Africa. PLoS Med. 2019;16(7):e1002874. https://doi.org/10.1371/journal.pmed.1002874.
38. Chi BH, Yiannoutsos CT, Westfall AO, Newman JE, Zhou J, Cesar C, et al. Universal definition of loss to follow-up in HIV treatment programs: a statistical analysis of 111 facilities in Africa, Asia, and Latin America. PLoS Med. 2011;8(10):e1001111. https://doi.org/10.1371/journal.pmed.1001111.
39. Covidence. Cochrane Community. https://community.cochrane.org/help/tools-and-software/covidence. Accessed June 2018.
40. Hanrahan CF, Schwartz SR, Mudavanhu M, West NS, Mutunga L, Keyser V, et al. The impact of community- versus clinic-based adherence clubs on loss from care and viral suppression for antiretroviral therapy patients: findings from a pragmatic randomized controlled trial in South Africa. PLoS Med. 2019;16(5):e1002808. https://doi.org/10.1371/journal.pmed.1002808.
41. Geldsetzer P, Francis JM, Sando D, Asmus G, Lema IA, Mboggo E, et al. Community delivery of antiretroviral drugs: a non-inferiority cluster-randomized pragmatic trial in Dar Es Salaam, Tanzania. PLoS Med. 2018;15(9):e1002659. https://doi.org/10.1371/journal.pmed.1002659.
42. Woodd S, Grosskurth H, Levin J, Amuron B, Namara G, Birunghi J, et al. Home-based versus clinic-based care for patients starting antiretroviral therapy with low CD4+ cell counts: findings from a cluster-randomized trial. AIDS. 2014;28(4):569–76.
43. Amuron B, Levin J, Birunghi J, Namara G, Coutinho A, Grosskurth H, et al. Mortality in an antiretroviral therapy programme in Jinja, south-East Uganda: a prospective cohort study. AIDS Res Ther. 2011;8(1):39. https://doi.org/10.1186/1742-6405-8-39.
44. Selke HM, Kimaiyo S, Sidle JE, Vedanthan R, Tierney WM, Shen C, et al. Task-shifting of antiretroviral delivery from health care workers to persons living with HIV/AIDS: clinical outcomes of a community-based program in Kenya. J Acquir Immune Def Synd (1999). 2010;55(4):483–90.
45. Tun W, Apicella L, Casalini C, Bikaru D, Mbita G, Jeremiah K, et al. Community-based antiretroviral therapy (ART) delivery for female sex Workers in Tanzania: 6-month ART initiation and adherence. AIDS Behav. 2019;23(2):142–52. https://doi.org/10.1007/s10461-019-02549-x.
46. Pasipamire L, Nesbitt RC, Ndlovu S, Sibanda G, Mamba S, Lukhele N, et al. Retention on ART and predictors of disengagement from care in several alternative community-centred ART refill models in rural Swaziland. J Int AIDS Soc. 2018;21(9):e25183.
47. Myer L, Iyun V, Zerbe A, Phillips TK, Brittain K, Mukonda E, et al. Differentiated models of care for postpartum women on antiretroviral therapy in Cape Town, South Africa: a cohort study. J Int AIDS Soc. 2017;20(Suppl 4):21636.
48. Vogt F, Kalenga L, Lukela J, Salumu F, Diallo I, Nico E, et al. Brief Report: Decentralizing ART Supply for Stable HIV Patients to Community-Based Distribution Centers: Program Outcomes From an Urban Context in Kinshasa, DRC. J Acquire Immune Def Synd (1999). 2017;74(3):326–31.
49. Tsondai PR, Wilkinson LS, Grimsrud A, Mdlalo PT, Ullauri A, Boulle A. High rates of retention and viral suppression in the scale-up of antiretroviral therapy adherence clubs in Cape Town, South Africa. J Int AIDS Soc. 2017;20(Suppl 4):21649. https://doi.org/10.7448/IAS.20.5.21649.
50. Decroo T, Telfer B, Dores CD, White RA, Santos ND, Mkwamba A, et al. Effect of community ART groups on retention-in-care among patients on ART in Tete Province, Mozambique: a cohort study. BMJ Open. 2017;7(8):e016800. https://doi.org/10.1136/bmjopen-2017-016800.
51. Auld AF, Shiraishi RW, Couto A, Mbofana F, Colborn K, Alfredo C, et al. A Decade of Antiretroviral Therapy Scale-up in Mozambique: Evaluation of Outcome Trends and New Models of Service Delivery Among More Than 300,000 Patients Enrolled During 2004–2013. J Acquir Immune Defic Syndr (1999). 2016;73(2):e11–22.
52. Grimsrud A, Lesosky M, Kalombo C, Bekker LG, Myer L. Implementation and Operational Research: Community-Based Adherence Clubs for the Management of Stable Antiretroviral Therapy Patients in Cape Town, South Africa: A Cohort Study. J Acquir Immune Defic Syndr (1999). 2016;71(1):e16–23.
53. Okoboi S, Ssali L, Yansaneh AI, Bakanda C, Birungi J, Nantume S, et al. Factors associated with long-term antiretroviral therapy attrition among adolescents in rural Uganda: a retrospective study. J Int AIDS Soc. 2016;19(5 Suppl 4):20841. https://doi.org/10.7448/IAS.19.5.20841.
54. Jobarteh K, Shiraishi RW, Malimane I, Samo Gudo P, Decroo T, Auld AF, et al. Community ART support groups in Mozambique: the potential of patients as Partners in Care. PLoS One. 2016;11(12):e0166444. https://doi.org/10.1371/journal.pone.0166444.
55. Luque-Fernandez MA, Van Cutsem G, Goemaere E, Hilderbrand K, Schomaker M, Mantangana N, et al. Effectiveness of patient adherence groups as a model of care for stable patients on antiretroviral therapy in Khayelitsha, Cape Town, South Africa. PloS One. 2013;8(2):e56088. https://doi.org/10.1371/journal.pone.0056088.
56. Kipp W, Konde-Lule J, Saunders LD, Alibhai A, Houston S, Rubaale T, et al. Antiretroviral treatment for HIV in rural Uganda: two-year treatment outcomes of a prospective health Centre/community-based and hospital-based cohort. PLoS One. 2012;7(7):e40902. https://doi.org/10.1371/journal.pone.0040902.
57. Chimukangara B, Manasa J, Mitchell R, Nyabadza G, Katzenstein D, Masimirembwa C. Community based antiretroviral treatment in rural Zimbabwe. AIDS Res Hum Retrovir. 2017;33(12):1185–91. https://doi.org/10.1089/aid.2017.0029.
58. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P: The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
59. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.
60. Campbell MMJ, Sowden A, Katikireddi SV, Brennan SE, Ellis S, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. BMJ. 2020:368.
61. Wools-Kaloustian K, Sidle J, Selke H, Vedanthan R, Kemboi E, Boit L, et al. A model for extending antiretroviral care beyond the rural health Centre. J Int AIDS Soc. 2009;12(1):22. https://doi.org/10.1186/1758-2652-12-22.
62. Jaffar S, Amuron B, Foster S, Birungi J, Levin J, Namara G, et al. Rates of virological failure in patients treated in a home-based versus a facility-based HIV-care model in Jinja, southeast Uganda: a cluster-randomised equivalence trial. Lancet (London, England). 2010:374.
63. Kipp W, Konde-Lule J, Rubaale T, Okech-Ojony J, Alibhai A, Saunders D. Comparing antiretroviral treatment outcomes between a prospective community-based and hospital-based cohort of HIV patients in rural Uganda. BMC Int Health Hum Rights. 2011;11(Suppl 2):S12. https://doi.org/10.1186/1472-698X-11-S2-S12.
64. Marseille E, Kahn JG, Pitter C, Bunnell R, Epalatai W, Jawe E, et al. The cost effectiveness of home-based provision of antiretroviral therapy in rural Uganda. Appl Health Econ Health Policy. 2009;7(4):229–43. https://doi.org/10.1007/BF03256157.
65. Long L, Kuchukhidze S, Pascoe S, Nichols B, Cele R, Govathson C, et al. Differentiated service delivery models for antiretroviral treatment of HIV in sub-Saharan Africa: a rapid systematic review. AMBIT Project Report Number 04. Boston: Boston University and HE2RO; 2020.
66. Decroo T, Van Damme W, Kegels G, Remartinez D, Rasschaert F. Are expert patients an untapped resource for ART provision in sub-Saharan Africa? AIDS Res Treat. 2012:749718.

Publisher's Note

3.3. Supplementary Information

Supplementary Figure 4 | Forest plot for estimated pooled risk difference comparing viral suppression among those receiving health facility based care (HFBC) and non-health facility based care (nHFBC), including results from randomized controlled trials and observational studies.





VS – Virally suppressed

Supplementary Table 2 | Quality Assessment of Randomised Control Trials using Cochrane Tool for Risk of Bias

Table 2: Quality Assessment of Randomised Control Trials using Cochrane Tool for Risk of Bias						
	Fox	**Selke**	**Hanrahan**	**Geldsetzer**	**Woodd**	**Amuron**
Sequence Generation						
Allocation concealment						
Blinding (participants & personnel)						
Blinding (outcome assessment)						
Incomplete outcome data						
Selective reporting						
Other bias						

Table 2 Legend

 = low risk of bias

 = high risk of bias

 = not enough information to determine

Supplementary Table 3 | Quality Assessment of Included Cohort Studies using the Newcastle-Ottawa Scale

Table 3: Quality Assessment of Included Cohort Studies using the Newcastle-Ottawa Scale									
Study	**Selection***				**Comparability****	**Outcome*****			**Total Stars**
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome not present at the start		Assessment of outcome	Long follow-up	Adequacy of follow-up	
Fox 2019[26]	★	★	★		★	★	★	★	**7**
Tun 2019[190]	★	★		★	★			★	**5**
Pasipamire 2018[169]	★	★	★	★	★★	★	★	★	**9**
Myer 2017[191]	★	★	★		★★	★		★	**7**
Vogt 2017[192] §	-	-	-	-	-	-	-	-	**-**
Tsondai 2017[30] §	-	-	-	-	-	-	-	-	**-**
Decroo 2017[193]	★	★	★	★	★	★	★	★	**8**
Auld 2016[194]	★	★	★	★	★	★	★		**7**
Grimsrud 2016[29]	★	★	★		★	★		★	**6**
Okoboi 2016[195]	★	★	★	★	★★	★	★		**8**
Jobarteh 2016[162]	★	★	★	★	★	★		★	**7**
Okoboi 2015[196] §	-	-	-	-	-	-	-	-	**-**
Decroo 2014[161] §	-	-	-	-	-	-	-	-	**-**
Luque-Fernandez[173] 2013	★	★	★		★	★	★	★	**7**
Kipp 2012[197]	★	★	★		★	★	★	★	**7**

Table 3 Legend

*Selection

1) Representativeness of the exposed cohort: ★ Truly representative or somewhat representative
2) Selection of the non-exposed cohort: ★ Drawn from the same community as the exposed cohort
3) Ascertainment of exposure: ★ Secure record or structured interview
4) Demonstration that outcome of interest was not present at start of study: ★ Yes

** Comparability

1) Comparability of cohorts on the basis of the design or analysis controlled for confounders: ★ Study controls for age and sex OR viral load or CD4 count, ★★ Study controls for age and sex AND viral load or CD4 count

*** Outcome

1) Assessment of outcome: ★ Independent blind assessment or record linkage
2) Was follow-up long enough for outcomes to occur: ★ Follow up longer than 24 months
3) Adequacy of follow-up of cohorts: ★ Complete follow up- all subject accounted for, or subjects lost to follow up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost

§No score given to studies that did not include a comparator cohort

Quality Assessment

Quality assessment of the 6 randomised control trials was done using the Cochrane Risk of Bias Tool[198]. The risk of bias in the eight different categories was generally determined to be low for most studies. Selection bias was low for most studies rated through the sequence generation and allocation concealment. Reportive bias was determined to be low, and many studies had a study protocol published. Detection bias was reduced as many of the outcome assessors were blinded through follow up of patient through anonymized records. Attrition bias was determined to be low for all studies due to relatively low loss to follow up rates. The exception was high risk of performance bias, as none of the studies were able to blind the participants and personnel, due to the nature of the intervention. Other sources of bias were difficult to determine. Quality assessment of the 15 cohort studies was done using the Newcastle-Ottawa Scale [199]. Four out of the 15 cohort studies [30, 161, 192, 196] did not have a control group and were therefore not evaluated using the scale. Of the cohort studies that did have a comparator group, 10 of the cohort studies were rated as Good Quality, 1 was rated as Fair Quality and none were rated as Poor Quality as per the AHRQ standards. Being stable on ART was an inclusion criterion for most community interventions, which was acknowledged by the papers to be a confounding factor. Therefore, these cohorts were considered to be somewhat representative. Comparability of cohorts were generally adequate with similar baseline characteristics. Quality was maintained by using records rather than self-reporting in the ascertainment of exposure to the intervention and assessment of outcomes in all but one cohort study. Furthermore, loss of follow up rates were below 20% for the majority of studies. The follow up duration for outcomes was more than 24 months for 10 of the 16 articles.

Supplementary Table 4 | Loss to Follow-Up and Retention outcomes of nHFBC compared to HFBC

Source	Country	Model Name	Follow-up time	Outcome definition	Findings
LOSS TO FOLLOW-UP					
Hanrahan 2019[174]	South Africa	Community Adherence Clubs	24 months	Patients who missed a club visit and did not pick up ART medications within 5 days, had 2 consecutive late ART pick-ups, developed a comorbidity or had viral rebound were referred to standard of care	During the 24 months follow up, there was no significant difference in loss to ART between clinic and community clubs. 12% among community club's vs 7% among facility clubs [HR 1.69, 95%CI 0.98, 2.91] Overall, 10% loss from ART clubs
Geldsetzer 2018[32]	Tanzania	Home Delivery model	326 days	Patients in the intervention arm who did not have a VL measurement after enrolment were considered LTFU	18.9% in Home delivery model vs 13.6% in HCF
Selke 2010[179]	Kenya	Home Delivery model	28 months	Point at which the person was no longer in care (moved out, quit medications or shifted to another facility).	LTFU was 5.2% in Home delivery model and 4.5% in HCF.
Wood 2014[200]	Uganda	Home Delivery Model	28 months	Participants who were no longer in care during the study period	1.8% among those with CD4 <50 and 2.6% among those with CD4 > 50cells
Grimsrud 2016[29]	South Africa	Community Adherence clubs	12 months	LTFU defined as having no visit in the first 12 weeks (excluding mortality) after analysis closure. Analysis closure was at the end of 2013 and database closure was 24th March 2014. LTFU was defined as having no visit in the in the first 12 weeks of 2014.	Community clubs were associated with a substantial decrease in the risk of LTFU compared with the community clinic. However, LTFU was twice as likely in youths compared to older patients. Clubs in the community (CAC) were associated with a reduction in the risk of LTFU compared with clinic with a two-third reduction in the hazard of LTFU
Auld 2016[194]	Mozambique	Community ART Support Group (CASG)	4 years	LTFU was defined as > 60 days late for their next scheduled drug pick up.	Participating in CASG was associated with a 35% lower LTFU rates (AHR 0.65; 95%CI: 0.46, 0.91). LTFU incidence was 2.9% at 2 yrs. and 10.1% at 4 years. In a sensitivity analysis, when restricting the cohorts to the clinics that only offered CASG models during the 4 years of follow-up, CASG participation was associated with a 55% reduction in LTFU rates [AHR 0.45 95%CI 0.32-0.64]
Decroo 2017[193]	Mozambique	Community Adherence groups (CAGs)	4 years	LTFU was defined as being more than 2 months overdue for their most recent appointment or scheduled ART refill.	Combined LTFU and mortality CAG members had a greater than fivefold reduction in the risk of dying or being LTFU [AHr 0.18; 95%CI 0.11, 0.29]
Jobarteh 2016[162]	Mozambique	Community ART Support groups	12 months	LTFU > 60 days late for their next scheduled appointment	LTFU among CASG and non-CASG members were 7.25 and 15.9% respectively.

		(CASG)			Non-CASG members had significantly higher LTFU [HR 2.36 95%CI: 1.54, 3.17]
Luque Fernandez 2013[173]	South Africa	Community Adherence Clubs	3 years	Combined outcome of time to either death or LTFU. LTFU – not having any contact with the service in the 6 months following analysis closure	12.8% were LTFU or died. Both outcomes less frequent in club members [Crude RR 0.25 95%CI: 0.14-0.41]
Tun 2019[190]	Tanzania	Community distribution points (CDP)	6 months	LTFU was defined as any patients who had died, transferred out or withdrew from the model	53 in the intervention arm and 55 in the HCF
RETENTION					
Fox 2019[26]	South Africa	Adherence clubs	12 months	Retention in care at 12 months after model eligibility. Defined as 100% - % attrition, with attrition as the sum of reported deaths, LTFU and transfers. LTFU was defined as failure to attend the clinic within 90 days of a scheduled appointment.	ACs had a higher retention rate 81.6% participants retained in facility; 89.5% participants retained in the community. Risk difference 7.8% (95% CI; 2.1%, 13.6%).
Fox 2019[26]	South Africa	Community distribution points (CDP)	12 months	Retention in care at 12 months after model eligibility. Defined as 100% - % attrition, with attrition as the sum of reported deaths, LTFU and transfers. LTFU was defined as failure to attend the clinic within 90 days of a scheduled appointment.	Retention was high overall (about 85%) 87.2% patients retained in the facility; 81.5% patients retained in the community. Risk difference -5.8% (95% CI; -11.75%, 0.2%).
Jobarteh 2016[162]	Mozambique	Community ART support groups (CASG)	12 months	Retention defined as patients who were in care at the end of 12 months [excludes LTFU]	Overall patients in CASG had better retention rates Having excluded those who were LTFU and died the number of patients retained in CASG was 91.4% and 82.9% in Non-CASG models
Decroo 2017[193]	Mozambique	Community ART support groups (CASG)	24 months	Patients retained in care [excluding those LTFU or died]	Retention in care among patients in CAGs was substantially higher than those in individual care. Overall RIC was 90.8% at 12 months and 86% at 24 months. At 12 months: 89.5 % retained in care (95% CI; 87.9, 90.8) in the facility, 99.1% retained in care (95% CI; 97.3, 99.7) in the community. At 24 months 82.3 % retained in care (95% CI: 79.9, 84.5) in the facility, and 97.5% retained in care (95% CI; 95.4, 98.6) in the community.

Kipp 2012[197]	**Uganda**	**Home delivery**	**24 months**	**Patients who remained active in care at the end of the study period [excludes LTFU and mortality]**	**71% were retained in care in the health care facility and 70% retained in the home delivery model**
Source	**Country**	**Model name**	**Follow-up time**	**Outcome definition**	**Findings**
Tun 2019[190]	Tanzania	Community distribution points (CDP)	6 months	Patients active in care at 6 months	82.8% patients retained in CDP models at 6 months vs 82.1% retained in the facility. No formal analysis done.
Okoboi 2016[195]	Uganda	Community distribution points (CDP)	5 years	Retention was defined as any patient who had at least one clinic visit in the six months before June 2013; was still alive at the end of June 2013, excluding those deaths reported to TASO stopped ART; or LTFU.	83.9% retained in the facility, 82.9% retained in the community. P value 0.670. Univariate analysis of factors associated with attrition: 1.00 (0.76-1.34), P value 0.972.
Selke 2010[179]	Kenya	Home ART delivery	28 months	Defined as point at which patient was no longer in care (transfer, quit medications]	91.1% retained in the facility and 90.6% retained in the community – no formal analysis
Geldsetzer* 2018[32]	Tanzania	Home ART delivery	326 days	Patients who were still active in care	81.1% retained in the community and 86.4% retained in the facility – no formal analysis done.

Legend: ** The inverse numbers of attrition reported here as retention*

Supplementary Table 5 | Loss to Follow-Up and Retention outcomes of nHFBC without HFBC comparison

Source	Country	Model Name	Follow-up time	Outcome definition	Findings
LOSS TO FOLLOW-UP					
Vogt 2017[192]	Democratic Republic of Congo	Community based refill centre	24 months	Defined death and LTFU as attrition LTFU was defined as having had no contact with the services between 2011 and 2013	LTFU was 9.0% at 24 months Deaths were not well captured so could have overestimated the LTFU rates and reduced mortality rates.
Tsondai 2017[30]	South Africa	Adherence clubs	24 months	LTFU was defined as having no contact with the club or clinic in the 6 months following analysis closure and was determined to have happened on the date of last contact with service	4.2% of patients were LTFU Cumulative incidence of LTFU was: 2.6% [95%CI 2.1-3.2] at 12 months 12.2% [95%CI 9.7, 14.7] at 36 months Risk of LTFU was observed in younger patients
Okoboi 2015[196]	Uganda	Community distribution points (CDP)	5 years	Combined mortality and LTFU LTFU was defined as having had no visit or contact with the service during the study period	LTFU 1.59 per 100-person per years
Decroo 2014[161]	Mozambique	Community Adherence Groups (CAGs)	4 years	LTFU defined as being more than 2 months late for the last appointment/ refill	LTFU rate was 0.1 per 100 person yrs.
Pasipamire 2018[169]	Swaziland	Community adherence groups (CAGs) Facility based groups Treatment outreach	12 months	Patient LTFU was defined as patients without recorded visit for 120 days or more before Database closure. LTFU from care was time from enrolment to the composite endpoint of LTFU and death, regardless of whether the outcome occurred while enrolled in the care model or in routine facility-based ART care	Of the 918 total patients included, 27 were LTFU (2.94%). Patients in CAGs had a higher risk of disengaging from care models (aHR 3.15 95%CI 2.01, 4.95) Note this was comparison between two models and not the facility
RETENTION					
Pasipamire 2018[169]	Swaziland	Community adherence groups (CAGs) Facility based groups	12 months	In the primary analysis, Retention in care model, the outcome of interest was time to the composite endpoint of LTFU, death or exit from specific care model at enrolment. In the secondary analysis, Retention in ART	**Retention in the care models** Overall care model retention was 90.9% at 6 months and 82.2% at 12 months. Retention in care models differed significantly by model types, lowest in CAGs. 70.4% retained in CAGs at 12 months compared to 86.3% in outreach and 90.4% in clubs. Patients in CAGs had a higher risk of disengaging from care models compared with treatment clubs

		Treatment outreach		care, outcome was time from enrolment to the composite endpoint of LTFU and death regardless of whether the outcome occurred whilst enrolled in the model of care or routine HCF.	[adjusted HR 3.15, 95% ci 2.01, 4.95]. **Retention in ART** Overall, ART retention was 96.7% at 6 months and 93.7% at 12 months. It was over 90% for all 3 models at all time points and no difference between care models
Tsondai 2017[30]	South Africa	Adherence clubs	12 months 24 months	Primary outcome was LTFU and viral rebound Competing risk regression was used to estimate the cumulative incidence for LTFU, transfer out and mortality which were then used to calculate the corresponding cumulative retention	Of the 3216 adults contributing 4019 person yrs. follow up, retention was 95.2% at 12 months [95% CI 94.0, 96.4] and 89.3% at 24 months [95%CI 87.1, 91.4] after club enrolment.
Okoboi 2015[196]	Uganda	Community ART distribution	5 years	Retention to care was defined as any patient with at least one visit in the 6 months	More than 69% of patients who initiated ART from 2004 to 2009 were retained in care after more than 5 years of treatment. These finding demonstrated that high retention rates are possible even in rural resource limited settings.
Decroo 2014[161]	Mozambique	Community Adherence groups (CAGs)	4 years	Patients who were still active in the models of care at follow up intervals	Retention among CAG members: At 1 year – 97.7% [95% CI 97.4, 98.2] At 2 years- 96.0% [95%CI 95.3, 96.6] At 3 years- 93.4% [95%CI 92.3, 94.3] AT 4 years- 91.8% [95%CI 90.1, 93.2]

Chapter 4: Methodology

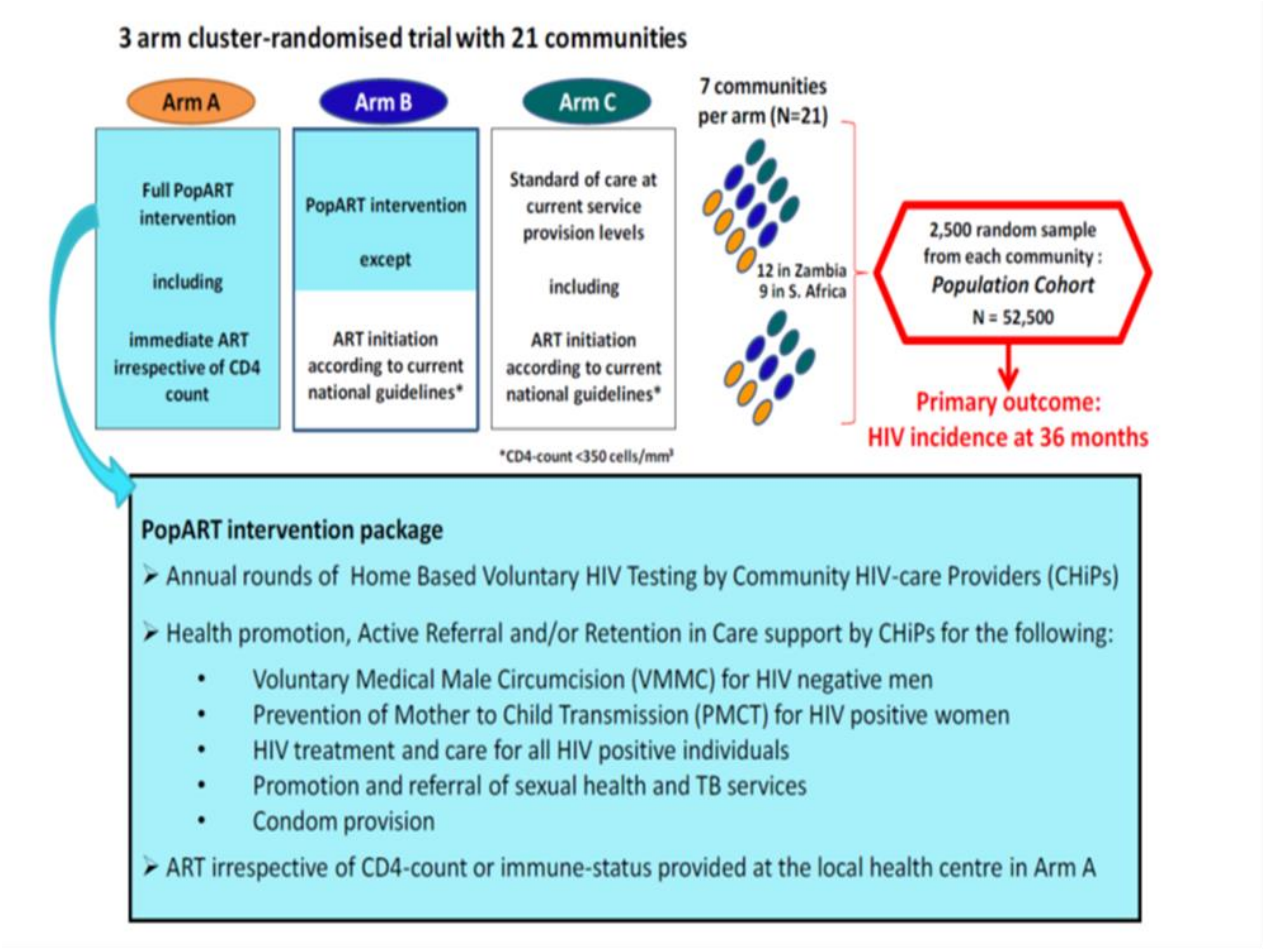
4.1 Outline of the chapter

This chapter provides an overview of the design of the nested community ART delivery randomized control trial (ComART) that makes up this PhD research. It describes the design of the main HPTN 071 (PopART) trial in which the ComART study was nested, the study setting and design, study interventions and procedures, sample size, and ethical considerations. A methodological research paper is included in this chapter, which looked at numerous aspects of the study design, including why we chose a cluster non-inferiority design versus individual randomization, as well as anticipated problems, advantages, and downsides of this study design. This chapter summarizes the ComART study design, protocol development, data and statistical analysis plan and operational issues that were required prior to commencing the trial. The operational challenges and success of implementing these models of ART delivery are described in chapter 5 and more detailed information on the results of this trial are included in subsequent chapters.

4.2 Background to the HPTN 071 (PopART) Trial

The ComART trial was undertaken in 2 large Lusaka communities taking part in the HIV Prevention Trials Network (HPTN) 071(PopART) trial. Details of the main HPTN 071 (PopART) trial have been published elsewhere [95]. The HPTN 071(PopART) trial was a three-arm cluster randomized trial that compared the impact of community level combination prevention package, which included universal HIV testing, active linkage to care and immediate antiretroviral treatment for all HIV positive individuals, with standard care, on population level HIV incidence[95]. The trial was implemented in 21 communities of which 12 were in Zambia and 9 in South Africa. The trial intervention consisted of 3 main components within the PopART intervention as shown in figure 4.1 below:

Figure 4.1: PopART/HPTN 071 Trial Schema

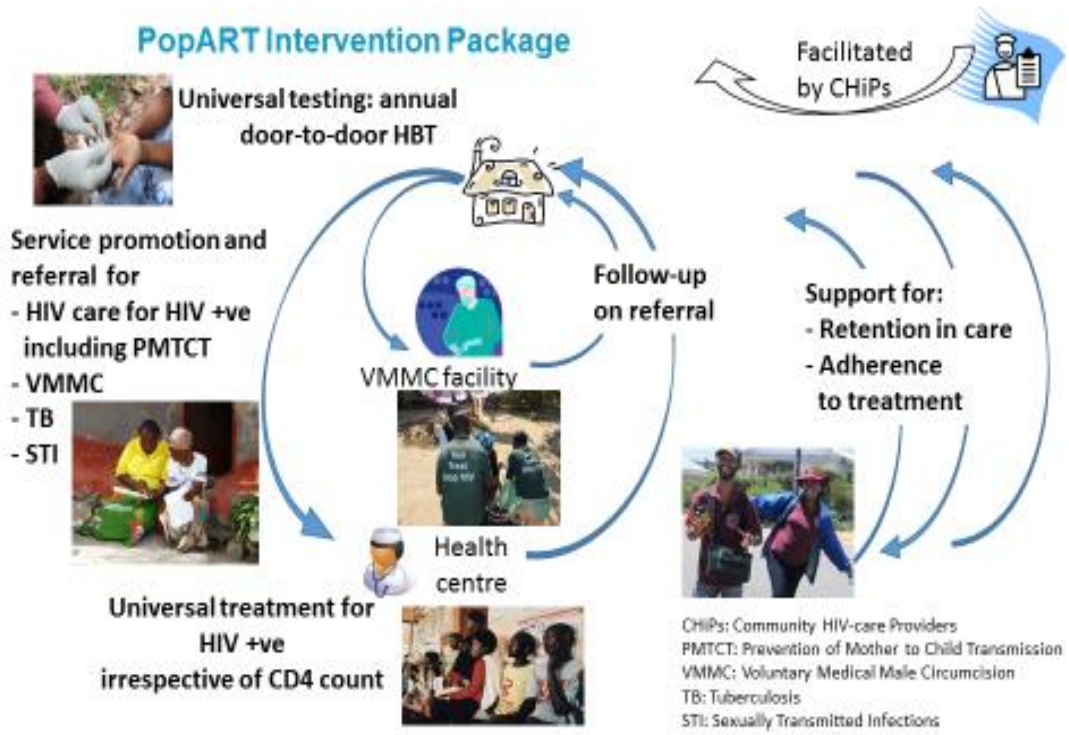


Source: HPTN 071 protocol

At the start of the trial ART initiation according to national guidelines in Arms B and C was CD4 <350 cells/mm^3 and then 500 cells/mm^3 in 2013 but as national guidelines adopted the 2015 WHO ART guidelines[6] both arms B and C transitioned to universal treatment in 2016. Since 2016 all individuals living with HIV in any of the 21 PopART communities were offered ART initiation irrespective of CD4 count. The household interventions were delivered by a cadre of staff specifically employed through the PopART study to implement the intervention package throughout the community. These Community HIV Providers (CHiPs) were themselves members of their local community, appointed to provide the PopART package of services at household level, particularly HIV counselling and testing, condom distribution, screening for TB, STIs and linking household members for appropriate HIV prevention, treatment and care services[24]. The CHiPs worked in pairs and in gender-balanced teams and were able to speak, read and write in English and be conversant with the local languages spoken in the communities[24].

They were able to record data using paper-based forms and electronic data capture devices. In addition, they were trained or had to be trained (after employment) in HIV testing and counselling services, adherence and psychosocial counselling, good clinical practice and basic knowledge on HIV and TB prevention, treatment, and care [95]. As they were members of the community, they were conversant with the local geography and able to walk long distances within the community. They also received all the appropriate training to ensure maintenance of client confidentiality. The CHiPs also went back to households throughout the annual "rounds "to ensure they picked up household members who were missed on previous visits and followed up PLHIV for linkage to care, ART adherence and TB/STI screening [Fig. 4.2].

Figure 4.2: Schematic overview of the PopART intervention package



Source: HPTN 071 trial protocol

The major findings of this trial revealed that a combined prevention package that included household HIV testing in addition to ART delivered in accordance with national guidelines resulted in a 30% reduced incidence of HIV infection than standard of care[201], although this effect was not seen within arm A communities who received exactly the same intervention as arm B but with universal ART from the beginning of the trial[105]. Other findings from the trial showed that delivery of the interventions resulted in high levels of HIV testing, knowledge of HIV status and treatment coverage[91]. The increase in knowledge of HIV status and timely linkage to the clinics for ART initiation or resumption was relevant for this nested study as more PLHIV were going to the clinic to initiate ART and therefore there was an urgent need to decongest the clinics.

4.3 Background to the nested ComART study: A comparison of different community models of ART delivery amongst stable HIV+ patients in two urban settings in Lusaka, Zambia.

Following implementation of the HPTN 071 (PopART) trial in 2013 and changes in the WHO guidelines in 2015 to initiate ART to all PLHIV irrespective of CD4 count, the demand for HIV treatment was seen as a challenge to the capacity of health care facility infrastructure. Without a paradigm shift in how ART care is delivered in resource-constrained settings such as Zambia, lifelong ART for all PLHIV would be unsustainable. Without a change in the current delivery model of ART care in resource-limited settings such as Zambia, lifelong ART for all PLHIV would be unsustainable. The HPTN 071 leadership, in-country PEPFAR implementing partners and Ministry of Health were concerned about the effect that congestion within the health care facilities would have on access to treatment and retention in care particularly in urban settings where there is a high concentration of HIV patients.

During this period there was a lot of interest in decentralizing ART care into the communities especially for those clients on stable ART, by focusing on innovative models of community ART delivery as a way of decongesting the clinics and improving patient outcome. As pilot projects on community models of ART delivery in sub-Saharan Africa yielded encouraging results, the Zambian Ministry of Health identified community models of ART delivery as a way of expanding and maintaining retention on treatment and through the National AIDS council, engaged several in-country partners and researchers to pilot different models of ART delivery in order to provide policy makers with evidence on patient outcomes, feasibility, acceptability and cost effectiveness of different models of ART[24].

The infrastructure that was developed through the main HPTN 071 (PopART) trial, in terms of the trained community HIV providers (CHiPs) provided a unique opportunity to test different models of ART delivery. At that time, the evidence base for community ART models were limited especially in urban settings and it was unknown which model of ART delivery was the best in terms of retention on ART and none of these models were compared to the standard of care with respect to clinical outcomes. Therefore, the ComART study was timely and innovative and designed to rigorously evaluate different community models of ART delivery and compare with the conventional model of care in an urban setting to provide critical information for the continued scale-up of universal ART.

For our study, we purposively selected Home-based ART delivery and Adherence clubs as our two intervention models over other DSD models for the following reasons:

1. At the time, the Ministry of Health had asked implementing partners and researchers to formally test in pilot studies different models of ART delivery, In-country partners had already piloted models of ART delivery that did not require the use of community health workers (multi-month dispensation, fast-track services and out-of-facility based care which included community adherence groups) and therefore this was an opportunity for me to determine whether these models outside the HCF would be feasible and effective using CHWs. This idea was also seconded by MoH and implementing partners who urged me to pilot these specific models as we were already utilizing the CHiPs to deliver HIV prevention combination package in these communities.

2. The CHiPs who were already in place through the ongoing PopART trial were well known and accepted by the communities they were working in and PLHIV were asking why they could not deliver ART drugs and provide adherence support during the household visits. In addition, the CHiPs who were not formally medically trained were very eager to take on this role of providing adherence support and pre-packed medications into the community. This was a unique opportunity to test home delivery and adherence club models for safety and effectiveness with the funding and support already generated through the early phases of the PopART intervention.

3. During the early stages of the main HPTN 071 (PopART) trial and planning stage of this nested trial, I worked with the HPTN 071 social science team in meeting with the community advisory board members and discussed the idea of having patients seen in their homes and community venues by CHiPs who would deliver pre-packed ART and adherence support to PLHIV. This was met with a lot of enthusiasm by the community advisory team. In addition, the CHiPs were

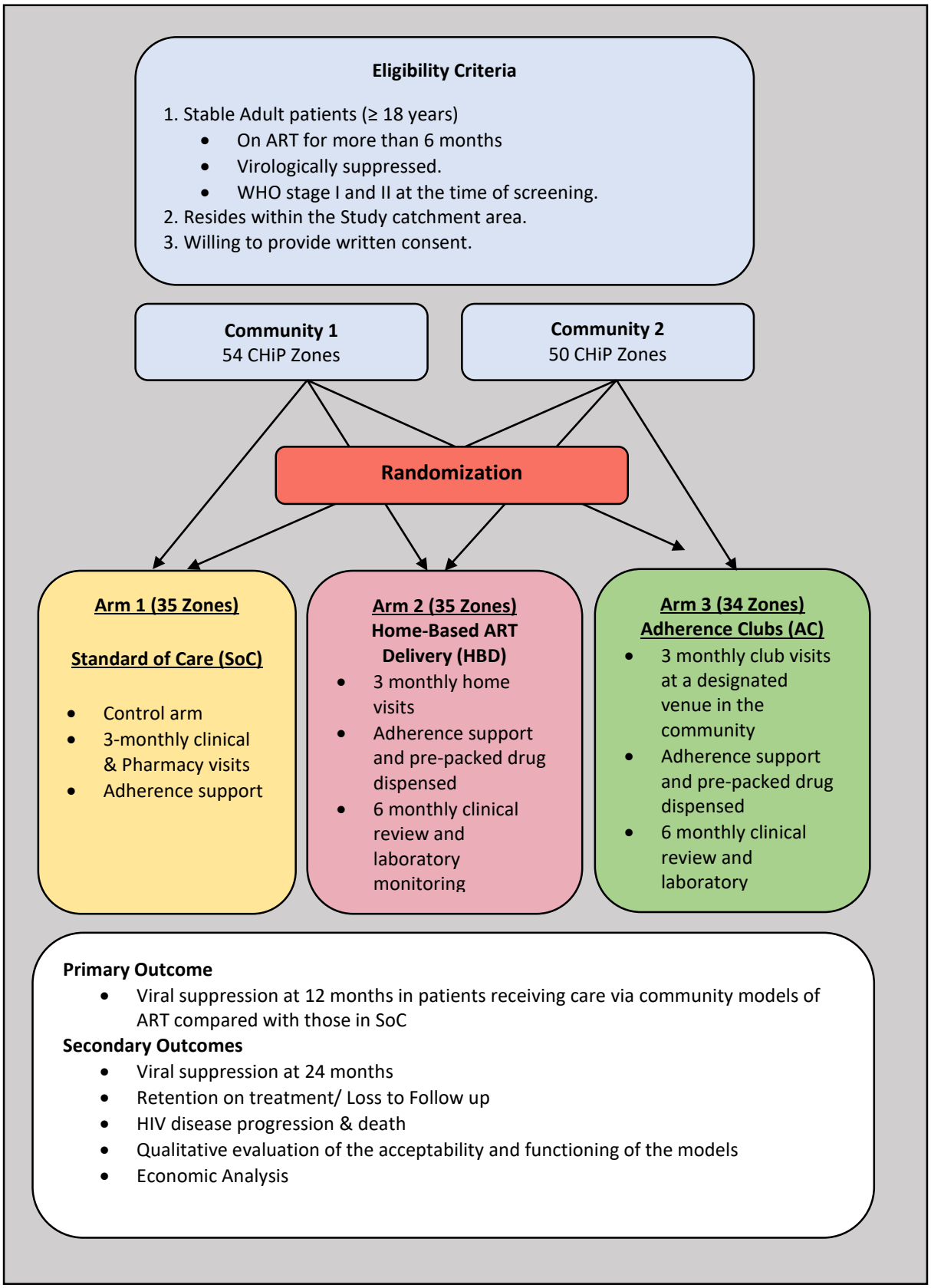
also asked to find out during their household visits from PLHIV whether these models of delivery would be ideal for them and their responses in having HIV care and support close to their homes was overwhelming.

4.4 Study Design

4.4.1 Overall design of the ComART study

Briefly, ComART was a three-arm cluster-randomized non-inferiority trial in a prospective cohort of adults already enrolled into ART care at two urban primary health care facilities that served two of the HPTN 071 trial communities in Lusaka, Zambia[24]. This included the HPTN 071 (PopART) trial is two intervention arms. The overall study design is summarized in Figure 4.1. And the full study protocol is available online [95]. The choice of a randomized trial was justified as in general a randomized comparison provides the highest level of evidence. At the time of ComART start, there was no information on how these models of community ART delivery would perform in comparison to the standard of care practice (clinic based ART drug distribution through facility based pharmacy) in Zambia. Further rationale and justification are described in the research paper included in this chapter.

Fig 4.3. Overview of study design and randomization scheme



4.4.2 Study Setting

The study was conducted in two urban communities/townships that were part of the HPTN 071 (PopART) trial communities. This included communities randomly allocated to arms A and B of the parent trial (HPTN 071) respectively. For our nested ComART study, it was irrelevant to which arm of the main PopART intervention the communities were allocated to as only those PLHIV on ART were enrolled. Both communities are predominantly low-income, high-density urban residential settings located about 10 km from the city centre and each of these communities had an estimated population of more than 120,000 people [95, 202]. Both communities have a mixed socio-economic status with predominantly poor residents the majority of whom are either employed in the informal sector, unemployed or low-paid jobs in the public and private sector [202, 203]. In each of these communities, health care services are provided by one government clinic which are currently overburdened due to the high number of HIV patients in care. Prior to the start of the HPTN 071 (PopART) trial, a census was conducted in all the communities that were taking part in the trial in 2013[24]. Both communities had an estimated population of over a 100,000 adults and children. At the time, the ComART study was designed in 2016, two years after the start of the main PopART trial, data derived from the main trial intervention showed an estimated HIV prevalence of approximately 20% amongst adults aged 18-44 years in both communities[24], and of these, an estimated 70% of all PLHIV were accessing ART [PopART intervention and Population Cohort data, 2016].

The two communities were purposefully chosen because they were randomized to the HPTN 071 (PopART) trial's intervention arms, where community HIV providers (CHiPs) were already in place to deliver the HIV combination prevention package through annual rounds of household visits throughout the entire communities[24]. Both communities have high HIV prevalence and high number of HIV patients in care (approximately over 10,000), with a high critical shortage of staff (1.2 physicians, nurses, and midwives per 1000 population)[204]. Before the start of the HPTN 071 (PopART) trial, mapping of the households and non-residential buildings was done, with a census to count the number of adults (16 years and older) and children (under 16 years of age)[24]. A map of the communities was created based on global positioning system (GPS) coordinates of all the households and non-residential buildings. In each of the communities, the PopART census covered a population of approximately 50,000 people.

Using the PopART census data in combination with the 2010 population census of the Zambian Bureau of Statistics, the intervention area was expanded to serve a population of approximately 100,000 people. The intervention community was subdivided into "zones" containing 400-500 households. CHiPs operated in pairs, with each pair in charge of a certain zone. The CHiPs repeatedly visited the households and in particular re-visited those households of PLHIV to ensure linkage to care, ART retention and adherence. Table 4.1 below shows the number of CHiPs teams/zones in the two communities with the population each CHiP team covered, and the number of HIV positive adults being cared for in each zone. Each zone was served by 2 CHiPs, giving them an average of 23-25 clients on ART who needed to be provided with ART within the community. For the ComART study, the CHiP zones were used as the unit of randomization to either receiving the model for ART delivery or standard of care.

Table 4.1: Total number of zones in the communities served by the CHiP teams

	Community 1 (54 Zones)			**Community 2 (50 Zones)**		
	HIV+ clients	**Total in care in the clinic**	**On ART in the clinic**	**HIV+ clients**	**Total in care in the clinic**	**On ART in the clinic**
Average per zone	99.3	56	51.3	98.6	56.38	46.7
Range in the zone **Min-max**	33-234	14-155	18 - 143	48 - 213	4 – 143	3 – 102

4.4.3 Study Population

Eligibility Criteria

All HIV+ adult patients (≥ 18 years) were screened for eligibility at the health care facility. The eligibility criteria included:

1. All adult patients who were stable. Guided by the WHO classification for stable patients[52], we included:
    - Patients on first line therapy for at least 6 months or more and retained in care
    - Virologically suppressed (using national guidelines [HIV RNA ≤ 1000 copies/ml] with a viral load taken in the last 12 months prior to screening
    - WHO stage I and II and did not require the attention of a clinician

2. Patients were residing within the main trial catchment area.

3. Willing to provide written informed consent.

4.4.4 Study Randomization

Our unit of randomization was a CHiP zone or "cluster", and the two communities were already divided into zones as part of the main trial. Both communities 1 and 2 were divided into 54 and 50 zones respectively and each zone consisted of around 500 households[24]. To achieve balance across the zones, statisticians from the London School of Hygiene and Tropical Medicine (LSHTM) stratified randomization by community and restricted the randomization within each community on average values of key outcomes that were measured during the PopART intervention rounds, which included population size, HIV prevalence, proportion of PLHIV who attended the health care facility, distance to the clinic to ensure overall balance across the three study arms[24].

A list of 10,000 randomized allocations meeting the restriction criteria was created for each of the communities, numbered 0000 to 9999. The 104 zones across both communities were randomized to one of the three arms:

1. Continue collecting ART at the clinic at the clinic standard of care (SoC) (control arm)
2. A choice of Home-Based ART delivery (HBD) or remaining in clinic-based care (SoC)
3. A choice of being in an Adherence club (AC) or remaining in clinic-based care (SoC).

Further details of the randomization ceremony and allocations are described in chapter 5.

4.4.5 Study Endpoints

For this trial, the primary endpoint was viral suppression at 12 months (+/- 3 months) after study entry across all three study arms. Virological suppression was defined as a VL ≤ 1000 copies (based on the parameters of any assay performed through routine laboratory monitoring).

Secondary endpoints include:

1. Proportion of patients virally suppressed at 20 and 24 months after study entry (as measured by last VL taken between 20 and 24 months after enrolment).
2. Proportion of patients lost-to-follow-up (LTFU) and died 12 months after study entry. LTFU was defined as having no contact >90 days after last missed scheduled appointment with unknown outcomes or the proportion of patients who are no longer retained on treatment with unknown outcomes after study enrolment.
3. Proportion of patients retained on treatment at 12 months after study entry. Retention on treatment during the study period was defined as a documented drug pick up within 120 days in the run up to 12 months after enrolment.

In addition to the above outcomes, the study also looked at the performance, acceptability, and feasibility of the two models of care using programmatic and routine health care facility data. This included patient choice of model of care, preferences, and retention within the intervention models of care.

4.4.6 Sample size and study power

The ComART study sample size was based on data that was derived from the first annual round of the main trial intervention. The number of adults who were known by the CHiP teams to be HIV+ and on ART averaged approximately 50 individuals per zone, with a harmonic mean of approximately 36 individuals per zone. Assuming that 80% of such adults agreed to participate in the study and had not moved out of the community within 12 months after enrolment, the number of study participants per zone who would contribute to the primary endpoint measurement would have a harmonic mean of approximately 30. Our study power calculations were done with an assumption that an average of 30 study participants per zone would contribute to the primary outcome measurement and given there were 104 zones randomized to the 3 arms this gave an estimated overall total sample size of 3120 participants. We also assumed that among study participants in the "standard-of-care" arm, the percentage who were *not* virally suppressed, 12 months after enrolment to the study would be in the range of 10-15%[24]. We fixed the non-inferiority margin to be at 5%. The NI margin of 5% was chosen based on clinical judgement as to what would be a meaningful increase in non-suppression from our prior estimate of 10% and was also guided by similar trials [31, 32, 205].

The coefficient of variation k, of the variation across zones in the percentage of study participants who were *not* virally suppressed at 12 months after study enrolment, was assumed to be in the range 0.25 to 0.3. If the percentage of participants who were *not* virally suppressed at 12 months after study enrolment is 10% in the "standard-of-care" arm, and k=0.25 or k=0.3, study power is 93% and 91% respectively to show that a trial intervention arm is not inferior to "standard-of care". The corresponding study power figures are 78% and 74% if the percentage of participants who are *not* virally suppressed at 12 months after study enrolment is 15% in the "standard-of-care arm". So, the study, for our expected sample size, was estimated to have a power of between 74-93% under a range of different scenarios (Table 4.2). Our estimate of 10% of those not virally suppressed is consistent with research data from these two communities.

Table 4.2. Study power to show that community ART provision is not inferior to standard-of-care, in terms of patient viral suppression 12 months after either enrolling into community ART or continuing with standard-of-care at the clinic.

Standard of care, % not virally suppressed at 12 months after enrolment	Non-inferiority Margin	Coefficient of variation k	Number of participants per cluster	Study power (%)
10%	5%	0.25	30	93%
15%	5%	0.25	30	78%
10%	5%	0.30	30	91%
15%	5%	0.30	30	74%

4.4.7 Description of the study interventions

The ComART study had three arms of which two were intervention arms and one the control arm. The interventions included Home-based ART delivery (HBD) and Adherence clubs (AC).

A. Home-based ART delivery

In this model, clinically stable patients received ART in the comfort of their own homes. CHiP teams would visit participants' homes every three months to give adherence support, symptom screening, and pre-packaged antiretroviral medications. In accordance with Zambian government monitoring requirements, participants were only required to visit the clinic once every six months (twice a year) for their routine clinical assessment and annual laboratory monitoring of CD4 count, HIV viral load, and serum creatinine. Table 4.3 below provides a broad overview of the models of care.

B. Adherence Clubs

Adherence clubs were made up of at least 20-25 stable patients who received HIV care in the community. The CHiP teams provided adherence support, symptom screening, and pre-packaged drugs to members of the club once every three months at an agreed communal venue. Club members were obliged to have two clinical/club visits per year (every six months) for routine clinical review and laboratory monitoring. [Table 4.3].

Table 4.3: Broad Overview of the three ART delivery models.

	Home Based Delivery (HBD)	Adherence clubs (AC)	Standard of care (SoC)	Comments
	Clients visited in their home by the CHiPs	Group of 20-30 clients met at an agreed community venue led by a pair of CHiPs	Clients visited the clinics as scheduled	
Number of visits/years	2 HBD 2 clinics	2 clubs 2 clinics	4 clinics	
ART dispensed	3 months	3 months	3 months	
Routine Laboratory testing	Every 6 months • CD4 • Creatinine /LFTs Every 12 months • Viral load	Every 6 months • CD4 • Creatinine /LFTs Every 12 months • Viral load	Every 6 months • CD4 • Creatinine /LFTs Every 12 months • Viral load	As per routine national guidelines
Frequency of clinical monitoring	2 (every 6 months)	2 (every 6 months)	2 (every 6 months)	
Process	• Symptom screening ǂ • Adherence support • Health education & provision of condoms • Dispensation of pre-packed drugs	• symptom screening ǂ • Adherence support • Group education and provision of condoms • Dispensation of pre-packed drugs	• Symptom screening ǂ • Adherence support • Health education and condom provision • Drug dispensation at pharmacy	

ǂ symptom screening included a checklist to determine if patient were experiencing any of the following symptoms: Cough, fever, night sweats, weight loss, headache.

C. Current standard of care in the management of stable HIV+ patients on ART in Zambia

All "stable" potentially eligible PLHIV on ART for more than 6 months were recommended to come to the ART clinic once every 3 months for adherence counselling and positive health dignity and prevention (PHDP) messages and collect their drug refill. At 6 monthly visits, patients would be reviewed by a clinician with a targeted history and examinations, screened for TB and STIs and laboratory monitoring including CD4 count, Liver function tests, and creatinine clearance. Viral load was done 12 months after ART initiation and thereafter annually. Patients who had undetectable viral load were switched to second-line regimen and a vial load was taken 6 months post switching to determine if they were undetectable.

Although the standard care included patients making quarterly visits to clinic, this was far from the reality as the high number of patients on ART resulted in overcrowding, long queues, missing clinical appointment and drug stock-outs, resulting in patients being given 1-2 months drug supply and therefore having to make more frequent visits to collect their drugs and have the laboratory tests done.

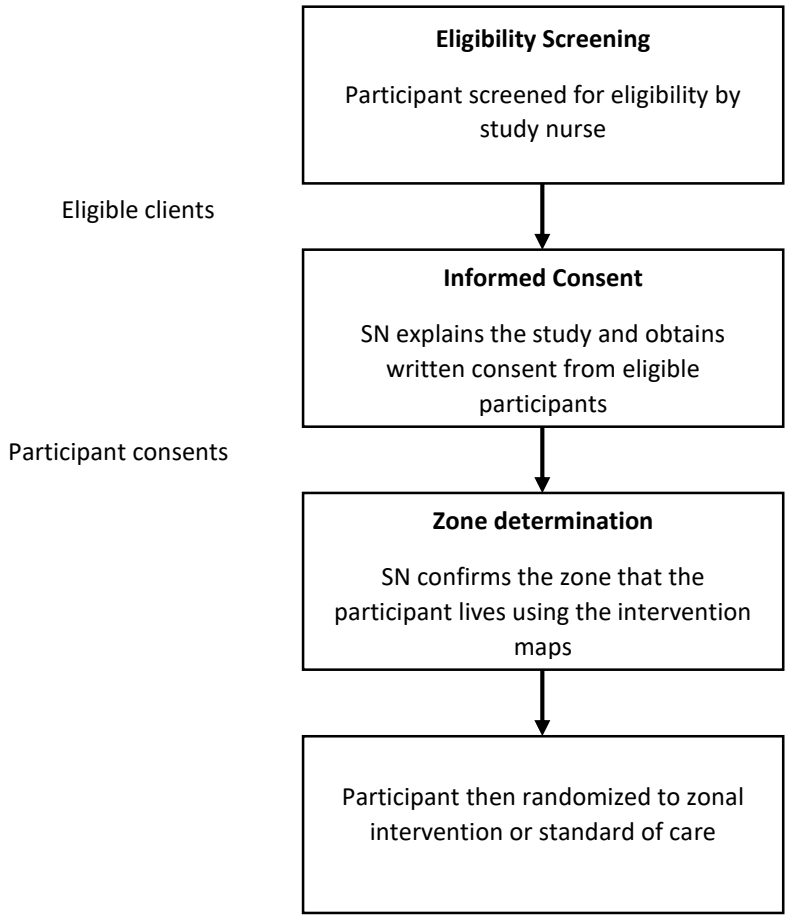
4.5 Study procedures

This section describes the study procedures. Details of each of these procedures and how they were carried out are further described in the subsequent implementation chapter [Chapter 5].

4.5.1 Screening and recruitment

All HIV+ Patients were screened for eligibility at the clinic. These were done by the study nurse and clinic staff. Potential candidates were referred to the study nurse for eligibility screening using a standardized eligibility screening form. The diagram below [Fig 4.4] shows the steps in recruitment.

Fig 4.4. Steps in recruiting participants.



Once a patient was screened and found to be eligible to participate in the study, a written informed consent was obtained after having explained the study in detail. If a participant agreed to consent, the study nurse would then determine which zone they were living in using the HPTN 071 trial intervention map. Having identified the zone, the participant's random allocation would be revealed to them. Those who were allocated to the intervention arms were then given a choice of the allocated intervention or to continue receiving care at the clinic (SoC). Participants allocated to the control arm did not have this option.

4.5.2. Follow-up of study cohorts

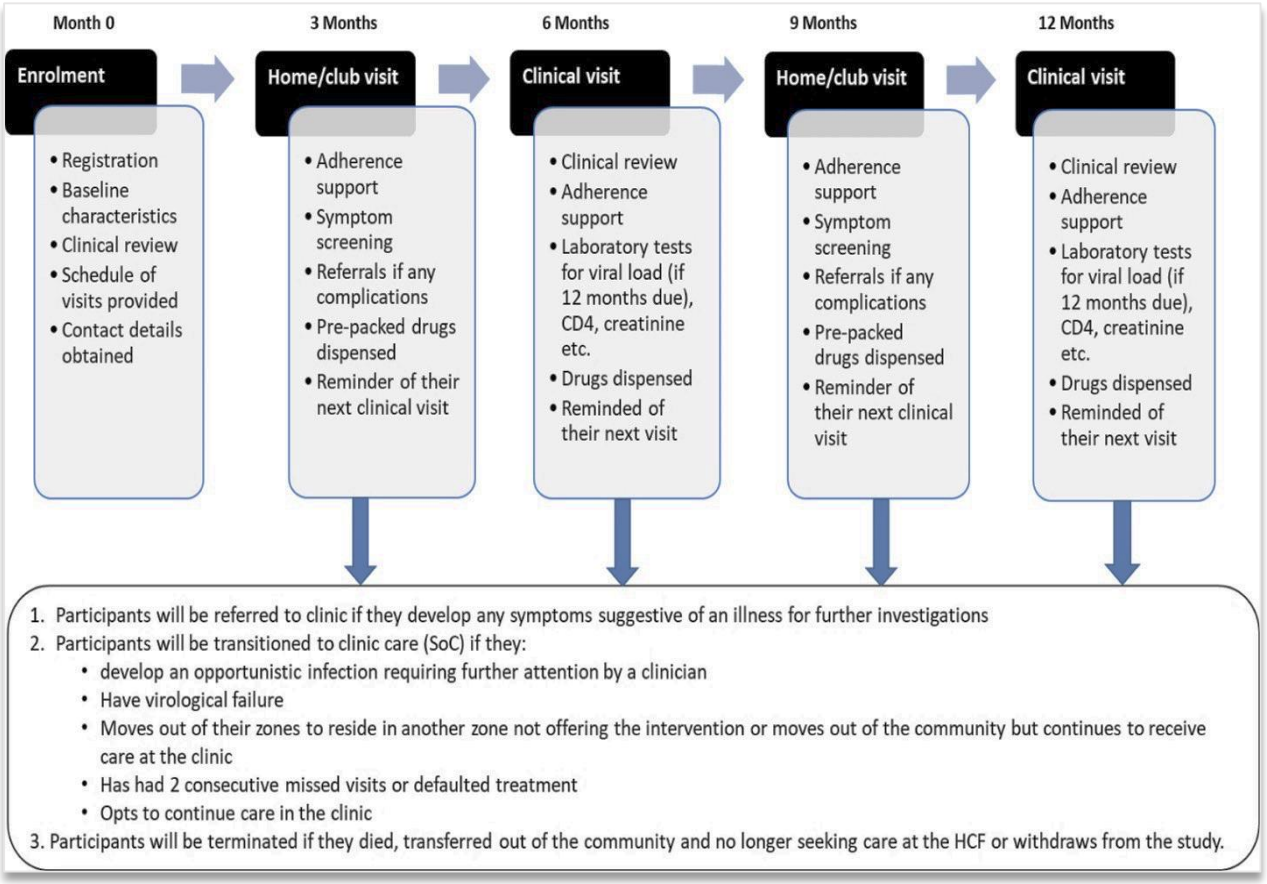
I. Schedule of Home and Club Visits

In both the intervention arms, participants were followed up once every 3 months. Following enrolment, participants were seen after 3 months in their homes or clubs and thereafter 3 months later at the clinic [Fig.4.5]. In a year, participants would only have to attend 2 clinical visits, every 6-monthly. All the participants were followed up for a minimum of 14 and a maximum of 24 months depending on the date of enrolment. Activities that were conducted during each visit are outlined in Table 4.3 above and figure 4.5 below.

II. Clinical visit every 6 months

The clinical visits that would occur every 6 months for participants in the intervention arms and SoC were part of the routine standard of care that was being provided in HIV care. This included a clinical review and routine laboratory tests that were due at the particular visit [Fig.4.5]. Viral load monitoring that measures the study's primary outcome was collected during these clinical visits. As participants were not necessarily enrolled at the time of their annual VL measurement, some adjustment of the timing of VL test were made to ensure that all fell within 9-15 months of enrolment. At every clinical visit, the study nurse would check when participants were due for a VL test and order a test if they were due. Participants were then required to collect their 90 days drug supply from the pharmacy and their next appointment date either in the club, home or SoC were provided to them.

Fig 4.5. Follow-up schedule for participants enrolled in the intervention arms



III. Transitioning participants to SoC.

Participants would be transitioned to clinic care (SoC) if:

1. Opted to go back to clinic care
2. Required a clinician's attention (treatment failure based on VL assays, developed WHO stage 3 and 4 conditions)
3. Moved out of their zone either outside or within the study catchment area. If a participant moved out of their zones into another zone offering a different intervention, they were transitioned to SoC.
4. Missed more than 2 scheduled appointments either at home or the club
5. Broke the clubs code of conduct
6. Moved out of the community but opted to continue care at the study clinic

Participants who were randomized to standard of care followed the visit schedule according to the national guidelines and information on their visits and laboratory monitoring were obtained using their clinic records. In all the three study arms, participants were terminated or withdrawn from the

study if they withdrew consent for study participation, opted to transfer their care to another health care facility or died.

IV. Missed visits

In both intervention arms, participants who missed a scheduled visit were followed up and either given a rescheduled visit date or had to come to the clinic. Details regarding a missed or rescheduled visit are described in the subsequent chapter [Chapter 5]. Any missed or rescheduled visits and reasons would be recorded in the study event forms.

V. Study exit plan

Prior to the end of the study, the research team planned with implementing partners and health care facility staff on transitioning participants from the intervention models to either standard of care or other DSD models that were in place in that particular community.

4.6 Data Management and Analysis

4.6.1 Data Collection

As the study endpoint was prospectively collected routine data gathered for monitoring and evaluation purposes for the National ART program, all participants were identified using their unique clinic numbers. Data collected was from three sources:

I. Clinic data

Routine data was collected at baseline, 6 months, and 12 months and at the end of the study period using the Ministry of Health electronic SmartCare database and patient clinic records. SmartCare database was developed by the Ministry of Health with support from United States Centre for Disease Control and Prevention (CDC) to improve continuity of care and monitoring and evaluation of HIV programs countrywide. Since 2005, the SmartCare database has been deployed to all health care facilities providing ART care.

At base line, the following variables were collected from patient files to determine their influence on the study outcomes: Sex, Age, Date of starting ART, Viral load in the last 12 months, CD4 count, WHO disease stage, and current ART regimen. During the course of the study, variables such as Viral load, CD4 counts, WHO stage, deaths, Loss-to-follow up and ART regimen were obtained using both clinical records and SmartCare database. To ensure the validity of these data, the study team collaborated closely with the health care facility to improve data collection and management.

During the course of the study, the study team also ensured that viral load results were being entered in the database and worked closely with the implementing partners to ensure that missing viral load results were traced and entered in the database.

II. Community SmartCare Module

The community SmartCare module, a pilot project initiated by the Ministry of Health aimed at collecting data for patients in DSD models outside the health care facilities was also used in our study. Data regarding ART registration details, date of community visit, symptom screening (fever, weight loss, cough, headache), pregnancy screening, adherence counselling, referrals and drug dispensation were collected using an electronic handheld device which was linked to the national HIV SmartCare database at the clinic.

III. Study related forms

In addition to collecting routine clinic and SmartCare data, we also collected data to assess the study's outcomes and processes. This included the clinical register, eligibility/enrolment forms, club and home registers, attendance registers, study event forms, termination forms and drug scripts. These forms are included in the appendices [Appendix III] and an overview of the forms and information collected are summarized in Table 4.4 below. In addition, these forms were also designed to collect data from the SmartCare module as a back-up since the community SmartCare module was still in a pilot phase.

IV. Qualitative data

Collection of qualitative data was designed as a secondary and complementary component to the quantitative methods. Social scientists from Zambart collected this data in order to ensure fair representation of the study sites. FGDs and audio-recorded in-depth interviews (IDIs) were used as research methods. Purposively sampling was also employed to select PLHIV from a variety of age and gender categories, as well as from a variety of geographic areas and socioeconomic status groups. Both FGDs and IDIs were conducted during the study period and towards the end of the study. IDIs were used to collect data from PLHIV, while FGDs were utilized to collect data from CHiPs that delivered the intervention. All IDIs and FGDs were then transcribed, and field notes were expanded and analysed using Office 2016 and Atlas.ti 7.

Table 4.4: Overview of the study related forms and data collected

	Study related documents	Purpose and type of Data collected
1.	Eligibility/enrolment form	This form was used to determine if a patient was eligible for the study. The following information was captured: • Date of screening for eligibility • If the patient met the study inclusion criteria • Date of his last VL test and result • Date of starting treatment and current ART regimen • If the patient consented to the study • Zone that the patient resides in • Study arm patient was allocated to and whether they take the offer of the intervention or continue with SoC • If patient had a preference or not and preference expressed
2.	Home-based register	This register was used for planning the home visits for participants in the HBD model of care. The following data was collected: • Date of enrolment • zone patient resides in • dates of scheduled home and clinical visits for the next 12 months • VL results • Participants contact number • CHiP team responsible for their home visits
3.	Adherence club register	This register was used for planning club visits for each zone. The following data was collected: • Date of enrolment • Zone patient resides in • Club number • Dates of scheduled club and clinical visits in the next 12 months • VL results • Participants contact number • CHiP team responsible for the club
4.	Attendance registers	This were paper based forms that were used by the CHiPs when conducting home and club visits. Attendance registers for HBD were pre-filled with the patient names, date of visit and scheduled visit dates for the clinical visit. Similarly, for AC the club member's names were pre-filled on a single paper register and their next clinical visit. During the visits, the following information was collected: • Was the participant present for that visit • Symptom screen checklist • Types of counselling provided • Were the drugs dispensed • If the participant required a referral to the clinic
5.	Study Event form	These forms were used when a patient was transitioned to SoC for the following reasons:

		• Relocated to another zone not offering the intervention but continue care at the study HCF • Transferred out of the community but continues with HIV care at the study HCF • Had an opportunistic infection and needs further management • opts out of the models of care to continue with SoC
6.	Drug scripts	These duplicate scripts were pre-filled with the patient's name and ART number prior to their visit dates: • date of visit • drug regimen • quantity dispensed • patient signature • Contact names of the CHiPs delivering the drugs.
7.	Termination form	This form was used when a patient was terminated for the following reasons: • withdraws from the study • died • lost to follow-up • Transfers out of the community and seeks HIV care in another facility.
8.	Clinical register [this register was created during the implantation period when challenges with aggregating data from SmartCare was observed	This register included all the participants in the study [SoC, HBD and AC]. It was updated on a 2-monthly basis as data for SoC patients had to be retrieved form SmartCare. Information collected included: • ART number and model of delivery • Date of drug dispensation and quantity • Viral load results at baseline and during follow-up • WHO staging during clinical visits? • CD4 count according to routine • Outcomes – LTFU, died, transfer, HIV opportunistic infections

4.6.2. Data Management and Cleaning

All hardcopies of the study records were kept in a secure location only accessible to authorized study staff, investigators, and monitors. Data security was ensured through password-protected databases accessible only to a selected group of people involved in the study. Data collected on the study forms underwent quality control by the study staff including myself and this included alerts for missing and abnormal values on a weekly basis and transferred to Zambart headquarters fortnightly where it would be double entered centrally, and inconsistencies were clarified by reviewing hard copies of the questionnaires by the data team and stored on the SQL server where standard access was in control. The data was retained in a central location until the study's data analysis was completed. Clinic and SmartCare data were periodically extracted after having sought permission from the Ministry of Health and Implementing partners. Data was imported in STATA (version 16.0).

I also conducted monthly quality assurance of all the data collected with help from the research nurses. Data cleaning prior to any analysis was my responsibility and any missing data found was counterchecked with the facility clinic records and SmartCare database.

4.6.3 Data Analysis

Data analysis was performed using STATA (version 15 and 16.0). For all comparisons by study arms, we used 'Intention to Treat' (ITT) analysis, with participants analysed according to the arm to which they were randomized. In addition to ITT, we also performed a 'Per-Protocol Analysis' (PPA) comparing the intervention arms to those who received the control arm[24]. Detailed analysis methods used for the specific objectives are described in the research paper in this chapter and subsequent chapters presenting papers addressing the objectives.

4.7 Ethical considerations

4.7.1 Informed Consent

Written informed consent (Appendix 4) was sought from all eligible participants attending the study health care facilities. Consent was done by trained staff (Research nurses and Pharmacists) who completed the CITI Human Subject Protection (HSP) training, Good Clinical Practice (GCP) training and study protocol training which included informed consent, confidentiality, interview techniques and study tools. All in-depth interview participants provided written and verbal agreement, including permission to record the interviews and publish anonymous quotations. FGD participants were asked to provide verbal consent. Participants were informed that they retained the right to withdraw at any stage from the study interventions. Those who withdraw from the intervention arms were transitioned to continue care at the clinic whilst remaining in the study. Eligible clients were provided with the following information either in English or local language as part of informed consent:

1. *Objectives of the study*
2. *Models of ART delivery being offered*
3. *Explanation that:*
    - *Participation is voluntary and can withdraw at any stage*
    - *Refusal to participate or withdrawing from the study will not affect their services they receive from the clinic*
    - *What will happen during the course of the study and potential benefits and risks*
    - *What will happen if they belong to an adherence club, home delivery or standard of care model*
    - *Participants responsibilities*
    - *How their confidentiality and privacy be protected*
    - *No information will be divulged to partners or other third parties*
    - *What will happen when the study ends or is discontinued*
4. *Contact details of the investigator, research nurse and CHiP team*

4.7.2. Confidentiality

Participant names and ART identification number were used in all forms and securely stored with access by study and clinic staff. Personal names were used only for tracing information and privacy was maintained during intervention visits.

4.7.3 Participants Risks and Benefits

We did acknowledge that there might be breach of confidentiality as other community members could learn of the study participant's status. The study team did everything possible to ensure that confidentiality was maintained and the study staff and CHiPs team who conducted these models of delivery in the community were trained in maintaining confidentiality. In addition, being part of an adherence club would mean that other members of the club would know the status of their group members that may result in unintended disclosure or stigma. All members of the club had to sign a "club charter of rights and responsibilities" which included a commitment to maintain confidentiality.

There was no direct and immediate benefit in terms of monetary and/or material benefit during and/or at the end of the study. For this reason, the participants were made aware that their involvement was entirely optional and that they might opt out at any time. Benefits anticipated to the participants included less frequent travel to the clinics for their pharmacy refill; reduce waiting time and privacy within the clubs and their homes.

4.7.4 Regulatory review

The University of Zambia Biomedical Research Ethics Committee (UNZABREC), the National Health Research Authority (NHRA), and the London School of Hygiene and Tropical Medicine (LSHTM) Ethics Committee all provided ethical approval [Appendix I]. Following ethical approval, the protocol was reviewed and approved by the Division of AIDS (DAIDS), the primary sponsor of the HPTN071 (PopART) study, who granted us permission to conduct this study as an ancillary study to the main HPTN 071 trial and registered at ClinicalTrials.gov [NCT03025165].

4.8 Funding

Funding for this study was embedded within the main HPTN 071 (PopART) trial. Most of the activities were already being carried out by staff already in position (Research team, CHiPs) in the main trial. Additional budget lines needed to support additional requirements for data, pharmacy and field staff were covered via the revised HPTN 071 budget which was put in place through research and PEPFAR country operating plans.

4.9 Research Methodology Paper 2: A comparison of different community models of antiretroviral therapy delivery with the standard of care among stable HIV+ patients: rationale and design of a non-inferiority cluster randomized trial, nested in the HPTN 071 (PopART) study.

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

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SECTION A – Student Details

Student ID Number	lsh 1602448	**Title**	Dr
First Name(s)	Mohammed		
Surname/Family Name	Limbada		
Thesis Title	A comparison of different community models of Antiretroviral Therapy delivery among stable HIV+ patients in an urban setting, Zambia		
Primary Supervisor	Prof Helen Ayles		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	BMC - Trials		
When was the work published?	12th January 2021		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	ML wrote the first draft of this manuscript. HA, SF, DM, SF, AS, and RH read and revised the manuscript and approved the final version. ML, HA, SF, and RH originally convieved and designed the trial in consucltation with the HPTN 071 protocol team and executive committee. SF, DM, and AS helped design the statistical framework of the trial and contributed to all drafts of this manuscript. The authors read and approved the final version.

SECTION E

Student Signature	[redacted]
Date	

Supervisor Signature	[redacted]
Date	

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Trials

METHODOLOGY Open Access

A comparison of different community models of antiretroviral therapy delivery with the standard of care among stable HIV+ patients: rationale and design of a non-inferiority cluster randomized trial, nested in the HPTN 071 (PopART) study

Mohammed Limbada[1*], Chiti Bwalya[1], David Macleod[2], Sian Floyd[2], Ab Schaap[1,2], Vasty Situmbeko[1], Richard Hayes[2], Sarah Fidler[3], Helen Ayles[1,4] and on behalf of the HPTN 071 (PopART) Study Team

Abstract

Background: Following the World Health Organization's (WHO) 2015 guidelines recommending initiation of antiretroviral therapy (ART) irrespective of CD4 count for all people living with HIV (PLHIV), many countries in sub-Saharan Africa have adopted this strategy to reach epidemic control. As the number of PLHIV on ART rises, maintenance of viral suppression on ART for over 90% of PLHIV remains a challenge to government health systems in resource-limited high HIV burden settings. Non facility-based antiretroviral therapy (ART) delivery for stable HIV+ patients may increase sustainable ART coverage in resource-limited settings. Within the HPTN 071 (PopART) trial, two models, home-based delivery (HBD) or adherence clubs (AC), were offered to assess whether they achieved similar viral load suppression (VLS) to standard of care (SoC). In this paper, we describe the trial design and discuss the methodological issues and challenges.

Methods: A three-arm cluster randomized non-inferiority trial, nested in two urban HPTN 071 trial communities in Zambia, randomly allocated 104 zones to SoC (35), HBD (35), or AC (34). ART and adherence support were delivered 3-monthly at home (HBD), adherence clubs (AC), or clinic (SoC). Adult HIV+ patients defined as "stable" on ART were eligible for inclusion. The primary endpoint was the proportion of PLHIV with virological suppression (≤ 1000 copies HIV RNA/ml) at 12 months (± 3months) after study entry across all three arms. Viral load measurement was done at the routine government laboratories in accordance with national guidelines, annually. The study was powered to determine if either of the community-based interventions would yield a viral suppression rate drop compared to SoC of no more than 5% in its absolute value. Both community-based interventions were delivered by community HIV providers (CHiPs). An additional qualitative study using observations, interviews with PLHIV, and FGDs with community HIV providers was nested in this study to complement the quantitative data.

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* Correspondence: Mohammed@zambart.org.zm
[1]Zambart, University of Zambia, School of Medicine, Zambart House, Ridgeway Campus, Off Nationalist Road, P.O. Box 50697, Lusaka, Zambia
Full list of author information is available at the end of the article

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Discussion: This trial was designed to provide rigorous randomized evidence of safety and efficacy of non-facility-based delivery of ART for stable PLHIV in high-burden resource-limited settings. This trial will inform policy regarding best practices and what is needed to strengthen scale-up of differentiated models of ART delivery in resource-limited settings.

Trial registration: ClinicalTrials.gov NCT03025165. Registered on 19 January 2017

Keywords: HIV, Anti-retroviral therapy, Home-based ART delivery, Adherence clubs, Zambia

Background

Survival for people living with HIV (PLHIV) has dramatically improved with access to potent safe antiretroviral therapy (ART) [1]. However, to be effective, this treatment is currently delivered as daily oral tablets that require lifelong adherence [2]. Failure to adhere to treatment leads to viral recrudescence, clinical symptoms associated with immune dysfunction, increased risk of HIV transmission, and potential development of drug resistance [1].

The scaling up of antiretroviral therapy (ART) has been one of the most remarkable public health achievements in the last decade [3, 4]. There are an estimated 37 million PLHIV globally of whom 21 million are currently accessing ART. Sub-Saharan African countries home to approximately 19.4 million PLHIV have implemented an unprecedented scale up of ART especially in East and Southern Africa [3]. However, *how* to deliver sustainable, affordable ART to all PLHIV is an unanswered question that challenges global HIV care programs in high HIV burden limited resource settings.

Maintaining patients on ART requires a robust framework to monitor processes, outcomes, and long-term impact both at individual and programmatic levels. Retention on ART is a crucial indicator both at individual and programmatic levels and patient outcomes may be threatened if ART retention is poor or deteriorating [5–10]. Adherence to ART is necessary for individual patient outcomes as well as to reduce the risk of drug resistance from a public health perspective [11, 12]. Many studies have identified existing fragile health systems, inadequate human resources, transportation costs, frequent pharmacy pick-ups, and long waiting times at the clinic as significant barriers to ART retention in resource-limited settings [13–18] and without a change in the current model of ART delivery in resource-limited settings, lifelong ART for PLHIV may be unsustainable. As treatment coverage increases in the coming years, it is unlikely that human, financial, and physical resources will grow in proportion to this increase and there is therefore an urgent need to develop innovative models of ART delivery that can be implemented sustainably without compromising the quality of care.

Decentralization of HIV services to community level may be an important strategy to improve sustainability of programs [18]. Community models of ART delivery are one example of decentralizing HIV services from the health care facilities to the community. These models have been developed in various resource-limited settings and hold the promise of improving the continuum of care by decongesting the clinics and strengthening community engagement by linking community-based programs with the health care facilities [1, 19, 20].

Furthermore, the 2015 WHO guidelines [2] have recommended the provision of ART services in the community, but there is need for operational guidance and further evidence for this to happen in practice [1]. This resulted in the development of the "Differentiated Care" framework which has been defined as a client-centered approach that simplifies and adapts HIV services across the cascade, in ways that serve both the needs of PLHIV better and reduce unnecessary burdens on health systems [21].

The purpose of the framework is to provide guidance on how to address the barriers to treatment access and retention in care by optimizing models of care and drug delivery [21, 22] and focuses on stable patients who are defined as PLHIV adherent to treatment, who have no opportunistic infections and do not require frequent clinical consultations. However, this definition varies across different models dependent on access to resources, such as viral load monitoring [21].

Evidence base of community models of ART delivery in resource-limited settings

Several studies have assessed the feasibility of community models of ART delivery in sub-Saharan Africa where the facility serves as the referral site, showing favorable outcomes in relation to retention in care and viral suppression [23, 24]. While 2 randomized trials have been conducted in Kenya and Uganda comparing home-based ART delivery to facility-based care [25–28], as well as observational studies on different models of ART delivery [23, 24, 29–33], most of these studies have been implemented in rural areas where patients live far from the health care facilities. We want to understand how such models would work in overcrowded, urban communities where community cohesion may be more limited. There is still a lack of evidence about which model is the most feasible and cost effective or whether

patient outcomes will be as good as the current standard quality of care in high prevalence urban resource-limited settings. Therefore, additional data are required from alternate models of ART delivery that support long-term retention and virological suppression and evaluate which is the most feasible to fit into the current health system and community as well as the most-cost-effective strategy.

Our trial differs from the previous two trials described above in several aspects. Firstly, this will be the first study to rigorously evaluate two different models of ART delivery, home-based ART delivery and adherence clubs in a high HIV prevalence resource-limited urban setting in SSA compared to SoC for ART delivery. Secondly, this study uses a cluster-randomized trial design to do a non-inferiority comparison between SoC and each of the two models of community ART delivery. Finally, this trial will be able to assess the effect of shifting patients from routine ART care into the community and assess patient preferences and satisfaction unlike the trials conducted in Uganda and Kenya [25–28].

We designed a three-arm cluster-randomized non-inferiority trial comparing two different community model of ART delivery with the current standard of care to gather evidence on the impact of these models on patients' clinical and virological outcomes, operational feasibility, acceptability, and cost-effectiveness to guide policy makers on best models to roll out in the context of universal treatment. An additional exploratory qualitative study was nested in this trial to complement the quantitative data. The reason for choosing this mixed-methods approach was to gather robust data to determine whether delivering ART and support outside the health care facility by community workers is safe and feasible and using viral suppression as our primary endpoint. In addition, several underlying social-contextual and health system factors such as delivering drugs outside the health care facility to patient homes or clubs, invasion of privacy, and community-based stigma needed to be explored. This design enabled us to robustly explore the safety, efficacy, acceptability, and feasibility of these models of ART delivery.

This paper looks at several aspects of our study design including why we chose a non-inferiority design, cluster versus individual randomization, as well as anticipated challenges, advantages, and disadvantages of the study design.

Methods

Study setting

This study was nested within the recently published HPTN 071 (PopART) trial and full details of this trial have been described elsewhere [34]. Briefly, HPTN 071 (PopART) was a cluster randomized trial done in 21 communities in Zambia and South Africa to estimate the effect of a combination HIV prevention package, which included door-to-door HIV testing services, linkage to care, immediate ART for HIV-positive individuals, and promotion of male circumcision for HIV-negative men, on HIV incidence between 2014 and 2018 [34]. Our nested study was conducted in the catchment population of 2 urban primary health care facilities that served two of the HPTN 071 trial communities in Lusaka, Zambia. The two sites were purposively selected for the following reasons:

1) Both communities were randomized to the intervention arms of the main HPTN 071 (PopART) trial, where community HIV care providers (CHiPs) were already employed to deliver the HIV combination prevention package through annual rounds of household visits throughout the entire communities.
2) Both communities have a high number of HIV patients in care (approximately 10,000) with a critical shortage of staff (0.8 per 1000 population) (http://www.aho.afro.who.int/profiles_information/index.php/Zambia:Health_workforce_-_The_Health_System) and are therefore an ideal setting to determine if these models of ART delivery benefit the health care facilities by decongesting the clinics and making treatment easier to access.

At the time of the study design (in 2016), the two communities had an HIV prevalence of approximately 20% among adults aged 18–44, and an estimated 70% of all PLHIV were accessing ART. This trial utilized existing CHiPs from the HPTN 071 trial to deliver the interventions. The CHiPs are trained members of the community, appointed to provide a package of basic services at household level, particularly HIV counseling and testing, screening for tuberculosis and sexually transmitted infections and linking household members for appropriate HIV prevention, treatment, and care services. The CHiPs work in pairs within allocated zones of the community (each zone consisting of 450–500 households), and this provided our study with the unique opportunity for them to provide the study intervention such as adherence support, symptom screening, and dispensation of pre-packed medications, while the CHiP zones offered a convenient and appropriate unit of randomization.

Study design

This study was a three-arm cluster-randomized non-inferiority trial in a cohort of adult HIV+ patients on treatment in two urban health care facilities. Prior to the start of the main HPTN 071 (PopART) trial, mapping of the households and non-residential buildings was done,

with a census to estimate the total number of adults and children allowing us to define a population of approximately 100,000 people per community to be included in the door-to-door intervention. This "intervention population" was then sub-divided into "CHiP zones" with each zone consisting of around 500 households and served by a pair of trained CHiPs. An additional qualitative study using observations of home delivery and clubs, interviews with PLHIV accessing ART via these models of delivery and group discussions with CHiPs delivering the intervention was nested within the main trial to complement the quantitative data.

Randomization

The unit of randomization was a CHiP zone and random allocation of zones was done prior to recruitment of eligible participants. There were two communities with 104 zones in total: 54 in community 1 and 50 in community 2. Randomization was performed separately in the two communities. We restricted the randomization within each community on average values of key outcomes measured during the PopART intervention rounds to ensure balance across the three study arms on these factors. These were population size, HIV prevalence, proportion of PLHIV who attend the local clinic, and distance to the clinic.

For each community, one million potential permutations of allocations of zones into three trial arms (A, B, and C) were generated. Each permutation was assessed for balance across arms on the five factors, and if they were not within acceptable limits, then that permutation was discarded. From those remaining permutations that were balanced on the five factors, 10,000 were selected at random and numbered from 0000 to 9999. This provided 10,000 acceptable random allocations for each community with the final allocation to be selected from these at a public randomization ceremony.

We conducted two randomization ceremonies, one for each community separately on the 11 and 13 April 2017. In one community, we used a church hall and in the other community, a school hall. In each of the randomization ceremonies, we invited the CHiPs (108 and 100 in communities 1 and 2 respectively), 4 CHiP supervisors, 10 members of the PopART intervention team, 5 health care workers, 4 community advisory board members, 5 health care staff, and 1 community mobilizer to select the final allocation of zones to one of the three study arms.

We numbered 10 balls from 0 to 9 and asked 4 individuals from each of the above cadres to pick a ball, record the number, and put it back in the bag, giving a four-digit number between 0000 and 9999. This four-digit number was then used to select a single final allocation from the 10,000 generated earlier, allocating each zone to a trial arm: A, B, or C. Once this was done, we asked the CHiPs to take note under which arm their zones were allocated to and asked them to move towards their allocated arm in 3 separate corners of the room. A verification process was done by the study team to ensure that CHiPs serving their zones moved to the correct arm allocation. The next step included taking 3 sheets of papers, each labeled either HBD, AC, or SOC, folded, and put in a small box. From each of the 3 CHiP corners, we asked an individual (agreed by the CHiP teams) to pick 1 paper from the box. Once a paper was picked, it was revealed and the model of delivery was allocated to them. (i.e., if a CHiP from the allocated arm A picked a paper that was written HBD that was the model allocated to arm A, etc.).

Study population and eligibility

All stable adult PLHIV (≥ 18 years) residing in the two urban communities enrolled in HIV care at the two primary health care facilities were eligible for study inclusion. Guided by the WHO classification for "stable" patients [22], we included all patients who were (1) on first-line therapy for at least 6 months, (2) virally suppressed using national guidelines [HIV RNA ≤ 1000 copies/ml] where viral load was taken less than 12 months prior to enrolment, and (3) had no other health conditions requiring the attention of a clinician. An additional eligibility criterion for our study included patients living within the study catchment area and being willing to provide written informed consent to participate in the study.

Study procedures: screening and enrolment

During the enrolment period, the study staff screened all PLHIV attending the health care facility to determine who was stable according to the above definition. Stable patients were then asked whether they resided within the facility catchment area. Those who reported living in the catchment area were then met by the community mobilizer who confirmed their residence using the main trial intervention map. Having confirmed this, they were seen by the study nurse who was responsible for introducing the study to the potential participants and obtaining written informed consent. All participants were consented and enrolled before their random allocation was revealed to them. Participants who were allocated to the intervention arms (home-based delivery and adherence clubs) were given the choice of the allocated intervention or to continue receiving care in the clinic (SoC).

Description of study interventions

A. Home-based ART delivery (HBD)

In zones randomized to HBD, a pair of CHiPs visited the participant in their homes once every 3 months to provide adherence support, symptom screening, and dispense pre-packed drugs. The participants were required to visit the clinic once every 6 months (twice in a year)

for a routine clinical review and laboratory monitoring as per national guidelines. Table 1 gives a broad overview of the HBD model.

B. Adherence clubs (AC)

An adherence club consisted of a group of at least 20–30 stable PLHIV living within the same CHiPs zone and enrolled at the community health care facility. Each zone had one club and club members met once every 3 months at an agreed communal venue where they received adherence support, symptom screening, and pre-packed medications delivered by a CHiP pair. Club members were required to have 2 clinical visits (every 6 months) in a year for their routine clinical review and laboratory monitoring (Table 1).

In both the intervention arms, participants who developed any symptoms or became ill were referred to the health facility for further investigations and management. Participants found to have detectable viral loads, tuberculosis, and other common conditions were transitioned to clinic-based care for further follow-up.

C. Standard of care (SoC)—control arm

Participants living in zones allocated the SoC arm continued receiving care and ART prescriptions at the clinic. Currently, standard of care in Zambia includes patients visiting the clinic once every 3 months for drug collection and clinical monitoring depending on their last clinical and laboratory monitoring.

Study hypothesis and rationale

The principal hypothesis is that clinical and virological outcomes in patients receiving the community-based interventions (HBD and AC) are non-inferior to those receiving care in the clinic (SoC) in an urban resource-limited setting. The rationale for the control arm selection is that care at the facility is the gold standard for stable ART patients in Zambia, and the rest of the world. The non-inferiority design applies to the primary outcome (proportion of participants who are virally suppressed), and the rationale for this design is that if viral suppression is found to be no worse in the intervention arms vs. the control arm, then the intervention will be preferable to the current standard of care. We set our non-inferiority margin at 5%, and the two primary comparisons will include a test of non-inferiority between home-based delivery vs. standard of care and adherence clubs vs. standard of care.

Study endpoints and definitions

The primary endpoint in this trial was the proportion of patients with virological suppression at 12 months (± 3 months) after study entry across all three study arms. Viral load measurement used for our primary outcome was the measurement taken closest in time to 12-month post enrolment. If no measurement was taken within 90 days before or after this 12-month point, then the primary outcome was considered to be missing. We used the routine viral load testing results which according to the Zambian guidelines is defined as VL RNA ≤ 1000 copies/ml (based on the parameters of any assay performed through routine laboratory monitoring) and conducted at 6 and 12 months post ART initiation and thereafter annually for all stable patients. Secondary endpoints of this trial (assessed at the end of the trial) are as follows: (1) proportion of patients virally suppressed at 20 and 24 months after study entry (as measured by last VL taken between 20 and 24 months after study entry) and (2) proportion of patients loss-to follow-up (LTFU)

Table 1 Broad overview of the three ART delivery models

	Home-based delivery (HBD) Clients are visited in their home by the CHiPs	Adherence clubs (AC) Group of 20–30 clients meet at an agreed community venue led by a pair of CHiPs	Standard of care (SoC) Clients visit the clinics as scheduled	Comments
Number of visits/year	2 HBD 2 clinic	2 clubs 2 clinic	4 clinic	
ART dispensed	3 months	3 months	3 months	
Routine laboratory testing	Every 12 months • Viral load • CD4 • Creatinine	Every 12 months • Viral load • CD4 • Creatinine	Every 12 months • Viral load • CD4 • Creatinine	As per routine national guidelines
Frequency of clinical monitoring	2 (every 6 months)	2 (every 6 months)	2 (every 6 months)	
Process	• Symptom screening • Adherence support • Health education and provision of condoms • Dispensation of pre-packed drugs	• Symptom screening • Adherence support • Group education and provision of condoms • Dispensation of pre-packed drugs	• Symptom screening • Adherence support • Health education and condom provision • Drug dispensation at pharmacy	

and died 12 months after study entry. LTFU was defined as having no contact > 90 days after last missed scheduled appointment with unknown outcomes after study entry. Study participants who were transferred out of the health care facility were not considered LTFU but terminated from the study and other reasons for termination included death, LTFU, and study withdrawal; (3) proportion of patients retained in the intervention models after 12, 18, and 24 months; (4) clinical disease progression 12 and 24 months after study entry; and (5) qualitative research to assess the acceptability and functioning of the two models of ART delivery based on systematic structured observations of delivery, in-depth interviews, and focus group discussions from both the participants and provider (CHiPs and HCWs) perspectives.

In addition to the above outcomes, the study also looked at the performance, acceptability and feasibility of the two models of care using programmatic and routine health care facility data.

Retention on treatment during the study period was defined as a documented drug pick up in the last 120 days during the first 12 months after enrolment. Participants who shifted to another zone with a different intervention or shifted outside the study catchment area but continued to receive care at the facility were considered as retained in care. HIV disease progression was defined as proportion of participants who developed a new or recurrent WHO stage 3 or 4 condition at any given time after enrolment into study and death was defined at any point during the study due to any cause.

Additional process data were used to determine model retention, drug refills, and unscheduled or missed appointments after enrolment. For retention in the model of care, participants were considered non-retained if they transitioned back to standard of care or out of the study arms for any reason including co-morbidities, LTFU, death, participant opting out of the intervention, or withdrawal.

Sample size and study power

Based on the data derived from the first annual round of the main trial, the number of adults who were known by the CHiP teams to be HIV+ and on ART at the time of the most recent follow-up visits averaged approximately 50 individuals per zone, with a harmonic mean of approximately 36 per zone. Assuming that 80% of such adults agree to participate in the study and have not moved out of the community within 12 months after enrolment, the number of study participants per zone who can contribute to the primary endpoint measurement will have a harmonic mean of approximately 30. Our study power calculations were done with an assumption that an average of 30 study participants per zone will contribute to the primary outcome measurement, and given there are 104 zones randomized to the 3 arms, this gives an estimated overall sample size of 3120 participants. We also assume that among the study participants in the "standard-of-care" arm, the percentage who are *not* virally suppressed 12 months after enrolment to the study is in the range 10–15%. The study was powered to determine if either of the community-based interventions would yield a viral suppression rate drop compared to SoC of no more than 5% of its absolute value.

To get the coefficient of variation k, formula $k = \sigma/\pi$. We assumed the lower end of our mean zone prevalence (to be conservative) so $\pi = 10\%$, and we assumed that there would be approximately a 10% difference in the prevalence of not being virally suppressed between the lowest and highest prevalence zones (therefore ranging from 5 to 15%), equating roughly to a standard deviation (σ) of 2.5%. So, $k = 2.5\%/10\% = 0.25$. We also checked the power at a more conservative value of 0.3.

If the percentage of participants who are *not* virally suppressed at 12 months after study enrolment is 10% using a two-sided alpha value of 0.05 in the "standard-of-care" arm, and $k = 0.25$ or $k = 0.3$, study power is 93% and 91% respectively to show that a trial intervention arm is not inferior to "standard-of care." The corresponding study power figures are 78% and 74% if the percentage of participants who are *not* virally suppressed at 12 months after study enrolment is 15% in the "standard-of-care arm." The power was calculated using the formula for cluster-randomized non-inferiority trials by Hayes and Moulton [35]. So, the study, for our expected sample size, was estimated to have a power of between 74 and 93% under a range of different scenarios (Table 2). Our estimate of 10% of those not virally suppressed is consistent with research data from these two communities.

Data collection and tools

This study was implemented by Zambart, a non-governmental research organization in Zambia recently having completed the HPTN 071 (PopART) trial and working closely with the Lusaka District Health Management Team and Implementing partners providing technical support to the health care facilities.

The study was based on prospectively collected routine data gathered for monitoring and evaluation purposes in the Zambian ART program. The study's trained staff are collecting data from three sources: (1) clinic data where routine data is being collected at baseline and at every visit using the national health monitoring and information system (HMIS) and patient clinic records, (2) community Smartcare module specifically designed for the study where community interactions are recorded in a hand-held device and later synced with the national Smartcare database, and (3) study-related forms

Table 2 Study power showing community ART provision is not inferior to standard-of-care, in terms of viral suppression 12 months after either enrolling into community ART or continuing with standard-of-care at the clinic

Standard of care, % not virally suppressed at 12 months after enrolment (%)	Non-inferiority margin (%)	Coefficient of variation *k*	Number of participants per cluster	Study power (%)
10	5	0.25	30	93
15	5	0.25	30	78
10	5	0.30	30	91
15	5	0.30	30	74

designed specifically for the study that will be used during enrolment and throughout the study period to measure the outcomes and processes of the study objectives. This will include consent forms, eligibility and enrolment forms, membership registers and attendance sheets, drug scripts, and study event forms.

To maximize the validity of this information, the study team worked closely with the health centers to improve the collection and management of these routine data. A CONSORT statement checklist has also been to improve the reporting of our RCT (Additional file 1) [36].

Analysis plan

For the study outcomes, data analysis was conducted as for a non-inferiority cluster-randomized trial following the methods outlined by Hayes and Moulton [35]. We estimated the prevalence in each zone within each arm. The mean of the zone-specific values was then calculated for each arm along with its corresponding standard error and confidence interval (CI). Our non-inferiority margin was set at 5%. We then compared the control arm with each of the intervention arms using a one-sample *t* test to assess the evidence as to whether the mean difference between the control and intervention arms is less than 5%. If the upper limit of the 95% confidence interval (CI) for the difference is less than 5%, then we accept the intervention as being non-inferior. The primary analysis was unadjusted.

For our primary analysis, which is viral suppression at 12 months, we used intention to treat (ITT) analysis. Since participants in the intervention arm were offered the option to remain in care at the clinic, any who did so were included in the intervention model they were allocated to even though they did not select the allocated model of ART delivery. However, a potential concern with an ITT analysis is if the uptake of the alternative methods is low, or if participants move between study zones or arms resulting in a change to their model of delivery, then the intervention arms become similar to the SoC arm and we may bias the results towards equivalence. So, in addition to the ITT analysis, we performed a per-protocol analysis (PPA) comparing the outcomes in those who received SoC (i.e., participants who were allocated to the SoC arm and those from the intervention arms who chose to receive SoC) with those that received HBD/AC. This would help in interpreting the overall result and should be able to detect if there is, e.g., a much worse outcome in those opting for home delivery. We used PPA as a supportive analysis for the non-inferiority assessment. We also adjusted for potential confounding in the secondary analysis as the participants may no longer be balanced, as those who choose an alternative model may be different from those who do not, in some ways.

If a participant moved from an intervention zone to another zone which did not offer the intervention (or offered a different intervention) and therefore reverted to SoC, we decided to include them in the analysis in their original arm as per the principle of ITT. A potential disadvantage of this choice is that by *including* these individuals, we are making the intervention arm more similar to the SoC arm and therefore in a non-inferiority design this is less conservative. However, mobility between zones was only tracked in the two intervention arms, so if we chose to exclude individuals who we knew had moved zones, we would be removing more mobile individuals from the intervention arms but not from the SoC arm, and assuming that more mobile individuals are at greater risk of viral rebound then *excluding* those individuals would be less conservative as it could make the intervention arms look better. Weighing up these two options, it was thought that the latter issue introduced a greater risk of bias so the primary analysis would *include* those participants (while a sensitivity analysis excluding them would also be performed).

During the study period and towards the end of the study (2 months before the end of the intervention), a team of social scientists collected qualitative data from the two study sites. To ensure fair representation of the study sites, purposive sampling was used to select PLHIV from different age and gender groups as well as different areas of residence and socio-economic status. For staff, CHiPs delivering care through the two models were also selected to participate. Audio-recorded in-depth interviews ($n = 24$) were used to collect data from PLHIV and FGDs ($n = 2$) were used to collect data from CHiPs. Data were then triangulated methodically by longitudinal observations of delivery of the two models ($n =$

18). All audio-recorded IDIs and FGDs were then transcribed, and notes taken during observations expanded in office 2016 and analyzed using Atlas.ti 7.

Ethical considerations

Approval

The study was granted ethical clearance from in-country authorities [University of Zambia Biomedical Research Ethics Committee (UNZABREC)], National Health Research Authority [NHRA], and the London School of Hygiene and Tropical Medicine ethics committee. The protocol had also been through regulatory review and approved by Division of AIDS (DAIDS) at NIH, who granted us permission to carry out this study as an ancillary study to the main trial and registered at ClinicalTrials.gov.

Consent

Written informed consent was obtained from all eligible participants and an information sheet about the study was provided to all participants by the research staff. Having signed the consent form, the research nurse then informed the participant which intervention they had been allocated to or whether they would continue to receive care at the clinic. Participants allocated to one of the two intervention arms were offered a choice of accepting the intervention model or to continue receiving care at the clinic. Participants who chose the intervention models could opt to receive care at the clinic at any point during the study period.

Participant safety and monitoring

Throughout the study, for all those participants who were receiving the interventions, study staff and CHiPs continuously assessed and monitored participant safety and ensured that participant confidentiality was maintained. Patients in the intervention arms who had symptoms requiring a clinician's attention were referred to the research nurse at the clinic and those who were not present during the home or club visit were followed up by the CHiPs to determine if they did come to the clinic to pick up their drugs. The study also anticipated social harms and stigma as these could occur as a result of taking part in the study and participants might be treated unfairly or could have problems being accepted by their families or community members. Although such effects were expected to be minimal, the study staff and the CHiP teams monitored these closely throughout the duration of the study.

Study implementation and challenges

Randomization

Randomization was conducted prior to the start of the study where statisticians provided 10,000 possible randomized allocations that met the restriction criteria, and a public randomization ceremony was held in both communities to select the final allocation of zones to the study arms. A total of 104 CHiP zones across both communities were randomized (35:35:34) to one of the three arms: (1) continue collecting ART at the clinic standard of care (SoC), (2) a choice of home-based ART delivery (HBD) or remaining in clinic-based care, or (3) a choice of being in an adherence club (AC) or remaining in clinic-based care (Fig. 1).

Recruitment

All potential participants who fulfilled the definition of "stable patients on ART" in accordance with the predefined eligibility criteria during the screening process were sent to the research nurse for eligibility screening. Eligible participants who were able to demonstrate understanding of the study were asked to provide written informed consent. Having consented to the study, the participant's residential address was located using the intervention map to identify the zone they were living in. Participants were then informed of the intervention arm they were allocated to. Participants allocated to the intervention arms had the option to take up the offer or continue receiving care at the clinic whereas those allocated to the control arm had no option but to continue care at the clinic. A total of 2503 stable patients were identified across the two communities between May and December 2017 who were eligible for inclusion in the trial and of these 2493 (99.6%) consented to participate and 10 (0.4%) declined consent (Fig. 2). Of the participants who consented, the majority were female (n = 1761, 71%). Median age of participants was 40 years (IQR 33–47) and the median years being on ART was 4 years (IQR 2–7).

Challenges with recruitment

A total of approximately 9962 patients were screened across both communities between May and December 2017. We experienced a number of challenges during the screening process. First, most participants did not have a viral load test taken or had not received their results in the preceding 12 months as recorded in their clinical records at the time of screening. Thus, the study team had to send a patient for VL testing. Viral load results from the laboratory took between 1 and 3 months and study staff had to wait for another 1–3 months to determine eligibility. Secondly, some participants were not physically present at the clinic as they had their treatment supporters or "buddies" come and collect their drugs. The study team had asked the treatment supporters to inform the patient to come the following week or during their next scheduled visit. Thirdly, some patients were on treatment for less than 6 months and could only be enrolled in their

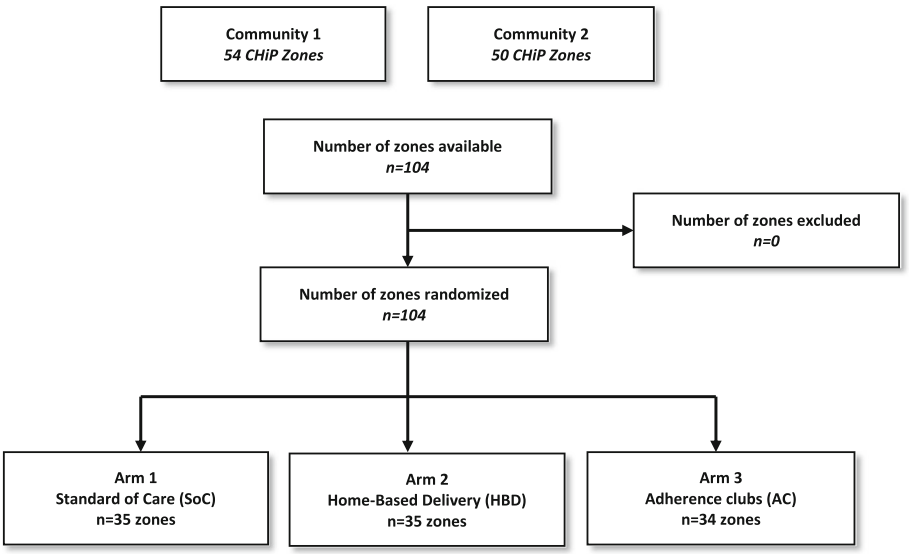

Fig. 1 Randomization scheme

consecutive visits if treatment duration was more than 6 months and they had a 6-month undetectable viral load result. Other reasons included having a detectable viral load, being on 2nd line treatment or having missed more than 2 clinical or drug pick up visit in the last 12 months.

Of the total number of patients who were considered stable, we further excluded a large number of patients as they were living either outside the study catchment area or in a community where the interventions were not offered.

Discussion

This was one of the first studies conducted in an urban resource-limited high HIV burden setting that rigorously compared clinical and virological outcomes of patients

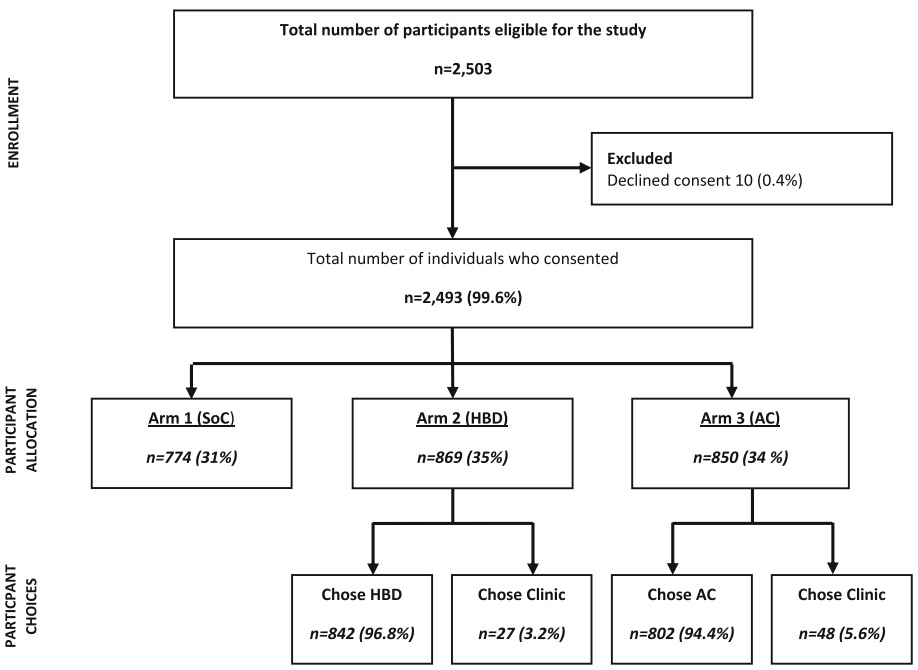

Fig. 2 Recruitment and enrolment flow chart

participating in community models of ART delivery to current facility-based ART delivery as standard of care. In this paper, we present and describe the rationale for conducting a cluster-randomized non-inferiority trial to compare patient outcomes in community models of ART delivery among stable HIV+ patients in Zambia.

Most randomized trials are superiority trials and assess whether a new treatment is more efficacious than a placebo or current standard of care [37], whereas non-inferiority trials are intended to test whether a new treatment is no worse than a standard treatment by more than a specified margin and such trials have gained much attention in the last decade [37]. For our study, the rationale is to provide evidence on patient outcomes, acceptability, and feasibility of different models of ART delivery in resource-limited settings and whether these are novel strategies to scale up in the context of universal treatment in an effort to minimize the barriers to accessing care and treatment as we move towards the UNAIDS target of ending the epidemic by 2030. We used this design because in resource-limited settings, such as in Zambia, community models of ART delivery are being identified as a way of expanding treatment and the government through the National AIDS Council has engaged several in-country partners and researchers to pilot different models of ART delivery in order to generate information required to inform model standardization at national level for wider roll-out. Community models of ART delivery are likely to become part of standard of care if it does not negatively affect patient clinical outcomes as compared to the gold-standard which is the current standard of care.

The choice of this non-inferiority design was to test that clinical outcomes of patients under different models of ART delivery are not significantly inferior to the current standard of care, thereby showing that in resource-limited settings, these models of ART delivery can be considered as standard of care. Introducing these models of ART delivery as standard of care may potentially have long-term benefits such as decongesting the overburdened clinics to allow health care workers to concentrate on more complex patients, reduce patients' financial and transport burdens of having to attend the clinics frequently for their drug pick-ups as well as improve community engagement and support towards HIV care and treatment. In contrast, a superiority trial design would not be feasible in resource-limited settings as it will require a lot of resources and would require health care workers to provide an intervention that shows superiority over the current gold standard of care.

This trial used cluster rather than individual randomization following in the footsteps of several large and ambitious trials of interventions against HIV and other infectious diseases in low and middle income countries that have helped guide health policy over the last decade or more [38]. These type of trials are used increasingly where delivery of intervention is at a group level and outcomes measured at patient level [39]. The decision to design a cluster randomized over an individually randomized trial for our study was that (1) it was ideally suited to study interventions that in practice had to be delivered at cluster (in this case, a zone) level, (2) it avoids the risk of contamination where participants from the control arm might receive some components of the intervention, and (3) this trial design was best designed to capture the effects of these interventions at community level.

In addition to the above, the communities were already divided into zones (clusters) by the main trial and it was logistically more feasible to train CHIPs on the particular interventions they would deliver rather than train them on all the interventions. It was also easier to control and monitor the interventions unlike individual randomization where it would have been difficult to deliver and monitor the interventions. In the case of adherence clubs, a club could be set up within each AC zone, meaning the clubs are close to participants' homes, but if the trial was individually randomized, participants in the AC arm would be more geographically disparate and therefore in some cases far away from their allocated club, which could result in patients opting out of interventions.

This study has a robust design in being the first cluster randomized trial to explore outcomes of virological suppression, retention, feasibility, and acceptability of different ART delivery models and comparing it to the standard of care in a high prevalence urban setting and therefore provide us with evidence that could be generalizable to other sub-Saharan African settings and also inform policy regarding the best models to scale up. In addition to the above outcomes, this study also provided participants with a choice of continuing care at the clinic or receiving a community-based intervention and considered participant's preferences towards the different models of ART delivery.

Despite the study strengths, non-inferiority trials have several challenges and limitations. As discussed in the analysis plan above, one of the challenges will be how best to analyze the data and whether to use ITT or PPA as we will have to deal with movements of participants between zones resulting in a change to their model of ART delivery. Assuming that both intervention arms are non-inferior to the standard of care arm, it would be desirable to determine whether one intervention arm is superior to the other (home delivery vs. adherence clubs). Although the study will not necessarily be powered to test this, other indexes on model uptake and retention,

drop-out rates, and cost effectiveness can still be used to inform policy makers on model preferences.

Other limitations include the possibility of selection bias, where patients in the control arm may hear about the two models of delivery and may move from one zone to another which is providing the intervention. To avoid this, we asked patients at enrolment where they actually live and confirmed this with CHiPs who worked in those zones. Uniformity of implementing the interventions may change over time due to external factors such as bad weather and political climate. Another limitation was the substantial mobility and in-migration of participants within these urban communities as observed in the main trial [40, 41] thus requiring consideration of how to handle patients who relocate from one zone to another zone or community. There is also a source of bias as to who consents and who does not and those who take part in the study may not be representative of the general population. Another factor to be considered is that the study power might leave us underpowered if more than half of the adults in each zone opt to withdraw and return to standard of care as a result of stigma and disclosure. Other challenges included using routine data for measuring outcomes such as viral load results as most of these results were either missing or yet to be updated in the facility health care database and patient clinical records. To address this challenge, the study team worked closely with the clinic staff and laboratory staff to have viral load results entered in the clinic database and patient files.

As we move towards scale up of ART services to meet the UNAIDS target, there is need to provide evidence on the feasibility, outcomes, and cost effectiveness of differentiated care models and how best they can be combined alongside routine ART services. This trial will provide important data informing policy regarding best practices and what is needed to strengthen the scale up of differentiated care.

Trial status

Enrolment into the trial commenced on 2 May 2017 and completed recruitment on 15 December 2017. The study recruited 2493 patients across the two urban communities and follow-up of participants ended in April 2019. The main trial outcome will be reported in 2020.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-020-05010-w.

Additional file 1.

Abbreviations

AC: Adherence clubs; AIDS: Acquired immune deficiency syndrome; ART: Antiretroviral therapy; CI: Confidence interval; HAART: Highly active antiretroviral therapy; HBD: Home-based delivery; HIV: Human immunodeficiency virus; HMIS: Health management information system; HPTN: HIV Prevention Trials Network; IAS: International AIDS Society; IQR: Interquartile range; ITT: Intention to treat; LTFU: Lost to follow-up; NHRA: National Health Research Authority; PLHIV: People living with HIV; PPA: Per protocol analysis; RNA: Ribonucleic acid; SOC: Standard of care; SSA: Sub-Saharan Africa; UNAIDS: Joint United Nations Programme on HIV/AIDS; VL: Viral load; VLS: Viral load suppression; WHO: World Health Organization

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Authors' contributions

ML wrote the first draft of this manuscript. HA, SF, DM, SF, AS, and RH read and revised the manuscript and approved the final version. ML, HA, SF, and RH originally conceived and designed the trial in consultation with the HPTN 071 Protocol team and executive committee. SF, DM, and AS helped design the statistical framework of the trial and contributed to all drafts of the manuscript. The authors read and approved the final manuscript.

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Availability of data and materials

Further details on data collection tools and any data presented in this manuscript can be obtained from the corresponding author.

Ethics approval and consent to participate

The University of Zambia Biomedical Research Ethics Committee (UNZABREC) and Ministry of Health, Zambia, approved the trial in July 2016. The trial was also approved by the London School of Hygiene and Tropical Medicine (LSHTM). Written informed consent was obtained from all participants prior to enrolment into the trial. Zambart and LSHTM affiliated investigators will have full access to all datasets collected from this study. HPTN investigators will only have access to de-identified versions of the datasets.

Consent for publication

Not applicable

Competing interests

The authors declare they have no competing interests.

Author details

[1]Zambart, University of Zambia, School of Medicine, Zambart House, Ridgeway Campus, Off Nationalist Road, P.O. Box 50697, Lusaka, Zambia. [2]Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK. [3]Imperial College and Imperial College NIHR BRC, London, UK. [4]Department of Clinical Research, London School of Hygiene and Tropical Medicine, London, UK.

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References

1. World Health Organization. March 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2014.
2. World Health Organization. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. 2015. http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/. Accessed 13 Mar 2017.
3. UNAIDS. Fact sheet - Latest statistics on the status of the AIDS epidemic. 2018. [Available from: http://www.unaids.org/en/resources/fact-sheet]. Accessed 4 Jan 2019.
4. UNAIDS. Global AIDS Update. Geneva: UNAIDS; 2016. http://www.unaids.org/en/resources/documents/2016/Global-AIDS-update. Accessed 17 July 2018.
5. Rosen S, Fox MP, Gill CJ. Patient Retention in Antiretroivral Therapy Programs in Sub-Saharan Africa: A Systematic Review. PLOS Medicine. 2007; 4(10):e298. https://doi.org/10.1371/journal.pmed.0040298.
6. Tassie JM, Baijal P, Vitoria MA, Alisalad A, Crowley SP, Souteyrand Y. Trends in retention on antiretroviral therapy in national programs in low-income and middle-income countries. J Acquir Immune Defic Syndr (1999). 2010;54(4):437–41.
7. Assefa Y, Van Damme W, Haile Mariam D, Kloos H. Toward Universal Access to HIV Counseling and Testing and Antiretroviral Treatment in Ethiopia: Looking Beyond HIV Testing and ART Initiation. AIDS patient care STDs. 2010;24:521–5.
8. Assefa Y, Jerene D, Lulseged S, Ooms G, Van Damme W. Rapid scale-up of antiretroviral treatment in Ethiopia: successes and system-wide effects. PLoS Med. 2009;6(4):e1000056. https://doi.org/10.1371/journal.pmed.1000056.
9. Assefa Y, Lynen L, Wouters E, Rasschaert F, Peeters K, Van Damme W. How to improve patient retention in an antiretroviral treatment program in Ethiopia: a mixed-methods study. BMC Health Serv Res. 2014;14(1):45.
10. Harries AD, Zachariah R, Lawn SD, Rosen S. Strategies to improve patient retention on antiretroviral therapy in sub-Saharan Africa. Trop Med Int Health. 2010;15 Suppl 1(s1):70–5.
11. Chammartin F, Zürcher K, Keiser O, Weigel R, Chu K, Kiragga AN, et al. Outcomes of patients lost to follow-up in African antiretroviral therapy programs: individual patient data meta-analysis. Clin Infect Dis. 2018;67(11):1643–52.
12. Brennan AT, Maskew M, Sanne I, Fox MP. The importance of clinic attendance in the first six months on antiretroviral treatment: a retrospective analysis at a large public sector HIV clinic in South Africa. J Int AIDS Soc. 2010;13:49.
13. Hirschhorn LR, Oguda L, Fullem A, Dreesch N, Wilson P. Estimating health workforce needs for antiretroviral therapy in resource-limited settings. Hum Resour Health. 2006;4:1. https://doi.org/10.1186/1478-4491-4-1.
14. Ware NC, Wyatt MA, Geng EH, Kaaya SF, Agbaji OO, Muyindike WR, et al. Toward an understanding of disengagement from HIV treatment and care in Sub-Saharan Africa: a qualitative study. PLoS Med. 2013;10(1):e1001369.
15. Tuller DM, Bangsberg DR, Senkungu J, Ware NC, Emenyonu N, Weiser SD. Transportation costs impede sustained adherence and access to HAART in a clinic population in southwestern Uganda: a qualitative study. AIDS Behav. 2010;14(4):778–84.
16. Hardon AP, Akurut D, Comoro C, Ekezie C, Irunde HF, Gerrits T, et al. Hunger, waiting time and transport costs: time to confront challenges to ART adherence in Africa. AIDS Care. 2007;19(5):658–65.
17. Tomori C, Kennedy CE, Brahmbhatt H, Wagman JA, Mbwambo JK, Likindikoki S, et al. Barriers and facilitators of retention in HIV care and treatment services in Iringa, Tanzania: the importance of socioeconomic and sociocultural factors. AIDS Care. 2014;26(7):907–13.
18. Fox MP, Rosen S. Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007–2009: systematic review. Trop Med Int Health. 2010;15:1–15. https://doi.org/10.1111/j.1365-3156.2010.02508.
19. Fatti G, Grimwood A, Bock P. Better antiretroviral therapy outcomes at primary healthcare facilities: an evaluation of three tiers of ART services in four South African provinces. PLoS One. 2010;5(9):e12888.
20. Mills EJ, Nachega JB, Bangsberg DR, Singh S, Rachlis B, et al. Adherence to HAART: a systematic review of developed and developing nation patientreported barriers and facilitators. PLoS Med. 2006;3(11):e438. https://doi.org/10.1371/journal.pmed.0030438.
21. International AIDS Society (IAS). Differentiated care for HIV: a decision framework for antiretroviral therapy delivery: International AIDS Society; 2016.
22. WHO. Consolidated guidelines on the the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2nd ed; 2016.
23. Tsondai PR, Wilkinson LS, Grimsrud A, Mdlalo PT, Ullauri A, Boulle A. High rates of retention and viral suppression in the scale-up of antiretroviral therapy adherence clubs in Cape Town, South Africa. J Int AIDS Soc. 2017; 20(Suppl 4):21649.
24. Hagey JM, Li X, Barr-Walker J, Penner J, Kadima J, Oyaro P, et al. Differentiated HIV care in sub-Saharan Africa: a scoping review to inform antiretroviral therapy provision for stable HIV-infected individuals in Kenya. AIDS Care. 2018;30(12):1477–87.
25. Amuron B, Coutinho A, Grosskurth H, Nabiryo C, Birungi J, Namara G, et al. A cluster-randomised trial to compare home-based with health facility-based antiretroviral treatment in Uganda: study design and baseline findings. Open AIDS J. 2007;1:21–7.
26. Jaffar S, Amuron B, Foster S. Rates of virological failure in patients treated in a home-based versus a facility-based HIV-care model in Jinja, southeast Uganda: a cluster-randomized equivalence trial. Lancet. 2009;374(9707):2080–9.
27. Kipp W, Konde-Lule J, Saunders LD, Alibhai A, Houston S, Rubaale T, et al. Antiretroviral treatment for HIV in rural Uganda: two-year treatment outcomes of a prospective health centre/community-based and hospital-based cohort. PLoS One. 2012;7(7):e40902.
28. Kipp W, Konde-Lule J, Rubaale T, Okech-Ojony J, Alibhai A, Saunders D. Comparing antiretroviral treatment outcomes between a prospective community-based and hospital-based cohort of HIV patients in rural Uganda. BMC Int Health Hum Rights. 2011;11(Suppl 2):S12.
29. Decroo T, Rasschaert F, Telfer B, Remartinez D, Laga M, Ford N. Community-based antiretroviral therapy programs can overcome barriers to retention of patients and decongest health services in sub-Saharan Africa: a systematic review. Int Health. 2013;5(3):169–79.
30. Bemelmans M, Baert S, Goemaere E, Wilkinson L, Vandendyck M, van Cutsem G, Silva C, Perry S, Szumilin E, Gerstenhaber R, Kalenga L, Biot M, Ford N. Community-supported models of care for people on HIV treatment in sub-Saharan Africa. Trop Med Int Health. 2014;19(8):968–77. https://doi.org/10.1111/tmi.12332.
31. Wilkinson LS. ART adherence clubs: a long-term retention strategy for clinically stable patients receiving antiretroviral therapy; 2013.
32. Decroo T, Koole O, Remartinez D, dos Santos N, Dezembro S, Jofrisse M, et al. Four-year retention and risk factors for attrition among members of community ART groups in Tete, Mozambique. Trop Med Int Health. 2014;19(5):514–21.
33. Luque-Fernandez MA, Van Cutsem G, Goemaere E, Hilderbrand K, Schomaker M, Mantangana N, et al. Effectiveness of patient adherence groups as a model of care for stable patients on antiretroviral therapy in Khayelitsha, Cape Town, South Africa. PloS one. 2013;8(2):e56088.
34. Hayes R, Ayles H, Beyers N, Sabapathy K, Floyd S, Shanaube K, et al. HPTN 071 (PopART): rationale and design of a cluster-randomised trial of the population impact of an HIV combination prevention intervention including universal testing and treatment - a study protocol for a cluster randomised trial. Trials. 2014;15:57.
35. Hayes RJ, Moulton LH. Cluster randomised trials, second edition. CRC Press; 2017. p. 398. https://doi.org/10.4324/9781315370286.
36. Schulz KF, Altman DG, Moher D, the CG. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Med. 2010;8(1):18.
37. Scott IA. Non-inferiority trials: determining whether alternative treatments are good enough. Med J Aust. 2009;190(6):326–30.
38. Hayes R. Randomising towns to fight HIV. Significance. 2018;15(2):28–31.
39. Elley C, Chondros P, Kerse N. Randomised trials-cluster versus individual randomisation: Primary Care Alliance for Clinical Trials (PACT) network; 2004. p. 759–63.
40. Floyd S, Ayles H, Schaap A, Shanaube K, MacLeod D, Phiri M, et al. Towards 90-90: findings after two years of the HPTN 071 (PopART) cluster-randomized trial of a universal testing-and-treatment intervention in Zambia. PLoS One. 2018;13(8):e0197904.
41. Hoddinott G, Myburgh H, de Villiers L, Ndubani R, Mantantana J, Thomas A, et al. Households, fluidity, and HIV service delivery in Zambia and South Africa – an exploratory analysis of longitudinal qualitative data from the HPTN 071 (PopART) trial. J Int AIDS Soc. 2018;21(Suppl Suppl 4):e25135.

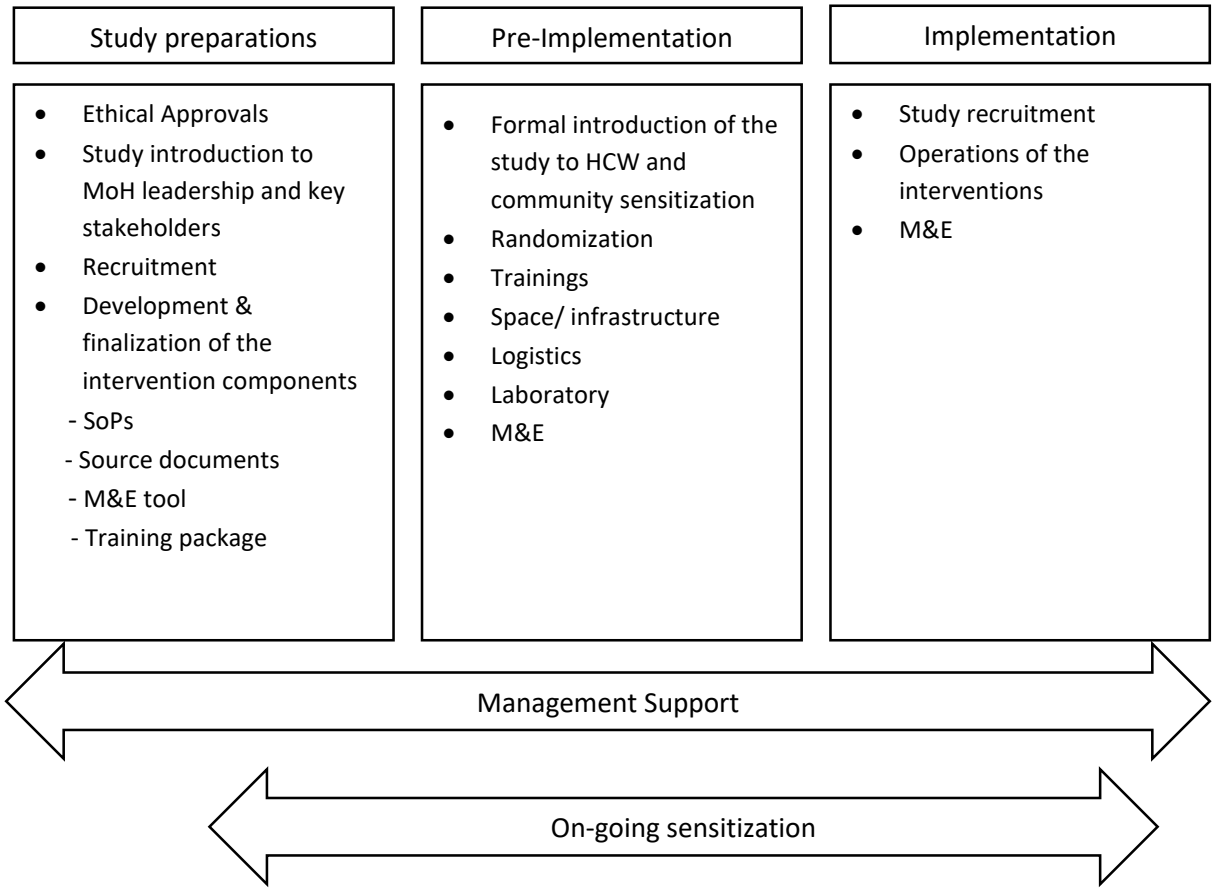
Publisher's Note

Chapter 5. Implementation of the trial

5.1 Chapter overview

This chapter describes the implementation of the trial in a high prevalence HIV urban setting in Zambia. It provides an insight on the current facility-based care (SoC) and how and what it took to implement the 2 models of non-facility-based ART delivery models that were tested using a non-inferiority randomized controlled study design and described in the thesis. The first section of the chapter describes the planning process from the time of study approval and prior to study recruitment. The next section describes the operations of the intervention models and the facility-based care (SoC), recruitment of study participants, follow-up, and data collection. The third section of this chapter describes the successes, challenges, and limitations of implementing the non-facility-based models of care (HBD and AC) and the study exit plans. An overview of the implementation steps is outlined in Figure 5.1

Fig 5.1: Implementation steps of the study

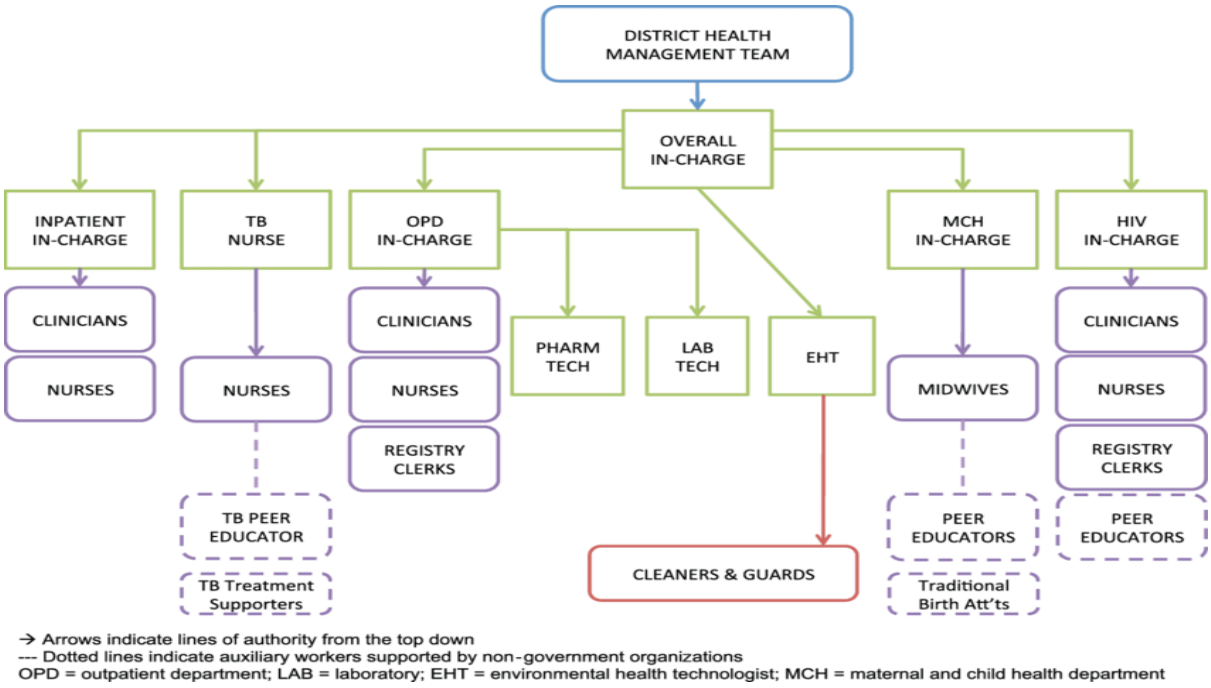


5.2 Overview of the planning

At the time, the study was being designed, the Zambian Ministry of Health had identified community models of ART delivery as a way of expanding treatment in the context of universal treatment. The Ministry of health, through the National AIDS Council (NAC), had engaged several in-country implementing partners and researchers to pilot different models of ART delivery in order to provide policy makers with evidence on patient outcomes, operational feasibility, and acceptability of the different types of community models of ART delivery. MoH had formed the Differentiated Service Delivery (DSD) task force comprising of members from MOH, Provincial Health Office (PHO), District Health Management Team (DHMT), and Centre for Disease Control (CDC), PEPFAR and USAID implementing partners and researchers from Zambart who were involved in piloting the various DSD models countrywide. The aim of this task force was to gather information from pilot studies being conducted and develop a national DSD framework to provide guidance on how DSD models should be implemented. This framework ensured that implementation of DSD models should leverage on existing structures and resources and guided by several principles such supplies, trainings, monitoring and evaluation (M&E) systems and quality of HIV care. This was a timely and innovate move for me to design and conduct this study using the guiding principles set forward to gather evidence on the impact of these models of ART delivery on patient outcomes, their acceptability and feasibility in an urban setting as the information obtained would be of great value to both national policy makers and PEPFAR.

During the planning stage, I visited the two communities and health care facilities [HCF] to familiarize myself with the HCF management and staff, logistical supplies, procurement system and flow of patients during their HIV clinical and pharmacy visits. The Primary health care centres account for approximately 79% of Zambia's health care facilities and approximately 29% are located in urban settings[206]. Depending on the location and resources available, the HCF may include an outpatient department (OPD), an inpatient department (IPD), a maternal and child health department (MCH), a labour ward, an HIV care and treatment department, a TB department, a laboratory, and an environmental health team (EHT)[206]. The HCFs fall under the DHMT and in each facility there is an overall In-charge who is a medical doctor responsible for managing the health care facility. The administrative structure and hierarchy of the primary health care facility is outlined in figure 5.2 below.

Fig 5.2. Overview and hierarchy of the Primary health care facility in Zambia



Source: Topp et al. Health Policy and Planning, May 2014

During the visits to the HCFs, I held several meetings with the clinic staff and implementing partners with regards to the following:

- Understanding the flow of patients in the ART clinic, logistical supplies, and identification of space within the ART clinic or premises to conduct the study
- Understand the routine laboratory schedule from time of sample collection to result feedback as this was critical since the study's primary outcome on viral suppression rates was dependent on routine laboratory monitoring.

One of the advantages we had was that the HPTN 071 (PopART) trial was already implemented in both communities and CHiPs teams were already well established and familiar within the community and health care facility. This enabled us to easily familiarize with key community members, community maps, distances between the health care centres and zones. As the CHiPs were already providing a combination prevention package at household level, it was easy for us to add in a few further responsibilities the CHiPs had to include as an addition for the study.

Prior to developing the protocol, I sought permission from the HPTN executive committee to conduct this study as an ancillary study to the main trial and after several discussions and submissions, permission was granted. Members of the HPTN 071 protocol team (including the Chair, co-Chair and Principal Investigators) were frequently updated with regards to protocol development and guidance was provided where needed. The in-country research team (including social scientists, data managers) were actively involved in the development of the consent forms, data collection tools and standard operating procedures.

5.3 Study Preparations

Having developed the study protocol and obtaining regulatory approval from our local regulatory ethics committee, the next step involved preparations for study activation and implementation in the two communities in Lusaka. As shown in figure 1, the steps included study preparation activities, pre-implementation steps and finally implementation following study activation. This section will go over the steps involved in each step of the plan in detail.

5.3.1 Introducing the study to relevant authorities and key stakeholders

Engagement with key stakeholders during and after the development of the study protocol was a crucial step as it allowed me to use the DSD framework to guide on how the study procedures should leverage within the existing health system such as monitoring and evaluation. On-going stakeholder sensitization and engagement throughout the study implementation until study completion was critical. This was to ensure there was effective communication plans and feedback as well as reporting the progress of the study interventions. The key stakeholders that we engaged with continuously included Ministry of Health, President Emergency Plan for AIDS Relief [PEPFAR] implementing partners, health care workers in the facilities, community members and leaders, community health workers and patients.

Once the protocol was finalized, I introduced the study to the Ministry of Health DSD task force, PEPFAR implementing partners and the District Health Management Team (DHMT) to explain the study aims and objectives. This generated much excitement, as the study's findings would provide information on the effects of various ART delivery strategies on patient outcomes and clinic operations, which will be critical for policymakers as they consider rolling out large-scale DSD models countrywide.

In addition, I visited the two health care facilities serving the study communities and held bi-weekly meetings with key health care staff (Medical superintendent, ART In-charge nurse, data technician and pharmacist) to sensitize them over the proposed interventions. This was key as it allowed me to identify the following:

- What the HCFs needed in terms of logistical supply, space, and infrastructure
- Understand the patient flow in the clinics and laboratory schedules that would help in developing our standard operating manuals for screening, recruiting and follow-up of patients
- Anticipated challenges that would come along with the study such as staffing, data collection, drug logistics and access to laboratory testing and results
- Needs and concerns of health care workers
- Concerns using community health workers to deliver the interventions and distribute ART in the communities.

Having identified the concerns that would come along with the implementation of the study interventions and activities, allowed me to work with the HCW and management on what measures to put in place to mitigate their concerns. Table **5.1** below addresses the key concerns raised and what measure would be put in place.

Table 5.1: Summary of the concerns raised by various teams and ways to mitigate them

	Concerns raised	Mitigation
1	**Health care staff concerns**	
	I. Space within the facility to recruit, screen and monitor patients who would be enrolled in the study	
	• *Where will patients be screened and recruited within the clinic space available?*	• *Staff identified spaces (rooms) at the clinic that were being used by the HPTN 071 (PopART) trial and allocated these for recruiting patients* • *Screening of patients would be conducted at the HIV clinic with additional staff to assist with screening* • *Procurement of additional furniture's (desks, chairs and filing cabinets)*
	II. Human resources	
	• *Packaging of drugs for delivery into the community*	• *Recruitment of a pharmacy technician in each facility to assist with the packaging of drugs* • *In addition, the pharmacy technicians would work with the existing staff in dispensing drugs at the clinic pharmacy for all patients*
	• *Completeness of pharmacy registers and SmartCare database*	• *Pharmacy technician would be responsible for completing the registers and study nurse would ensure that at the end of the participants visit, files are taken to the data clerks for entry into SmartCare.*
	III. Drug dispensation in the community	
	• *Concerns over having community health care workers dispensing pre-packed medications* • *How will drugs be concealed in the community* • *How will drugs dispensed into the communities be audited*	• *Drugs would be pre-packed by the pharmacy technician and placed in black bags with a label indicating the drugs and quantity prescribed. Bags containing the drugs will only be provided to the CHiPs on the day of their scheduled visits.* • *Drugs will be carried out to the community by CHiPs in the backpacks.* • *For club visits, where a large quantity of drugs is to be dispensed, we will provide a trunk to carry these drugs which will be transported by a study vehicle.* • *A triplicate prescription slips specifically made for the study would be used where patient's name, drugs and quantity are indicated, and patient will have to sign on the slip after having received them.* • *Audits would include random calls to the patients to determine if they received their drugs on time and the right quantity.* • *Inclusion of key messages to study participants during enrolment into the intervention to contact study staff should they encounter any delays or missing drugs during their visits.*
	IV. Laboratory testing	
	• *Inadequate supply of blood collection specimen bottles for viral load testing* • *Patients in the interventions who were found to have detectable viral load*	• *The study staff would ensure that specimen collecting tubes (vacutainers) are provided to the phlebotomist in the event the clinic runs out of supply.* • *All patients who were found to have a detectable viral load were followed up in the intervention arms and referred to the clinician to have them appropriately managed either by repeating the viral load to*

		confirm virological failure or switch to second-line regimen. This was in accordance with the standard of care guidelines.
	V. SmartCare database	
	• *How will we ensure that patient monitoring data is entered in the existing database*	• *All study participants in the intervention arms who completed a successful visit in the community would have their files taken to the data clerks for data entry by the study nurse and pharmacy technician.*
	• *What will happen to patient records as they transition from paper-based clinical records to electronic records*	• *In order to ensure that patient's records are entered electronically, the study sought to have the participant's visit details entered manually in the patient files and later be entered into SmartCare. This was to ensure that we do not create gaps in the data entry system*
	VI. Appointment spacing for 6 monthly clinical reviews	
	• *How will the study staff ensure that participants who are enrolled in the intervention arms do not cause congestion in the clinics when it is time for their 6 monthly clinical review and laboratory monitoring?*	• *Study staff would work with the ART nurse in-charge to ensure that patients in the intervention arms are first seen by the study staff who would assist the clinic staff in recording vitals and fast tracking them for a clinical review.* • *Study staff (study nurse) would also assist the phlebotomist in specimen collection* • *The study principal investigator if present at the site would also assist in screening and reviewing patients.*
2.	**Study Staff concerns**	
	I. Laboratory Testing and turnaround time	
	• *How do we ensure that participants have the viral load samples taken at the right time and results turnaround time*	• *The study staff will work closely with the clinic staff to ensure that study participants are reminded of their 6 monthly visit and importance of having a viral load test done.* • *Study staff will assist the clinic staff in collecting samples* • *The principal investigator and study nurse will work closely with the laboratory staff in following up results*
	• *Laboratory results entry in patient files*	• *Study will hire staff on a part time basis to retrieve results and file them in patient files.*
	II. Study participants records	
	• *How do we ensure that patient's clinical files are stored within the facility and easily accessible by both study staff and HCW?* • *How does the clinic identify who is a study participant or not*	• *All study participants would have a colour coded sticker with their details inserted on their files for easy identification of study participants. These files would be kept in a safe and secure cabinet in the study nurse's room and accessible to the clinic staff. For patients in the standard of care, arm, their files would also be identified by a colour coded sticker and space was created in the registry room for filing.* • *We also committed to hiring peer educators on a part-time basis to help identify files with the colour coded sticker to ensure that they are filed appropriately and kept in the right filing cabinets for easier accessibility by both the research and clinic staff.* • *Study participants also had a colour coded sticker with the intervention model they were assigned to on their HIV care cards for easy identification.*

	• *How do we ensure confidentiality and privacy of patient's data collected for both the research questions and clinical care?*	• *Data will be collected and stored in accordance with ministry of health and SmartCare requirements, which are already in place for all HIV treatment centres.* • *Access of data in the SmartCare database will be based on user right and every user in the facility must agree to the terms of use, which is currently in place.* • *Data collected by the CHiPs during the club and home visits will be entered manually in the study forms and will be handed to the study nurse at the end of the visit for quality control and safely securing in locked cabinets.*
	• *How does the study staff gain access to patient clinic data in SmartCare*	• *Study staff will obtain permission form Ministry of Health and implementing partners to access SmartCare data for monitoring and evaluation as well as for data analysis for the study's objectives. Data extraction for the purpose of analysis will be periodically extracted*
	III. how do we follow up patients who have missed their clinical visits	
	• *How do we trace patients in the control arm who miss their visits*	• *Study staff will work closely with staff at the clinic to follow up patients who have missed their visits either through phone calls or tracking in the community. Participants identified to have missed their last visit will be brought to the CHiPs attention to trace them in the community.*
	IV. Transitioning of patients in the intervention arms to clinic-based care after the study ends	• *The principal investigator and overall, in charge of the clinics will have several meetings with implementing partners towards the end of the study on the transitioning of patients form the intervention arms to the clinic-based care or any new models for ART delivery that will be implemented by the supporting partners.*
3	Community Health care workers concerns	
	I. Delivering the intervention	
	• *Additional data collection will be time consuming*	• *CHiPs will be guided by their supervisors and study nurse on how to plan accordingly for their home and club visits on a monthly basis.* • *CHiPs will work in pairs to ensure the responsibilities are shared accordingly.* • *Planning on how many home or club visits they should conduct per week*
	• *How will they carry the drugs and forms for club meetings consisting of more than 15 members*	• *Provision of transport using a vehicle to carry materials for club meetings.*
4.	**Community Advisory Board concerns**	
	I. Stigma and discrimination	
	• *How will patient's privacy in the community be protected*	• *Study participants will be introduced to CHiPs working in their zones and their contact numbers will be provided.* • *Home visits will be conducted in participants homes or anywhere near depending on the participants preference* • *Study team will do everything to ensure that confidentiality is maintained through trainings.*

5.3.2 Recruitment of Staff

In addition to the staff who were already recruited in the main HPTN 071 trial (study coordinator and CHiPs), further additional staff with different roles to operationalize the study were recruited. This included study nurses, pharmacy technicians and data managers. Table **5.2** outlines the roles and responsibilities of the existing and newly recruited staff that were hired for the study.

Table 5.2: Roles and responsibilities of ComART study staff

Staff	Primary Role	Responsibilities
Principal Investigator	Assumes overall responsibility of the study's conduct.	• Designs the study protocol and related SoPs • Ensures that resources are available to conduct the study (time, space, staff, funding etc.) • Compliance with protocol and communications with IRB/ethics committee • Randomization procedures • Informed consent of participants • Oversee the study activities and collection of data • Work and communicate in close collaboration with key stakeholders • Ensure participants safety by working closely with the clinic staff • Trial records and reports • Delegate tasks to other to ensure that research is conducted in compliance with protocol • Data and study records are securely stored, retained, and protected • Conduct trainings and supervisory mentoring sessions • Present preliminary and final findings of the study • Build capacity within the staff
Study coordinator (1)	Oversee the two communities delivering the intervention and ensure smooth operations of the study under the leadership of the PI	• Assists the PI in his roles and responsibilities • Supervises the research staff in their respective sites and provides feedback to the PI • Assists the PI in trainings, conducting supervisory visits • Ensures the study staff comply with the protocol and standard operating procedures • Identify challenges faced in implementation of the intervention and feedback to the PI and study staff • Providing support to pharmacists packaging and prescribing ARV drugs and oversee the implementation of the interventions across both communities.
Study nurses (also referred as research nurses) 4 (2 in each facility)	screen, recruit, and follow-up patients in the intervention models whilst at the same time assist the existing staff in the health care facility with day-to day activities	• Identification and recruitment of eligible participants for the study • Obtaining informed consent • Ensures that SoPs are followed • Plans and prepares for the intervention models visit schedules

		• Works with the pharmacy to ensure that drugs are pre-packed prior to visit dates • Works with the facility health care staff to ensure that patients in the study are compliant with routine clinical follow-up and laboratory monitoring • Supervises the intervention model visits monthly • Update's intervention registers • Supervises the CHiPs delivering the intervention • Quality assurance of the source documents following club and home visits • Ensures that data collected at community level is updated in patient clinical records • Follows up on patient laboratory results and transition patients to mainstream care if needed • Works closely with the clinic staff to ensure that patient clinical care is not disrupted because of the interventions • Provides feedback to the health care staff and the study coordinator and PI
Pharmacy technician 2 1 in each facility	Oversee the pharmaceutical aspects of the study and other related activities	• Pre-packing medication for the interventions • Completing and updating the pharmacy registers and auditing drug deliveries in the community • Works with the pharmacy and HCW in the clinics to ensure that pharmacy is running smoothly without any disruptions that would occur as a result of introducing the interventions • Assists the study nurse in some of the activities such as planning and preparations for a scheduled visit, updating study registers and quality assurance of the source documents
CHiPs In the first year of the trial (2 CHiPs per Zone) In the final year of the trial, 2 chips served a maximum of 4 zones	Delivering the interventions	• Working closely with the study nurse and pharmacy in planning for the follow-up visits • Visiting the participants in the homes or clubs • Providing adherence support and distributing pre-packed drugs • Completes the attendance registers and any other source documents that would be needed such as missed visit, referral forms etc. • Provide clients with their next scheduled community or clinic visit • Contacting clients prior to their scheduled visits • Follow-up clients who have missed visits or lost to follow-up • Report any outcomes to the study nurse such as transfers out of the community, relocations, death etc.

Data clerk 1 (based at research headquarters)	Data entry	• Collecting source documents from the study sites every fortnightly to entre in the research database • Quality control of source documents and data entry • Providing data to PI and study coordinator on a monthly basis for study progress
CHiP Supervisors 4 in each site	Oversee the CHiPs activities for over the main and ancillary trial	• Works closely with the study nurse with regards to monitoring and supervising the CHiPs conducting the home and club visits. • Ensures CHiPs assigned to deliver the interventions are reminded of their upcoming activities • Ensures that the club and home visits are planned on time with the study nurse and identifies venues for the club meetings • Collects monthly CHiP reports on their activities
Part-time lay workers 1 in each site		• Assist in retrieving files of all participants prior to their upcoming clinical visits • Filing patient files in the clinic registers and taking patient files to data room for data entry • Assist the study nurse in escorting participants to the phlebotomy room or other departments in the clinic such as TB department etc. • Assist with filing viral load result sheets into patient files
Community mobilizer 1 in each site		• Assist with sensitization activities at clinic and community level • Help study nurse identify participants residence and zones using the intervention maps • Provides communications and feedback with key community members over the study progress and liaise with the community leaders over venues for clubs etc.

5.3.3 Development of the intervention components

In order to ensure that study is operationally efficient and of high quality, we developed standardized operating procedures for the interventions, data collection tools and training packages for study staff. This section describes what we put in place beyond the clinic standard of care procedures to ensure that study participants in all 3 arms were safely managed with respect to their clinical care.

I. Regulatory changes on drug dispensation

Prior to the start of the trial, there was no official national policy on dispensation of pre-packed drugs by community lay workers. Following ethical clearance and permission from MoH to allow CHiPs to deliver pre-packed drugs in the community, additional measure was put in place to ensure that patients received their drugs in the community. We developed prescription forms specifically for the study which had to be signed for by the participants upon receipt of their drugs and these forms were

also used for audit purposes. In addition to the prescription forms, the team also had to provide small re-usable bags to deliver the drugs to the participants.

II. Intervention Guidelines and Manuals

Due to the complexity of the interventions, a manual on the standard operating procedures (SOP) for each of the intervention model was developed. The SOPs detailed the study procedures and described the study-specific documents that needed to be used [Appendix IV]. It included the following:

- Study protocol or synopsis
- Description of the intervention
- Roles and responsibilities of the study staff
- Screening and eligibility criteria and processes
- Informed consent
- Enrolment procedures
- Visit schedules post-enrolment
- Planning and preparation for each intervention visit
- Clinical management
- Indications for referral
- Pharmacy activities (Drug packaging and dispensation)
- Monitoring and evaluation
- Data collection and study forms
- Data management
- Quality control procedures

III. Development of the SmartCare module

The SmartCare module was a pilot project by MoH funded by CDC implementing partner BroadReach International. This software was designed for electronic handheld devices to capture relevant information during community visits and later synced at the facility with the SmartCare database. All implementing partners piloting DSD models of care had to use this module to ensure that information captured during interaction with a patient at community level was synced with the national database. The module was designed to maximize the quality of data collection using drop down lists and incorporating check to avoid simple data entry errors. Data that was captured at clinic level included Patient registration details and care number and at community level, data collected included date of visit, symptom screening, and type of counselling provided, services referred to and pre-packed drug dispensation.

This was to ensure that indicators used for routine monitoring and follow-up were entered into the SmartCare database. For our study, we also incorporated this module to collect data at community level for all participants enrolled in the intervention models and had it installed in hand-held electronic devices which the CHiPs used for the main trial. In addition to this module, we created paper-based forms that captured all relevant data both for our research, monitoring and evaluation and as a backup in an event the SmartCare module encountered technical challenges.

IV. Development of the training package

I developed the training package materials that would be used to train all the study staff, CHiPs, community mobilizers and core health care workers responsible for HIV care in the facilities (overall in charge, nurses, pharmacists, and data clerks). The training package included the following:

1. Power point presentation - this included the overall design of the study and the research aims. It also gave a brief overview of the interventions and the procedures to carry out such as screening, consenting enrolment and follow-up visits. This also included adherence counselling sessions, how and when to refer patients to the clinic and health promotion messages.
2. Standard operating procedure manuals for each of the interventions (Appendix IV). This manual provided detailed information on the intervention and the processes involved.
3. Study forms – all the study forms were included for illustration and practical session.
4. Materials including flipcharts, stationery, and notepads
5. Power-point presentations on using the SmartCare module
6. Electronic Data collection (EDC) handheld devices to be used for practical session in collecting data.

An additional set of training slides was developed by the data manager on how to use the electronic hand-held device for data collection at community level with specific instructions on how to sync this data with the facility database at the end of each visit.

5.3.4 Management support

Management support was ongoing throughout the study and in order to ensure smooth implementation of the study activities, the following were put in place to ensure that both sites conducting the studies would not encounter challenges with implementing the intervention activities. This included:

- Transport (funds and vehicles) in each site to transport study staff from Zambart headquarters to the sites, CHiPs conducting club visits and specimen samples to the laboratory in the event the clinic encounters transportation problems. We also decided to use transport for health

care workers from the clinics who wanted to monitor the activities we were carrying out in the communities.

- Monthly meetings with the study staff to monitor progress of the activities, review documentations and discuss challenges that were encountered and how to mitigate them.
- Monthly meetings with CHiPs and their supervisors to get feedback and monitor their progress
- Quarterly meetings with the health care staff to provide feedback and recommendations and address any concerns arising from delivering the interventions
- Recruiting part time workers from the community who assisted the clinic and study staff in tracking patient files, retrieving and filing patient files in the registry at the time of participant's clinical visit.
- Mobile phones and airtime for study staff and CHiPs for contacting participants and other members of the study team.
- Monthly conference calls with the HPTN 071 ComART working group to provide updates on study progress.

5.4 Pre-implementation procedures

This section describes the procedures that had to be undertaken in readiness for the trial to be activated and start recruiting patients. It highlights the goals we were achieving, the challenges and how we mitigated them.

5.4.1 Study sensitization in the selected communities and health care facilities

Having all the regulatory approvals formalized and permission from MOH to conduct the study, we then sought permission from the Lusaka DHMT (who oversee all the primary HCFs in Lusaka) to work in the two clinics hand in hand with their staff and IPs in the daily operations of the clinic, sharing of data and other clinical activities such as clinical meeting etc.

In each facility we conducted a full-day meeting which included HCWs primarily working in the HIV care, implementing partners working in the facilities, overall medical superintendent, and in-charge nurse. The goal of this meeting was to provide an overview of the study aims and design, the two interventions and their operations, laboratory, and data management. The purpose of these meetings was to create a partnership with both HCF and IP staff and identify key or focal point staff from these teams to assist the study staff in clinical, laboratory and data management as study participants were clinically managed according to routine SoC. In addition, we also had a day meeting with the CHiPs and community Advisory Board (CAB) members in the two communities over the study and readiness to start the study.

As the two communities were already participating in the HPTN 071 (PopART) trial, we had already established a good partnership with both the health care facilities and the communities, and this created a favourable environment for us to integrate with the HCF and IP. Table **5.3** below shows the responsible parties for the daily ART clinic operations and how we integrated study staff with their activities.

Table 5.3: clinic operations and responsible parties

	Responsibility	**Study staff**
HIV ART clinic • Screening patients in the triage • Clinical review • Phlebotomy room for Routine laboratory monitoring	1.DHMT/ MoH 2.IP (CIDRZ) provides technical support in all the clinic activities by recruiting additional quality assurance and control nurses, clinical officers to screen patients and adherence support workers to provide adherence counselling	2 study nurses: • Assist with the screening and recruiting patients for the study. • Work closely with clinical officer during participant's clinical review Part time lay workers to assist with file retrievals and filing in the registry room
ART pharmacy	1. DHMT/MoH 2. CIDRZ provides technical support by providing a pharmacy technician to assist with the daily operations of the pharmacy	1 research pharmacy technician to pre-pack drug and ensure pharmacy registers are updated
Laboratory	1. DHMT/MoH for certain routine tests that are available at the HCF laboratory including CD4 count, full blood count, TB screening 2. CIDRZ provides support in Viral load testing and transport of specimens to the central laboratory	Identified focal point person in the central laboratory who would provide us with the results for study participants Assist with procuring specimen collection bottles in the event of stock-outs
Data management	1. DHMT /MoH 2. CIDRZ provides additional staff to assist with data entering the facility database. 3. CIDRZ M&E provides overall facility aggregate data form the SmartCare database.	Identified a focal point person in the facility to provide patient data Identify focal point person from CIDRZ who would assist us with SmartCare data for monitoring and evaluation purposes and analysis of study outcomes.

5.4.2 Randomization ceremony

Like many clinical trials or public health interventions, randomization is usually conducted as part of a public ceremony to avoid suspicions of unfairness or bias because investigators could intentionally or unintentionally favour some of the clusters or interventions. It is aimed at increasing awareness of a trial in a community or setting, develop an understanding of the rationale for randomization, and convincing the patients and key stakeholders that it was fair and transparent[207]. For this study,

randomization ceremony was done to allocate the zones to one of the three study arms. This was a crucial step in the planning process as once the zones allocated to the study arms was revealed, our trainings would then include the CHiPs who were allocated the intervention arms. Our study was activated whilst the main PopART trial was still in its third round of the intervention and each community had approximately 108 CHiPs working in pairs. Therefore, for logistical reasons, we only included CHiPs who were serving the zones allocated to the intervention arms the training package.

Having set the date, we invited the following for each of the two randomization ceremonies in the two communities:

- Representatives of the health care facilities (overall in-charge and ART in-charge nurse)
- Representatives from the community (community mobilizer and 2-3 members from the community advisory board)
- ComART study staff
- All the CHiPs serving both communities with their supervisors (CHiP supervisors)
- PopART intervention teams (Study and intervention managers)
- Representatives from Zambart from the Social science team
- Representatives from Zambart community engagement team
- Members from the data and information technology (IT) teams

The unit of randomization, which was the CHiP zone, methods for stratification to achieve balance across the zones were developed with help from statisticians from the London School of Hygiene and Tropical Medicine (LSHTM) and have been described in chapter 4. A list of 10,000 randomized allocations meeting the restriction criteria was created for each community, numbered 0000 to 9999 [Table 5.4].

Table 5.4: List of 10000 allocations created for each community

ID	Comm_8_zone_1	Comm_8_zone_2	Comm_8_zone_3	→	Comm_8_zone_50
0	B	B	A		C
1	C	A	A		B
2	C	B	B		A
3	A	C	C		B
↓					
9999	C	A	C		C

We conducted 2 randomization ceremonies for each of the communities separately on the 11th and 13th April 2017. We used a church hall in one community and a school hall in the other. The procedures that took place during both ceremonies were led by me and the study staff. To ensure fairness and transparency, we asked a member from the community, other Zambart teams to record the procedures and allocations. The randomization procedure was as follows:

1. A screen was projected showing the spreadsheet of the list of randomized allocations.
2. The study staff numbered 10 balls from 0-9
3. We next asked four people from each of the aforementioned cadres to select a ball, note the number, and place it back in the bag.
4. Having recorded the 4-digit number [e.g., 3157], we then highlighted it from the spreadsheet onto the screen so that it was visible to everyone.
5. We then followed the allocations for each arm, labelled A, B and C and determined the zones that fell under each arm.
6. The next step was to instruct the CHiPs teams to take note and record which arm their zones were assigned to, and then to proceed to their assigned arms, which were labelled “A, B, and C” at three separate corners of the hall. Following that, the research personnel and CHiP supervisors verified that the CHiPs serving their zones moved to the correct allocation.
7. I folded three sheets of paper, each labelled HBD (Home-Based Delivery), AC (Adherence club), or SoC (standard of care), and placed them in a little box.
8. At each of the three CHiPs corners, I requested a CHiP volunteer (as agreed upon by the CHiPs team) to come up and select one paper from the box.
9. When a CHiP chose a paper, the delivery model was revealed and assigned to them. (For example, if a CHiP from the assigned arm A chose a paper labelled HBD, which was the model assigned to arm A "Arm 1," and so on.)
10. A verification process was conducted at the end of each ceremony to ensure that the zones were allocated to the correct arms.

Having done the above procedures in both communities and the CHiPs and study staff were aware all the zones to which the study arm was allocated, we then compiled the results and a total of 104 zones from both communities were randomly assigned to one of the three arms (35:35:34). [Fig 5.3 and 5.4]:

1. Continue collecting ART at the clinic standard of care (SoC)
2. A choice of Home-based ART delivery (HBD) or remaining in clinic-based care
3. A choice of being in an Adherence club (AC) or remaining in clinic-based care

The maps were colour coded according to the study arms and provided to each facility and the Chip supervisors. We used yellow colour to denote SoC, pink for HBD and green for AC. This was equally done for all the registers, study documents and patient file stickers for identification purposes.

Fig 5.3: Randomization Scheme

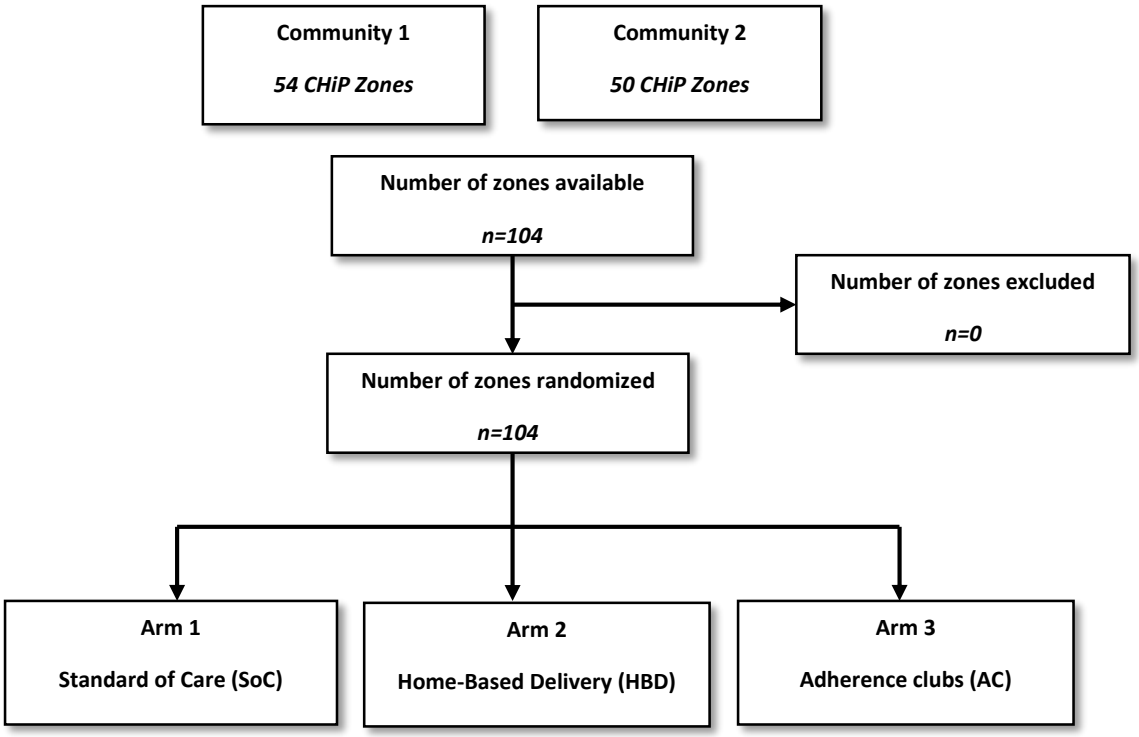
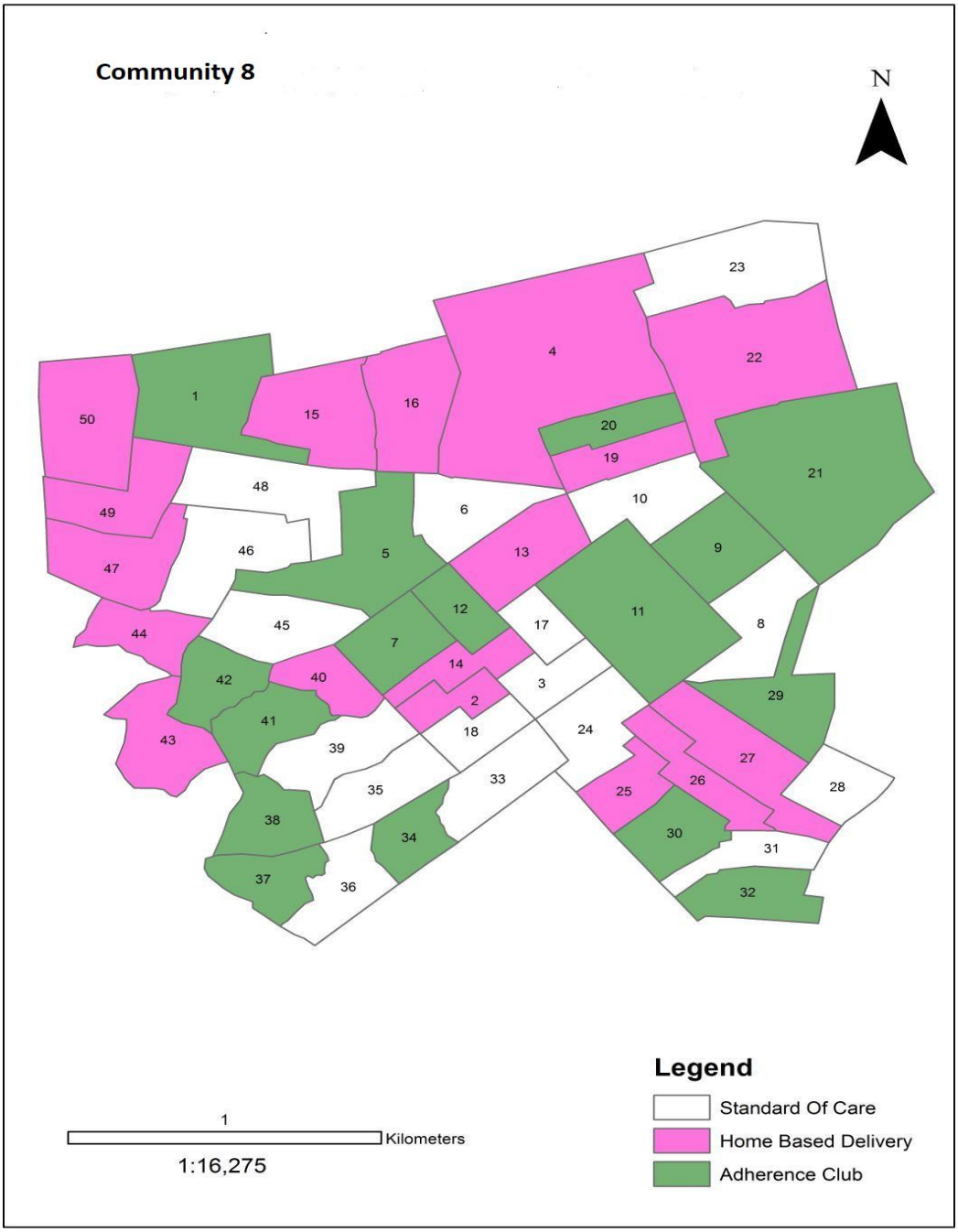
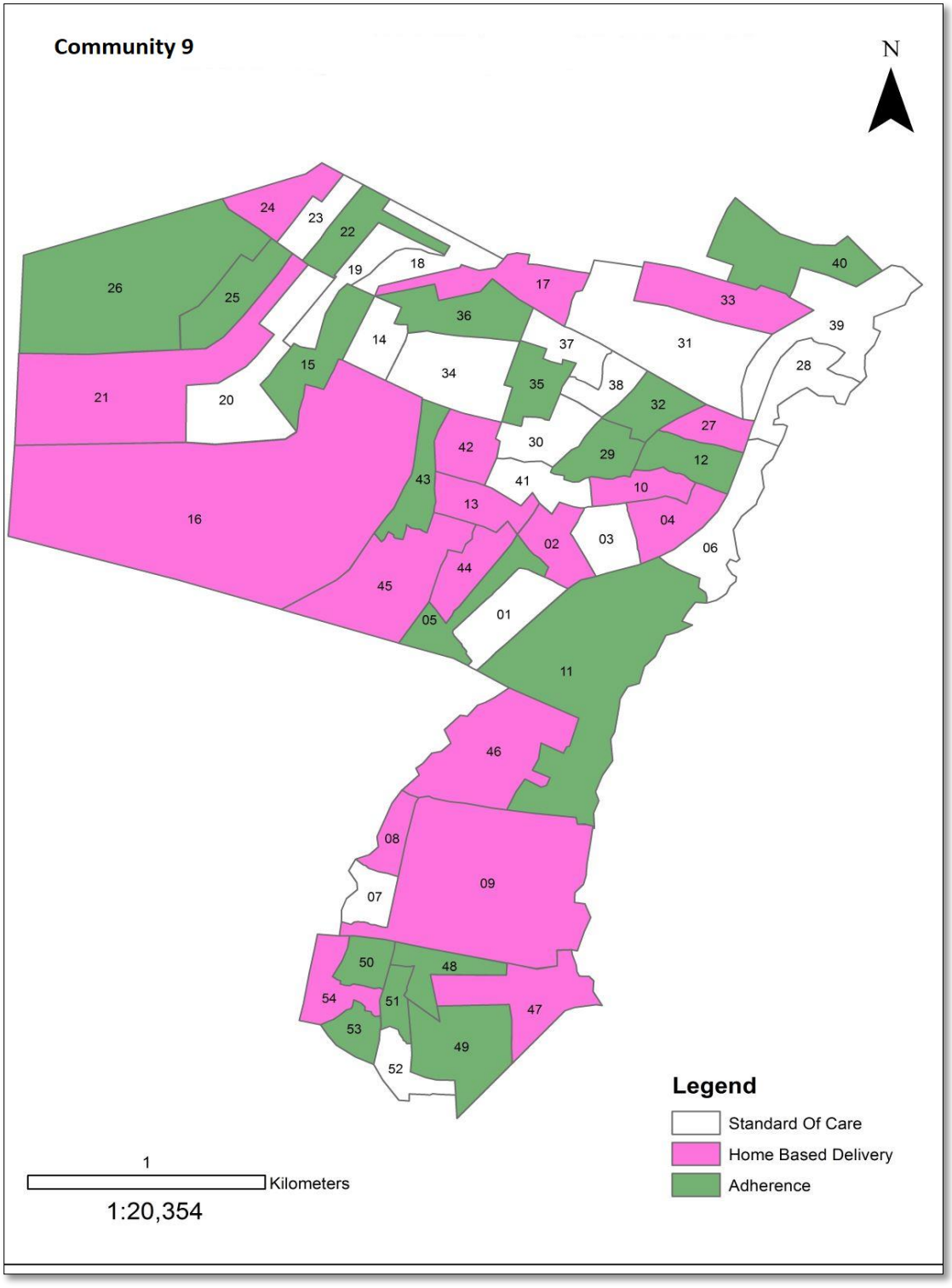


Fig 5.4. Maps of the communities with the zones allocated to the interventions

A. Community 8



B. Community 9



Having randomized the community zones to the allocated interventions and completion of trainings, we set out to conduct sensitization talks both at community and HCF level. In both communities we met with the community advisory board and community mobilizers to sensitize the communities about the models of ART delivery that were to be offered. The CHiPs were also encouraged to sensitize household members during the main trial intervention rounds about the models of delivery and encouraged patients who were interested to participate to go to the clinic to determine their eligibility.

In addition, the community mobilizers, a CHiP, and the study nurse would give talks in the mornings to PLHIV in the ART facility waiting room about the study and models of ART delivery and encouraged them to speak to the study nurse or staff at the clinic for more information or determine if they were eligible to participate in the study.

5.4.3 Trainings

We conducted trainings for each of the two interventions (HBD and AC) separately. For each community, we conducted 2 sets of trainings each over a 3-day period. For each set of training in each community, we invited the following participants:

1. All the CHiPs who were serving the zones allocated to the intervention
2. CHiP supervisors
3. Representatives from the HIV clinic [medical doctor, clinical officer, ART in-charge and additional 2-3 ART clinic nurses, ART pharmacist, data clerk].
4. 1 community mobilizer
5. Study staff [Study coordinator, study nurses, pharmacist technician, and data clerk]
6. 1-2 members from our social science and data team who would be part of the study.

The characteristic of the trainings is outlined in Table 5.5 below.

Table 5.5: Characteristics of the trainings

	Initial training prior to recruitment	Additional trainings in the intervention clinics
Description	3-days of training comprising of lectures and practical sessions	Refresher trainings one-or two-hour session once every 3 months
Trainers	Principal investigator, study coordinator, regulatory officer, and data manager	Principal investigator and study nurse
Trainees	Study staff (nurses, data clerks and pharmacy technicians) CHiPs, CHIP supervisors, and HIV clinic staff (doctors, clinical officers, ART in-charge and nurses, Pharmacists, and data clerks)	CHiPs and study staff New study staff/ CHiPs
Setting	Zambart headquarter conference room Health care facility	Training session held at facility
Model of delivery	Lectures, face-to-face small group discussion	Face-to-face group discussion
Intensity and duration	4.5 hours of lectures in a day with 4.5 hours of practical session	1-2 hours mostly practical sessions

I. Training methods

Training methods involved conference room lectures, small group discussions and practical sessions (use of study forms and data collection techniques).

II. Training schedule and content

The training focused on basic information related to HIV prevention, treatment and adherence support and the description of the intervention model and core contents of each intervention model using the standard operating procedures. The practical aspect included on how and when to use study related forms and orientation with the community SmartCare module. Key aspects on the training focused on delivery of the interventions with a lot of emphasis on dispensation of pre-packed medications and monitoring and evaluation. Case scenarios were also conducted to impart basic skills and at the end of the training, we conducted a 1-day practical session at the clinic in each community for each of the two intervention where we did role plays of screening, consenting, pre-packing drugs and use of registers and forms.

A key focus in the trainings included the delivery of drugs by the CHiPs. As the CHiPs were already familiarized with delivering a combination door-to-door HIV prevention package including HIV testing and collection of sputum for TB screening, delivering drugs in the communities would require them to understand the importance of delivering the drugs to the right participant with the correct drug scripts. As all our participants would be on standard first-line therapy, except for a few who might be on alternative first line therapy, the importance of ensuring that patients were receiving the correct drugs was emphasized and this included verification of drugs with the pharmacy during each visit. An additional plan put in place was having the scripts signed by the patient and returning a copy of the script to the pharmacy who does the verification process to ensure that drugs were delivered to the correct person. The training also included audit measure put in place to ensure that no drugs would be pilfered during the delivery.

5.4.4 Clinic space and Infrastructure

Clinic space and infrastructure did not require major remodelling except to ensure that there was enough space in the pharmacy to store the pre-packed drugs and the registry room furnished with additional shelves to file study participants clinical records for easy retrieval during clinical visits. The existing infrastructure that was already placed by the HPTN 071 (PopART) trial such as additional rooms in the clinic were used for this study.

5.4.5 Clinic set up and logistics

Prior to study activation, we ensured all logistics were in place and this included:

- Clinic space [additional rooms] were ready for enrolment.
- Office furniture [desks, fans, chairs, benches and filing cabinets]
- Stationary [registers, study forms and binders]
- Cleaning materials
- Pharmacy – trunks and bags were procured and delivered to the pharmacy for packaging and storage of drugs
- Community maps and their respective zones

We also included additional furniture in the clinic triage room for our study staff to screen patients for eligibility. An additional task that was conducted by the study staff during this stage was to identify challenges that would hinder screening for eligibility such as entry of viral load results in patient files. The study staff assisted the clinic staff in tracking VL results and entering them into patient files.

5.4.6 Laboratory Procedures

The key outcome of this study was viral suppression 1 year after enrolment into the study. Laboratory management including HIV VL testing, stages of HIV disease progression and response to therapy are essential components of ART management. The laboratory monitoring for all the study participants would follow the routine laboratory requirements as per national standard of care guidelines. The existing health laboratory services under MoH and CIDRZ would provide the laboratory services for the study within the existing laboratory network, consisting of laboratories located in the clinic and a central laboratory that would conduct the HIV VL testing. We also utilized the existing sample transport system that facilitated the transportation of specimens from the HCF to higher-level central laboratory, including the return of client results. To maintain client confidentiality, laboratory results would be communicated directly with the study participants during their clinical visits.

5.4.7 Preparation of data collection tools

In addition to the study forms to be used for data collection purely for research purposes, existing tools in the national HIV programs would be used to monitor client care. This included the existing smartcare forms that records patients clinical records, laboratory results and drug prescription. For enrolment and efficient handling of the HBD and AC models of care, we would use the specific registers and forms that were designed for this purpose with the goal of improving management of the two modles of care as well as for reporting purposes. The general procedures for M& E would be followed and in relation to both HBD and AC models, the procedures would include:

- Document patients willingness to enrol in these modles of care in patient ART files and care cards
- Complete ART prescription in patient files and pharmacy registers and request laboratory investigations when due
- Ensure appointment dates are given and patients visit dates are recorded in the appropriate ART forms to avoid false defaulters
- Follow up on patients who are lost to follow-up or have missed appointments in the SoC arm, just as is done in mainstream care. For those in the HBD and AC models, tracking mechanisms are outlined in the SoPs.

5.5 Study Implementation and Procedures

In chapter 4 section 4.5, we outlined the study procedures from screening to study exit. In this section, we describe in detail how we carried out each of these procedures from the time of study activation upto study completion. The challenges that we encountered during each step and measure put in place to mitigate are detailed at the end of this section. This was written with a view to future implementation and what recommendations need to be put forward when implementing DSD models out of the health care facility on a large scale.

5.5.1. Screening for eligibility

The recruitment of eligible participants began on 5th May 2017 and ended on the 13th of December 2017. All adult HIV+ patients in care who attended the clinic for their routine clinical follow-up during this period were assessed for eligibility. Screening was done in the HIV clinic, a stand-alone building within the clinic premises every morning as that was the time patients in HIV care came to the clinic. Screening for eligibility was done by the study coordinator, study nurse and two facility ART nurses in each clinic. As the PI, I alternated between the two clinics daily to provide supervisory support. This step was done in the triage desk where all patients present on that day had their files retrieved and waiting to be triaged for either a clinical, laboratory or a pharmacy visit.

All Adult patient files were reviewed to determine if they met the WHO criteria for “stable” definition. This included a recent undetectable viral load result in the last 12 months, WHO stage I & II and on first line therapy for more than 6 months. Initially, virological suppression was defined as HIV RNA levels < 400 copies or < 50 copies/ ml depending on the viral load testing sensitivity platforms in the laboratory. This later changed in 2018 in the national guidelines to VL < 1000 copies/ ml as being virally suppressed.

We further determined whether potential participants were living within the study catchment area, as a study eligibility criterion, by asking them verbally and if they were, their files were flagged with a sticker and seen by the study nurse (as a potential study participant) after the patient completed his/her clinical visit on that day.

Potential study participants were then seen by the community mobilizer or the CHiP supervisors who confirmed their place of residence and the zone they were living in using the study catchment intervention map. Once confirmed as living within the study catchment area, they were given a slip of paper with their zone number and referred to the study nurse who would introduce the study and obtain written informed consent.

This step required active coordination and harmonization between the HCF and study staff as both teams had to identify potential participants and refer them for eligibility screening. During the recruitment stage, we screened a total of approximately 9,962 patient files across both health care facilities. For every patient file screened, we tallied it on a log chart and tallied reasons for not being eligible. Although this was a crude way of collecting data it gave us an estimate of how many patients were eligible for our study out of all the patients who were seen during that particular time frame. The teams managed to identify 2,503 potential patients who were eligible for the study across both health care facilities.

5.5.2 Obtaining written consent

Having identified potential participants during the screening process, they were referred to the study nurse who would then screen them for study eligibility. This included confirming participant met the "stable" definition criteria as well as the additional study criteria of living within the study catchment area. Once the participant met the eligibility criteria, the study nurse would then proceed to obtain a written informed consent.

Obtaining consent was done either at an individual level or in groups of 4-5 eligible participants. If there were several potential participants waiting to be consented, each one of them would be provided with a consent form and the study nurse would explain the study procedures. Thereafter, each patient would be called in privately into the study office and further questions were asked as to whether they understood the study and procedures and if they had any questions for further clarity or concerns.

A standardized consent form [Appendix II] which provided study information was used and three copies of signed consent forms were obtained from each participant where one copy would be given to the participant, the second copy attached to the participants clinic records and the third copy for the study records stored in a safe and secure cabinet [later transferred to research headquarter office].

Having consented to the study, participants were then assigned to the study arm, where the model delivery was revealed to them. Those who were assigned to either Home -based delivery or Adherence club models could choose between the assigned models of care or facility-based (SoC). Those assigned to the facility based (SoC) had no choice.

5.5.3 Enrolment

For all participants who consented, the following details were entered into the appropriate model registers (HBD, AC or SoC):

1. Participants details [name, sex, age, mobile phone number and residential address]
2. HIV care details [ART unique ID, date of ART initiation, current drug regimen, most recent VL result]
3. Date of enrolment, scheduled dates of next community and clinical visits [pre-filled dates]

Participants were also given the details of the CHiP team (names and contact numbers) who would be responsible for delivering the interventions to them. Participants who did not have a mobile phone contact detail were asked to provide a contact number of one of their household members (if willing) in case they were unreachable.

The study nurse would also provide them with the dates of their next scheduled visit in the community (HBD/AC) and the next clinical visit date, both of which were recorded in their HIV care cards and clinical records. Having completed the enrolment step, participants had to complete either their clinical or pharmacy visit for that day and collected their 90 days drug refill to last them till the next scheduled visit in the community. Participants who were assigned to the intervention arms but chose to continue care at the facility were still registered in the appropriate intervention registers and were told to continue coming to the clinic for their reviews. Those who were assigned to the SoC arm were also entered in the SoC registers and told to continue with clinic care.

Recruitment for the study began in May 2017 and the first home and club meetings took place in August 2017.

5.6 Operations of the intervention models [HBD and AC] and facility based SoC.

Following the procedures undertaken in screening and enrolling participants in the study, this section describes in detail how the two models of ART delivery (HBD and AC) were implemented and operated. It provides an insight on how we planned for their home and club visits and what activities and procedures were carried out during these visits. This section also describes in brief how patients in the SoC (Facility-based) are monitored under routine HIV care in our study setting. In Table 5.6, the standard of care is compared with the 2 models that were implemented.

For this study we used a color-coding system for the following reasons:

- Identify the model of care participants are receiving
- Retrieving participants clinical records for planning visits and follow-up
- Filing participants files in the appropriate places (for SoC participants, files were kept in the HIV clinic, whereas those in the HBD and AC models, files were kept in the study office secured cabinets)
- Filing of patient files in appropriate cabinets following clinical or pharmacy visit.
- Allow both study staff and HCW to identify study participant and ensure any events such as death or LTFU which has occurred to be reported to both teams in case it goes unnoticed by either the study staff or HCW.

Stickers that were coloured according to the model of delivery were attached on the participant's clinic records and HIV care cards which they carry with during each visit. In addition, the registers and study forms used for HBD and AC only were also printed in their respective colour for easy filing, monitoring and evaluation.

A. Health Care Facility (SoC) operation

Participants assigned to the SoC arm continued receiving care in the clinic and follow the routine schedule that was in place for HIV care according to standard of care guidelines. Under current routine HIV care, stable patients come to the clinic once every 3 months for their drug refills and adherence support. Every 6 months, the pharmacy visit is combined with a clinical visit for their clinical review and laboratory measurements that are due on that visit date [Table 5.6]. Laboratory measurements include VL test (6 months post ART initiation and thereafter yearly), CD4 count tests and other tests such as creatinine and Liver function tests.

Participants in the SoC arm could not be monitored for their follow-up visits by the study staff as they went directly to the ART clinic for their scheduled visits. Therefore, it was difficult to determine the dates of their scheduled visits and whether they had missed a visit or not. Details of their visits and outcomes could only be obtained from SmartCare database. A simple register was created to collect their identification details at enrolment (ART number, name, contact details and residential zone) and used at the end of the study retrieve their data from SmartCare and clinical records to measure the study outcomes.

Table 5.6: Comparison of facility based (SoC) and community models (HBD and AC) for management of patients[ŧ]

	Standard of care (SoC)	Home-based ART delivery	Adherence Clubs
Setting	Clinic based	Community based	Community based
Key personnel	Doctors/nurses	Community HIV providers (CHiPs)	Community HIV providers (CHiPs)
Frequency of visits	3-monthly	3-monthly	3-monthly
Frequency of clinical consultations	3-monthly (every visit)	6-monthly	6-monthly
Location of clinical consultation	Clinic	Clinic	Clinic
Units of care	Individual patients	Individual patients	Groups of 15-30
Peer-based support	Minimal emphasis	Strong emphasis	Strong emphasis
Patient self-management	Minimal emphasis	Strong emphasis	Strong emphasis
Frequency of laboratory monitoring	6-monthly	6-monthly	6-monthly
Management of clinical complications	On-site at the clinic	Referral or transition to mainstream care	Referral or transition to mainstream care
Drug dispensation	Dispensed from pharmacy	Pre-packed in pharmacy and dispensed at home	Pre-packed in pharmacy and dispensed in the club
Treatment supporter "buddy"	ART can be collected by the buddy	Patients have to be present at home to collect ART	Patients have to be present in clubs to collect ART

[ŧ] ***modified from*** *Grimsrud, Anna et al. "Implementation of community-based adherence clubs for stable antiretroviral therapy patients in Cape Town, South Africa." Journal of the International AIDS Society vol. 18, 1 19984. 27 May. 2015, doi:10.7448/IAS.18.1.19984 [175].*

B. Home-based ART delivery (HBD) and Adherence Club operations

For both HBD and AC models, Table 5.7 provides an outline of how the visits in both interventions were planned and carried out.

Table 5.7: Outline of the HBD and AC preparations and operations

	Home- Based Delivery (HBD)	Adherence Clubs (AC)
I. Venue	Home visits were conducted in the participant's home	Venues of clubs included: school halls, classrooms, church halls and communal meeting places within a zone (i.e., patient homes). Venues were identified and arranged by the CHiP teams working in the zones after having consulted relevant authorities (community stakeholders) over the use of these venues prior to the recruitment stage. During enrolment process, study nurse would inform the participants of the first meeting club venue. In the first club meeting, club members would be asked if they were comfortable with the chosen venue or wanted an alternate venue. In some zones, some group members offered their homes as club venue. All the club venues in the communities provided privacy.
II. Scheduling Appointments	• Participants scheduled to have home visits once every 3 months after date of enrolment and thereafter a clinical visit 3 months later. • Scheduled visits were planned 1-2 weeks earlier than actual date [to allow flexibility in case of unforeseen circumstances]. • At enrolment, the study nurse would enter the dates of the next 4 scheduled visits in the register [for planning purposes]. The first two visits [home/clinical] would also be recorded in patient files and care cards. • Each CHiP team would conduct at least 2-3 home visits/day [a zone that had 25 participants enrolled in HBD and had their home visits scheduled towards the end of the month, the teams purposefully planned to have the CHiP team conduct a maximum of 12 home visits per week]	• Having enrolled into a club model, patients ART number and baseline characteristics were entered in the AC registers. • As with the HBD registers, the AC registers were completed by the study nurse for the purpose of planning the club meetings. Participants from a zone allocated to the AC intervention were informed of their club meeting date and the club venue. • Each club was given a number corresponding to their zone and each zone had 1 club comprising of at least 15-30 members. Some zones had more than 30 members (extra 5 members) and allowed them to continue with the same club rather than creating 2 clubs within one zone for logistical purposes. • Club numbers and the first club meeting date were recorded on the patient's HIV care card by the study nurse.

III. Preparation for the visit	Prior to a scheduled home visit [a week in advance], study nurse would review the HBD register and determine the number of visits scheduled for the coming weeks. Preparatory steps included: • Retrieving patient details [ART number, zones and contact details] from the HBD register and responsible CHiP teams notified of their upcoming visits • Participant clinical files would be retrieved • Clinic files taken to the pharmacy for pre-packaging of drugs. Drugs pre-packed in black bags with dispensation slip attached to it and securely stored in a locked trunk in the pharmacy until the visit date [Fig 5.5 (a)] • Pharmacy enters the details of the participant and drug quantity in the ART pharmacy register • Study nurse arranges for the study documents to be used during the home visits and includes the attendance registers [with participants details and next two scheduled visits pre-filled] and study forms that may need to be completed [missed visit forms, referral forms and event forms] [Appendix III.A]. • CHiP team calls the participants 2-3 days prior to remind them of their upcoming visit using their diary.	Preparations for club meetings were similar to that of HBD. For club meetings: • Study nurse would use the club membership register (Appendix III.B) to retrieve the names of all the club members and their contact details and provide them to the responsible CHiP team to contact the members and remind them of the visit date and venue 2-3 days prior. • All the club members' clinical records would be retrieved by the CHiP team or lay worker from the registry and sent to the pharmacy technician who would pack the drugs in a trunk and fill out the drug slips. Having done this, the pharmacy register would be filled out. The drugs would be kept in the pharmacy until the day of the club meeting. • Study nurse would then fill out an attendance sheet that would need to be completed at the club meetings. For club meetings, a single attendance register (Appendix III) was filled out with the names of all the club members and the next scheduled visit (clinic visit). • The study nurse would also include a folder containing study forms in case needed [missed visit, referral slips, study event forms] and other commodities such as male and female condoms, leaflets containing key messages on HIV treatment, adherence etc.
IV. Conducting the visit	CHiP teams would receive the drugs and study documents on the day of the visit and carry them in their backpacks [Fig5.5 (b)]. The following procedures would occur during the visit [Fig 5.5 c-d)]: • Introduction [first visit] • Symptom screen checklist • Adherence support and risk reduction counselling • Pre-packed drugs dispensed, and drug slips signed • Provision of condoms and promoting key health messages • Completion of attendance registers • Reminding participant of their next visit and recording dates on their cards • Laboratory results [usually in the successive visits]. For patients with a detectable viral load, the staff would contact participants even prior to the scheduled visit	The CHiP teams in charge of the club meeting would gather all essential documents and commodities on the day of the club visit. The trunk carrying the pre-packaged medications and drug slips would be picked up from the pharmacy as well. Transportation from the clinic to the club location was supplied by one of the study vehicles for club meetings. The first club meeting lasted longer than the subsequent club meetings. During the first club meeting, formal introductions were conducted, and rules and regulations of club meetings were highlighted. This included punctuality and maintenance of confidentiality; not disclosing club members or club discussions to non-members [outside of the club meetings] and agreeing on the club venue. Any members found to have broken the club conduct would be given a stern warning and if found to continue breaking the club norms would result in transition to facility-based standard of care.

	• Referrals for participants who exhibited symptoms to the clinic	During the club meetings: • One of the CHiPs would conduct group adherence counselling and health promotion [Fig 5.5 (e-g)], whilst the other CHiP would call each member aside and conduct a brief symptom screen, one-on-one counselling if needed, dispense the pre-packed drugs, provide a referral slip if they have any symptoms and distribute condoms [Fig.5.5 (h)]. • The club members were reminded of their next clinical visit and were also informed about the importance of contacting the CHiP or the study nurse if they will be unable to make it for their next clinical or club meeting in an event they need to travel out or have other work commitments.
V. End of visit procedures	Average time for a home visit was approximately 20-30 minutes. At the end of the visit: • Study forms handed to the study nurse who checks for completeness • Signed drug slips handed over to pharmacy technician who would then update the pharmacy register and Daily Drug register (DAR) for having had the drugs dispensed • Study nurse then updates participant clinic files to indicate participant seen in their homes and drug dispensed • Files then sent to the data room for entry into the SmartCare database. • Study forms are stored in a secured cabinet	Club meetings with group members exceeding 20 patients on average lasted for 1.5-2 hours whereas those with less than 15 members lasted approximately 1 hour. The duration in time varied as some members would turn up 10-15 minutes late and depending on whether participants had further questions or concerns regarding their care which needed clarity and additional adherence counselling messages. The procedures at the end of the club visit were similar to that of HBD. The CHiPs returned the study forms and registers to the study nurse who checks for completeness. Drug slips are returned to the pharmacy and the pharmacy register and DARs are updated. The study nurse then enters the date of that particular visit and the quantity of drugs dispensed on the patient's clinic records to be entered into SmartCare database.
VI. Missed Visit	If a participant were not present during a home-visit even after having successfully contacted them prior, the CHiP had to contact the participant to determine if the visit could be postponed to a later time during the day or within a grace period of 5 working days provided that the participant had sufficient drug supply to last till the rescheduled visit. If a visit could not be made within this grace period, then the participant had to come to the clinic to meet the study nurse who would ensure that they were given a drug refill and their next appointment date. When a missed visit occurred, the CHiP would fill out a missed visit form (Appendix III.A) and the unissued drugs would be returned to the pharmacy.	Patients who missed a club visit were contacted via phone call by the CHiP after the club session. Once contact with the patient was made, reason for missing the visit was determined and a missed visit form would be completed. The patient would be given a grace period of 5 working days to come to the clinic to collect their drugs. If no contact were made, details of the patient would be provided to the study nurse who would follow it up with the CHiP to contact them over the next few days or the study nurse would try and contact the patient. For any patient who missed 2 consecutive visits (club or clinic), they would be transitioned to facility based (SoC). Procedures for patients who missed a club visit and did not turn up at the clinic to collect their refills or attempts to contact them proved to be futile with unknown outcomes were like that of HBD described above.

	For a participant who missed a home visit and did not come to the clinic after the grace period, another attempt would be made to contact the participant to come to the clinic or failure to do so would result in transitioning them to SoC. Following a missed visit and participant could not be contacted, the CHiPs would inform the study nurse who would flag their ART files and attempt to contact the participant either by phone or having the CHiP team track the participant during their visits and determine whether participant has relocated or not. If all tracking measures were exhausted and participant was found to be more than 90 days late after their last scheduled visit or drug refill with an unknown outcome, they were considered lost-to-follow up (LTFU).	
VII. 6-monthly clinical visit	• Participants in both intervention models were scheduled for a 6 monthly clinical visit for their clinical review and laboratory tests. • Laboratory tests included viral load, CD4 count and creatinine clearance. **All study participants in the HBD models** were encouraged to visit the study nurse's office during their clinical visit. Clinical records were retrieved, and details confirmed (updating their contact details and residential address if changed). Following this, they would be escorted to the ART building where they would be triaged, reviewed by clinician, have their laboratory tests (if scheduled) done and then to the pharmacy for their 3 monthly drug refills. After pharmacy participants would then go back to the study nurse's office where the study nurse would review the file to verify that participant was seen by the clinician, laboratory tests ordered and had collected their 3-monthly drug refill. The study nurse would then provide them with their next scheduled home visit and record their visit in the registers as having had their clinical visit. **For participants in the AC model**, the club members would be encouraged to gather as a group by the study nurse office, where they would have their files retrieved and then sent to the ART building. To help expedite the clinical visit for group, the nurses would take the participants vitals and record them in their files, conduct adherence counselling and send the participants to the ART waiting room to be seen by the clinician [Fig 5.5. I and j]. For those who were due for their laboratory tests (Viral Load), the nurses would collect the samples. Once the club members were seen by the clinician, they were then referred to pharmacy who prescribed drugs for 3 months and then sent to the study office where they would all be asked to sit in a group, reminded of their next scheduled visit in the community.	
VIII. Transition to SoC	Participants from both models of care were transitioned (up-referral) to facility-based (SoC) if: 1. Had evidence of treatment failure based on virological assays and clinical staging of the disease 2. Developed an opportunistic infection such as TB 3. Having missed more than 2 visits (either in the community or clinic) 4. Moves from one zone to another offering a different intervention 5. Patient request 6. Moves out of the study catchment area or out of the community but continues to receive his care from the facility. For women who became pregnant, they were given a choice to continue care in the models or receive care in the facility. For those who opted to continue receiving care in the models, they were advised to follow their routine antenatal scheduled visits in addition to the clinical visits.	

Figure 5.5(a). Pharmacist technician pre-packing drugs ready for distribution

Fig 5.5 (b). A pair of CHiPs going to a patient's home to conduct the home visit

Fig 5.5 (c). A pair of CHiP conducting a home visit

Fig 5.5 (d). A pair of CHiP during a home visit dispensing pre-packed ART

Note: ART regimen being dispensed included the single fixed dose combination of Tenofovir [TDF], Lamivudine [3TC] and Efavirenz [EFV] also called Atripla. Most patients on first line therapy were on this combination until towards the end of the study where national guidelines recommended Dolutegravir [DTG] in favour of EFV.

Fig. 5.5 (e). An adherence club meeting in a community hall

Fig.5.5 (f). A CHiP facilitating a club meeting in a classroom

Fig 5.5 (g). Chips conducting a club meeting in a market communal buildina

Fig 5.5 (h). During a club meeting, a chip takes a patient aside and conducts brief symptom screening and updates the attendance registers.

Fig 5.5(i). A study nurse conducts adherence support during one of the clubs 6-monthly clinical visit outside the ART building.

Fig 5.5 (j). One of the CHiPs with the club member's s waiting at the clinic for their 6-monthly visit

5.7 Monitoring and evaluation

All the data collected during the home and club visits were recorded on paper-based forms. In addition, the EDC device was also used to collect data for the SmartCare to ensure that indicators used for routine monitoring and follow-up was entered into SmartCare. The SmartCare module was installed in the CHiPs EDC and captured the following data:

- Date of visit
- Symptom screening
- Adherence counselling [whether counselling was provided or not]
- Referrals, if any
- Drug dispensation
- Next visit date

All this information was also captured in the paper-based study forms [attendance registers] by the CHiPs and served as a back-up in an event the EDC does not function properly during the visits or fails to sync with the facility database. For participants in the standard of care, routine data collected during the visits were retrieved from their clinical files and SmartCare. CHiPs conducting the home visits and club meetings compiled monthly group level reports for the study staff.

Data for study outcomes was extracted from participant's clinic records and SmartCare database. This was done at baseline and at 6 and 12 months after enrolment into the study. At 6 and 12 months, we collected dates of all visits (community and clinic) since enrolment, dates of transitioning to SoC, and (if known) cause of death for participants who died. In addition, at each data abstraction, we recorded the following: 1. Date and results of viral load after enrolment into the study and most recent CD4 count (if any); 2. HIV disease progression which was defined as having developed a new or recurrent WHO stage III & IV conditions after study enrolment; 3. Date of the last clinic encounter which was based on documented clinic visit; 4. Lost-to-follow up (LTFU), patients were considered LTFU if there was no contact for more than 90 days after the last missed scheduled appointment and if they were not known to have died or transferred out during this period and 5. Model retention, participants were considered non-retained in the HBD and AC models if they transitioned back to SoC or out of the study arms for any reason including co-morbidities, LTFU, death, opting out or study withdrawal.

5.8 Study exit

Several meetings were held with the facility and implementing partner with regards to transitioning participants from the two models of ART delivery when the study comes to an end. Towards the end of the study period, participants were informed about them being transitioned to SoC where they would receive the various formats of DSD services being offered by the clinic. This included multi-Month (6 months) drug refills, Community Drug Distribution Points (CDDP) or Urban Adherence Groups (UAG). At the end of the study, the study staff ensured smooth transition for all patients in the two models of ART delivery to SoC and this took about 2-3 months. Thereafter it was left to the HCF to decide which models the participants would be allocated to and this was also dependent on which DSD services were being scaled up.

5.9 Implementation successes and challenges

This section divides the overall study implementation findings into successes and challenges that would be pertinent to implementers and policy makers who want to scale up models of ART delivery outside the health care facilities.

Overall, we successfully modified and implemented the two community models of ART delivery (HBD and AC) from various pilot projects conducted over the last decade in sub-Saharan Africa. Since most DSD services were conducted in rural settings, there was a lot of scepticism as to whether these models would be feasible in a high HIV burden urban resource-limited setting. The outcomes from our trial are promising, as discussed in the next chapters in terms of uptake and acceptability, high rates of viral suppression and retention amongst the study participants.

Table 5.8 summarizes the key factors that we identified as either enablers or jeopardizers to successfully implementing and sustaining DSD models in resource-limited settings. One of the key factors in successfully implementing these models of care was ensuring that key stakeholders such as the health care facility workers, implementing partners and the patients were involved in the planning of the interventions with making decisions and providing suggestions for the models of ART delivery.

The characteristics of the communities were also critical to the effectiveness of implementing the models of care. The CHiPs were well known in the two communities as they had been delivering door-to-door HIV combination-prevention package of the HPTN 071 (PopART) trial for more than 2 years prior to implementing these models of ART delivery which solidified their relationship with the communities and health care facilities. This could have changed the community's perceptions towards these cadres and therefore willing to allow them to visit their homes or meet them in a club where

they were entrusted to provide them with HIV care and support. The health care facilities were also an important factor in the successful implementation as they created a friendly environment and enthusiasm for the study.

Participants found the two interventions acceptable, and this has been described further in Chapter 6. We successfully screened 2,499 potential participants of which only less than 1% declined consent to participate in the study. Although participants who were assigned to the community models of ART delivery were given the choice to continue with ART delivery from the health care facility or to accept the community models of care they had been allocated to, the majority chose the latter. Over 95% of participants assigned to the community models of ART delivery chose the models, reflecting a high acceptability towards these models of care.

Table 5.8. Summary of the main factors identified enabling or jeopardizing the implementation and sustainability of HBD and AC models

	Enabling Factors	Jeopardizing Factors
Leadership and Governance	• Providing policy framework with oversight, building coalitions, putting in appropriate regulations and accountability • Strong support from MoH and community leadership	• Over-dependence on NGO and other external funding sources to provide guidance and support
Stakeholder sensitizations	• Engaging key players within the health delivery system and communities that will be involved in service delivery • Effective communications and feedback with health care facility staff	• Patients in HBD and AC models not viewed as the clinic's responsibility
Staffing	• Should be inclusive of multidisciplinary team including a cadre of recognized CHWs • Inclusion of additional staff for pharmacy and packaging of drugs	• Dependent on donor support to hire additional staff and CHWs to deliver the interventions
Space and Infrastructure	• May be required to accommodate enrolment and follow up of DSD patients	• Inadequate spaces due to resources • Insufficient space and storage for pre-packed ART • Maintenance of community venues for club meetings
ART distribution and supply	• ART distribution by CHWs to be supported by pharmacy • Reliable uninterrupted drug supply • Flexible policies regarding distribution of ART in the communities	• Drug stockouts • Inefficient supply chain
Clinic changes	• Laboratory services, visit schedules and filing systems may need changes to gain efficiencies and ensure routine laboratory tests and results are provided • Up-referral and linkage to the facility for those needing additional care • Demand creation for access to VL testing	• Poor referral systems and linkage to care • Re-organization of registry rooms for easy retrieval of patient files • Inadequate demand creation for VL testing

Resources	• Additional resources for CHWs delivering care outside the facility – bicycles, mobile phones, drug dispensation bags, transport [vehicles for club meetings]	• Limited resources • Distance to patient homes and club venues
Monitoring and evaluation	• Strengthening and simplifying data collection tools for DSD patients • Standardization of data collection tools • Integration of DSD tools with existing HIV program monitoring tools	• Parallel data collection tools for M&E • Early detection and response to critical laboratory values • Effective and robust tracing mechanisms for LTFU patients
Community Embeddedness	• Patient empowerment over self-management • Social/peer support [patient participation] • Strong support from MoH and community leadership	• stigma
Organizational capacity	• Program flexibility regarding size of clubs, venues, and duration of drug refills • Flexibility over visit schedules • Adequate staffing and trainings/ mentorship • Adjusting the eligibility criteria • Improvements in the referral system	• Non-recognition of CHWs in the HCF • Poor referral system • Unreliable drug supplies
Enabling environment	• Political support and buy-in • High acceptance in the community and health care workers • Patient leadership • Stigma reduction activities	• Lack of recognition and standardization of CHWs • Lack of standard operating procedures and guidelines for DSD model operations • Lack of clarity on how the DSD models should work and their benefits

Although the roll-out of the community models of ART delivery were found to be feasible in our urban setting, we encountered several challenges during the implementation of the interventions and along the duration and at the end of the trial. In the following sections, challenges that were encountered during the start and end of the trial will be highlighted. The main challenges included:

1. Identification of eligible “stable” patients
2. Viral load testing and results
3. Recruitment of male participants
4. Service shortages
5. Participant mobility
6. Data availability for monitoring and evaluation.

I. Challenges in identifying "stable" patients for recruitment into the models of care

For our study we recruited a total of 2,489 participants across both communities. These numbers were lower than what we would expect in high volume ART clinics in urban settings like Lusaka where approximately more than 10,000 PLHIV are in care and the reasons for not able to recruit large number of patients in our study are described here.

There were a number of unforeseen challenges in identifying potential study candidates who met the study's "stable" definition criteria and therefore excluded from recruiting them and these are outlined in Table 5.9 below.

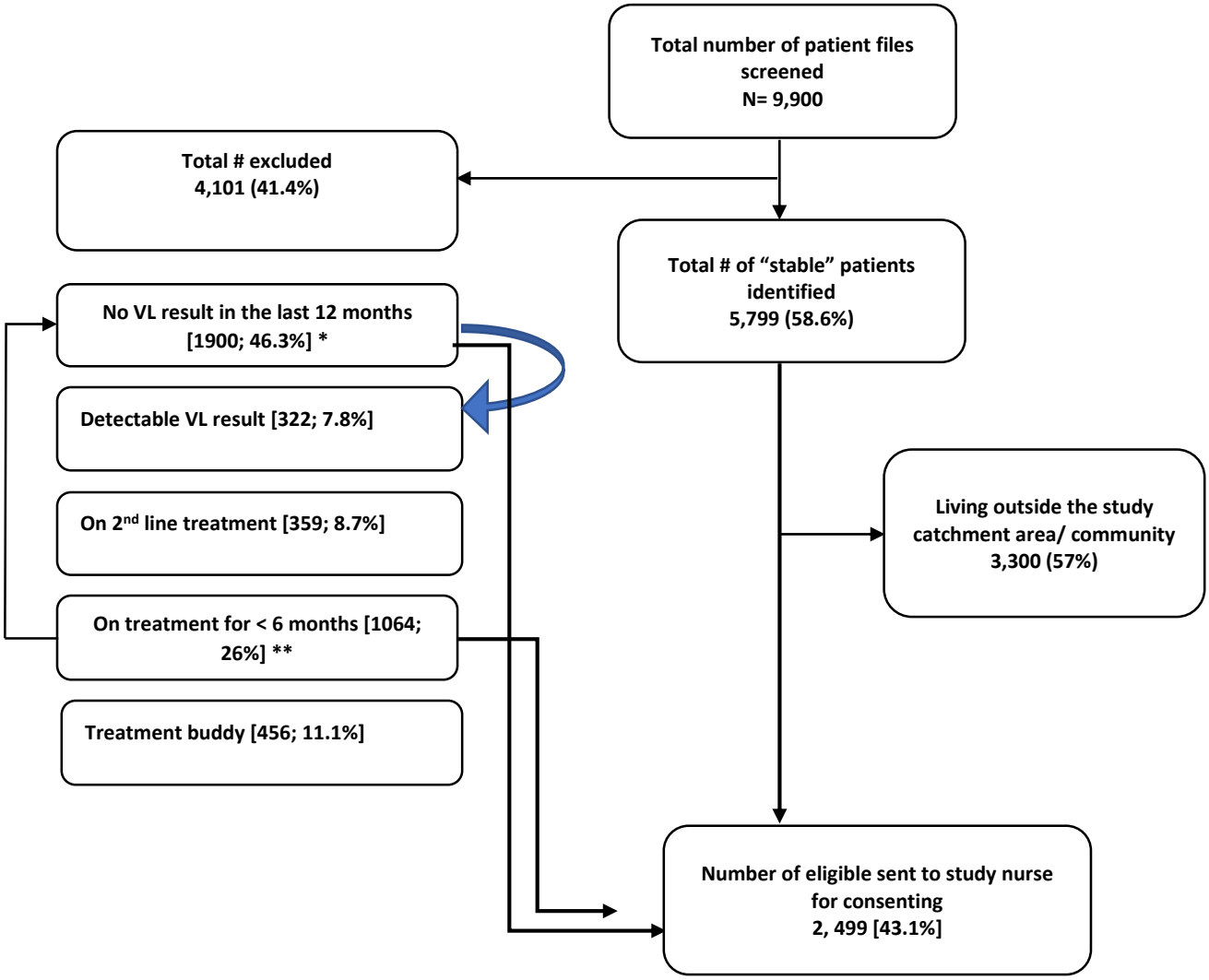
Table 5.9: reasons for excluding patients for study recruitment

Reasons for not being defined as "stable"	Stable but not eligible for the study
• No viral load result in the preceding 12 months • Detectable viral load result • On 2nd line treatment • On treatment for less than 6 months • Had missed 2 or more clinical visit in the last 12 months	• Living outside the study catchment or clinic community where the intervention could not be delivered • Not physically present – "treatment buddy" was present

One of the most common eligibility requirements for various formats of DSD models is clinical stability. According to the WHO, a stable patient is defined as having received ART for at least a year and have no concurrent illness that requires the attention of a clinician, have a good understanding of lifelong adherence and evidence of treatment success (either by having evidence of virological suppression or rising CD4 count in the absence of viral load monitoring[22]. However, this definition of a "stable" patient has varied across various formats of DSD models and countries dependent on resources available. Majority of programs implementing DSD models in resource-limited settings used clinical stability as the most common eligibility requirement which typically specified a duration on ART (6-12 months), evidence of viral suppression, though some offered an alternative lower CD4 threshold in the absence of Viral load monitoring and exclusion of HIV opportunistic infections[16]. Our definition of stable patients was guided by WHO, although we modified it in terms of ART duration (6 months or more), being on first line regimen (as this was simpler to deliver and monitor) and using VL as an indicator for ART success over CD4 count as that was now part of routine HIV care.

As shown in table 5.9, the reasons why patients were excluded were either not being classified as "stable" or were stable but ineligible as they were not living within the study catchment area. Viral load testing and availability of results was the biggest challenge as that was one indicator crucial for determining "stable" patients. During the screening process over a period of 7 months, we screened approximately 9,900 patients' files across both communities during their scheduled appointments. Of these we managed to screen, approximately 58% were found to meet the "stable" definition criteria and 41% were excluded as they did not meet the "stable criteria" [Fig 5.6]. The most common reasons for being classified as non-stable were not having a VL test or result (46.3%) and on treatment for less than 6 months (26%). 11.1% of the visits were made by a treatment buddy and therefore participants could not be consented and 8.7% were on 2nd line ART regimen. Of those who were classified as stable, a further 57% of them were living either outside the study catchment area where we could not provide the intervention or were living in another community. Of those who were considered stable we managed to recruit only approximately 43%. However, in a real world setting where our study catchment area would not be considered as an eligibility criterion, and with the recent inclusion of patients on 2nd line treatment as being stable, more patients would have been eligible for enrolment into DSD models as the numbers would have increased to over 90% of the "stable" population being enrolled.

Fig 5.6. Reasons for exclusion during the screening process



Note:

Data collected above is based on using the screening log form during the screening process at the triage desk and is subject to duplicate entries and under reporting.

**For patients with no viral load results, were sent for a VL test and results obtained could either classify them as stable and then sent to study nurse for consenting or would have a detectable VL result classifying them as "unstable"*

*** Patients who were less than 6 months on treatment were initially considered ineligible. Subsequent follow-up visits during the recruitment time frame where they were now on treatment for more than 6 months allowed them to be included for enrolment provided a VL result was available. Those without VL result would be ineligible*.

In order to try and recruit more potential participants, we asked the CHiPs to sensitize the communities about the study and models of ART delivery during their household rounds and refer any interested patient to the clinic outside their scheduled visit to determine their eligibility to participate in the study. This sensitization activity increased the number of patients coming forward outside of their clinical visits to come to the study building to determine their eligibility to participate. Although this strategy increased the number of potential participants who were eligible, we equally found patients who were not eligible due to the reasons outlined in Table 5.9.

For our study which was a RCT, this strategy could have could have introduced bias as some patients had found out what interventions their zones were receiving and could have prompted them to go the clinic outside their scheduled visit to determine if they were eligible especially if their zones were receiving the intervention models. These patients were likely to have found out from their peers who were enrolled into the models or from the CHiPs working in their zones. The CHiPs in all the zones regardless of whether they were allocated to the intervention or SoC arms had to sensitize patients and refer to the clinic, but there was a strong possibility that the CHiPs who were working in the zones allocated to the interventions were more likely to inform the patients that would receive the intervention models and therefore more likely to come to the clinic to be assessed for eligibility with the hope of being enrolled the intervention models.

To mitigate the challenges that we encountered during the screening process and identify more stable patients, we put in several strategies as listed in Table 5.10 and of all the strategies put in forward, getting the VL result on time was the biggest challenge to recruitment faced by the clinic and study staff and therefore recruitment was heavily dependent on availability of VL results.

Table 5.10: Strategies to increase the identification of potential eligible patients for the study

Challenge	Strategies	Outcome
Detectable viral load results	Patients who were on 1st line therapy and found to have a detectable viral load results in their files were managed as follows: 1. Those who had a VL<1000 copies had a repeat VL to determine if it was either a viral blip or early virological failure 2. Those with a VL> 1000 copies were sent to the clinician to manage accordingly	Patients with a viral blip were considered eligible provided they received intense adherence counselling. These patients were only enrolled once satisfied they were stable
No viral load testing in the last 12 months **Missing VL results** (VL tests ordered but no results) **Delayed VL results** (due to laboratory delays) **Delayed entry of VL results** (VL was processed in the laboratory and sent back to the clinic but not yet entered in the patient files or SmartCare database)	1. Partnering with IP to access VL results bi-weekly using the LIMS system 2. Accessing VL results directly from SmartCare 3. Using lay workers at the clinic to sort and file paper based VL results into patient clinic records and providing incentives to carry out this process 4. Request for VL testing for those who never had a VL done in the last 12 months or had a VL test ordered but had not received the results.	These strategies allowed the study team to access VL results quicker rather than waiting for the normal turnaround time which was 4-12 weeks.
On treatment for less than 6 months	Patient files were earmarked for eligibility screening in their successive 3 monthly visits once they were found to be 6 months post-ART initiation and had a viral load done which was undetectable.	Although we managed to successfully enroll patients once they had been on ART for more than 6 months and had a suppressed VL, we still faced challenges with getting VL results on time further delaying identification of stable patients.
Had missed 2 or more clinical visit in the last 12 months	These patients were sent for intense adherence counselling to the counsellors present at the clinics. They would need to have had one additional clinic visit after being found to have missed 2 or more clinical visit, have had intense adherence counselling during the last two visits and undetectable viral load	These patients were only considered stable once they had fulfilled the strategies put forward and delays in this process resulted in them being left out for consideration into the study
Not physically present – "treatment buddy" was present	For these patients we determined from the file if they met the criteria for stable and asked the buddy if the patient was living within the study catchment area. Patient buddies were encouraged to inform the patient to come to the clinic within a week or two for eligibility screening	Although clinic and research staff encouraged patient buddy to ask the patients to come to the clinic, this was difficult to record if the patient really came to the clinic

II. Challenges with viral load testing and results during the implementation of the interventions

Prior to the start of the study, the 2014 National Guidelines indicated viral load as the preferable monitoring strategy to establish an individual's ART effectiveness, and if VL is not routinely accessible, CD4 count and clinical monitoring should be used instead[208]. However, at that time implementation of viral load testing was slow and limited to a few urban settings like Lusaka. According to the Global AIDS Response Progress Reporting (GARPR), only 35,000 viral load tests were conducted in 2015[209] and efforts were being made to improve the viral load testing and infrastructure using a phased implementation of routine VL testing where 70% and 90% of patients on ART should access VL testing by the end of 2018 and 2020 respectively. In 2016, the national guidelines were further revised to reflect the "treat-all" approach to further accelerate efforts to meet the UNAIDS 90-90-90 targets by 2020[210]. This strategy also emphasized the importance of using viral load to monitor treatment in order to ensure viral suppression among PLHIV on ART, and VL is now included in regular HIV monitoring at six and twelve months following ART initiation, as well as annually thereafter[210].

Following the implementation of the 2016 HIV treatment guidelines, Ministry of health with support from PEPFAR implementing partners started to scale-up VL testing for all PLHIV on ART, and this created a backlog as there were only one 1-2 primary laboratories serving as a reference laboratory for molecular diagnosis [HIV, DNA, PCR and VL testing] for all health care facilities in Lusaka. The ideal turnaround time for VL results would be two weeks but due to the overwhelming numbers of sample to be tested from all the HCF's in Lusaka, the turnaround time took between 4-12 weeks.

Our primary outcome of the trial was HIV viral suppression and using the routine standard of care viral load testing to measure this outcome, we needed to make sure we understood how VL tests were requested, and results returned and recorded with timeframes. This was identified as the key challenge to the implementation of the trial as lack of VL data meant that the participant could not contribute to the primary outcome. Virological suppression was defined according to the current Zambian standard of care guidelines, which is VL RNA ≤ 1000 copies/ml (based on the parameters of any assay performed through routine laboratory monitoring). The window period used for our primary outcome analysis was having a VL result 9-15 months after study entry.

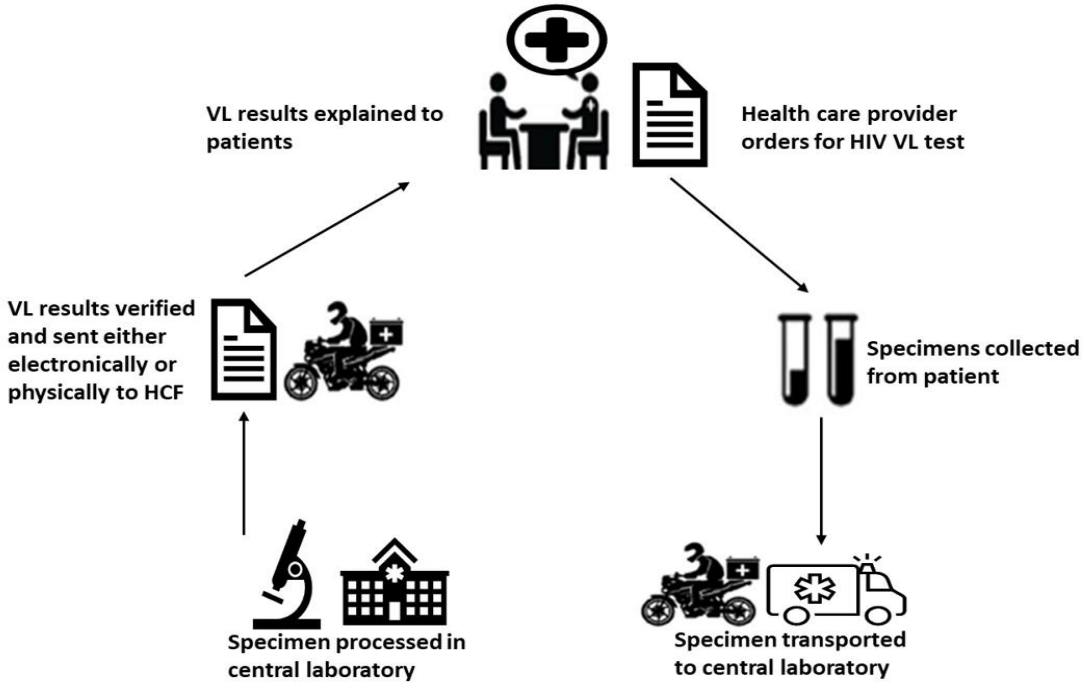
The viral load continuum [Fig 5.7] outlines how VL tests are requested and results returned to the health care facilities in our setting[211]. In the HIV ART clinics, viral load tests are ordered by either a clinician or a nurse. Clinicians usually order the tests following a clinical review either as part of routine monitoring or if they suspect patient is failing treatment for further management. ART nurses can also order for a VL test for stable patients who are found to be due or are overdue during a visit at the clinic. When VL tests are requested for, it is ticked on the ART forms in the patient files under the

laboratory section of tests ordered. Patients then queue up outside the phlebotomy room waiting for their turn to have a sample of blood drawn. When blood sample is collected from a patient, the date and time of collection with the patient ART number are entered in the laboratory requisition form and the ART number is also indicated on the specimen bottle. Both the laboratory requisition form and specimen bottle are then sent to the central laboratory which is located approximately 10-15 km from the health care facilities. Blood specimens for VL are usually collected in the mornings between 9.00 AM to 1.00 PM after which it is sent to the central laboratory using a designated motorbike or vehicle supported by the PEPFAR implementing partner.

Once samples reach the laboratory, they are first sorted out to ensure the samples meet the standard for testing criteria. This includes ensuring that the details on the specimen collection tube matches that of the laboratory requisition slip (Patient ART number, clinic, age, sex, date, and time of collection) and the volume of the sample is adequate for processing. Once the specimen has passed this criterion, the details are then entered in the Laboratory Information Management System (LIMS), and barcodes are printed and attached to the specimen bottle and laboratory requisition form. Samples usually have whole blood and therefore have to undergo centrifugation within 24 hours and the plasma is stored either at 2-8 degrees for 72 hours or longer for more than 3 months at -70 degrees. Once sample testing is completed, the results of the controls are analysed to ensure they pass the quality control step and then entered in the LIMS for final review and validation and thereafter printing of hard copies of the results to send back to the clinics for filing in patient charts. Ideally the quickest turnaround time for the sample to be processed and results ready is approximately 4 days but with the backlogs that the laboratory faces, it averages 14 days or longer (at the time we were recruiting, VL results would take 4-12 weeks to reach back to the facility).

Once the hard copies are received at the clinic, they are placed onto the patient files and then eventually these files are sent to the data room for all the data to be entered in to the SmartCare database. However, due to the large number of results and challenges in trying to put them into patient files, the hard copies of the results also end up being entered into SmartCare database first and then sent to the ART registry room for filing it in the correct patient files.

Fig 5.7. Viral Load continuum ǂ



ǂ modified from El-Sadr VM et al. Journal of the international AIDS society 2017, 20(S7): e25010. Available from http://onlinelibrary.wiley.com/doi/10.1002/jia2.25010/full | https://doi.org/10.1002/jia2.25010

The study encountered several challenges with VL testing and results and are no different from what is seen under routine HIV care in Zambia and other resource-limited settings in sub-Saharan Africa. These challenges included the following:

1. Long waiting queues in the phlebotomy room- patients who are stable and feel well did not see the urgency of having a viral done on a particular long day at the clinic especially after being seen by a clinician and having received their drug supply. Because of this lack of knowledge of VL importance, they opted to go home in the hope that they would get their VL test done in the next visit which would be three months later.

2. Inadequate or inconsistent supply of specimen collection tubes – a common problem faced by the clinics would result in patients having to be told to comeback another day or a week later to have their samples collected. Patients who received a three-month drug supply and were feeling generally well would not come back to have their blood samples drawn the following day or week and rather wait till their next clinic or drug scheduled visit.

3. Poor sample collection techniques would also account for VL tests not being done as samples sent to the laboratory would either be insufficient or haemolysed and there was no feedback mechanism in real time to inform the clinic or patient. This would only come to the HCW's attention when trying to retrieve or locate viral load results when patients come in for their next scheduled visit.

4. VL testing backlogs – the sheer volume of VL tests that needed to be performed on a monthly basis for over 150 health care facilities placed a huge strain on the two central laboratories conducting the viral load testing. This resulted in viral load testing backlog in the laboratories where samples would be stored for a long period of time and results not available in time for a patient's next visit.

5. Flexibility in the collection of blood samples was another challenge observed in the clinics. In most cases, sample collection was done in the morning hours as described above from 0900 am to 1.00PM after which samples had to be sent to the central laboratory. Patients who were seen in the late hours of the morning were rescheduled to come another day to have their samples collected and this demotivated patient coming back just for sample collection.

   Although implementing partners provided technical assistance by having additional staff conduct quality control on patient files and putting reminders for VL testing on patient files, this was poorly utilized due to staff burnout and demotivation.

6. Poor or weak feedback mechanism for VL results – samples processed and results once verified in the laboratories would take long to get back into patient files or the electronic SmartCare system. The weakness in the ART program to log, track, test and ensure results are transmitted back to the clinic either electronically or physically further compounded this challenge.

7. Transportation of samples from the clinic to the central laboratory was weak as transport was only available to transport specimens to the laboratory once a day at a specified time.

8. Entry of VL results into patient files was not done adequately resulting in HCWs ordering for VL results if not found in the file thus creating further burden for the laboratory staff and backlogs in sample processing.

During the study period, 56.0% (1,393/ 2,489) of our study participants across all three arms had a VL result available within the 9-15 months' time frame used for our primary analysis. 690 participants had a subsequent VL measurement taken between 15-24 months (giving a total of 2,083 (83.7%) who had a VL result between 9 and 24 months) and 254 participants never had a VL result and were known to be in care. Of those who had VL result between 9-15 months, a higher proportion had a VL

measurement in the HBD (518, 60.8%) and AC (485, 56.7%) arms than in the SoC arm (390, 49.9%). In the intervention models, our VL coverage was better than the SoC arm as the participants were constantly reminded during their home and club visits to have a VL test done on time and this motivated patients to have their tests done at the clinic in order to ensure that they continue receiving their care in the models. Nevertheless, the high rates of viral suppression among those who were tested was encouraging and suggested that patients receiving care in these community models had equally good clinical outcomes in terms of ART adherence and viral suppression.

III. Recruiting male participants

The majority of study participants recruited in our study were females (71%) reflecting the stable patient clinic population on ART. Despite community sensitizations and identifying men on ART in the communities by the CHiPs, who explained the intervention models to them, getting these men to come to the clinic to get enrolled into the models was a challenge. During enrolment of study participants, we encouraged participants to inform their spouses or any members of the household who were HIV+ and on ART to come to the clinic to determine if they were eligible for enrolment. The response we got from the participants were that either their spouses were too busy with work, living in another town, receiving HIV care in another health care facility or were HIV negative. Another possibility was that most of the men on treatment were not comfortable with receiving care in their homes for fear of being stigmatized.

IV. Service shortages and contextual factors

During the study period, there were occasional interruptions, or some modifications made in the operations of the HBD, AC and SoC models. For example, stock-outs of drugs in the clinics towards the end of 2017 meant that majority of participants in both the community models and SoC were given either 1- or 2-months drug supply instead of 3 months. This resulted in participants having to make an extra visit to the clinic to collect their drug supply. For those participants in the HBD and AC models, the study team asked them to come to the clinic just for their drug pick-up. In the beginning of 2019 towards the end of the trial, the ART guidelines had changed to transitioning all patients on first line therapy who were virally suppressed to Dolutegravir- based regime. This switch to Dolutegravir which was not provided as a fixed dose combination was a disadvantage in terms of simplifying the logistics and follow-up [as patients had to make an extra visit to the clinic for monitoring of side effects].

In the same communities during the cholera outbreak in late 2018, the health care facilities were the centre's responsible for admitting cholera cases and as the disease spread in the communities, it was considered a national disaster and curfews were put in place to avoid further spread. This included

banning of community gatherings or meetings which had an impact on one of our club visits and therefore had to be rescheduled to another date. The study staffs and the CHiPs discussed the implications of postponing the club and home visits and also the risk of having the participants come to the clinic for their visits which was the treatment centre for cholera cases. Having had urgent meetings with district health management team and medical superintendent, we decided to continue with the home and club visits and use this as a platform to promote hygiene practices such as hand washing techniques and administering the oral cholera vaccines to the participants. During the rainy seasons, some of the home visits had to be rescheduled if transportation for the CHiPs was not available to take them to their destinations.

Midway in the trial, Ministry of Health with support from Centre for Disease Control (CDC) implemented the E-first (Electronic-first) where patient's data were entered in real time as opposed to E-last (where data was retrospectively entered into SmartCare from paper-based forms). At each point in the ART clinic flow, computers were placed for real time data entry and meant that paper-based files were no longer used. Patient's files were kept in a separate container outside the ART clinic for long-term storage. However, with recurrent and long duration of power outages ("Load-shedding") that the country was experiencing at that time, patients who came for their visits could not have their paper-based files retrieved and therefore it was difficult to determine what the scheduled visit was for and if there were any laboratory tests due or results available for further management. Patients' ART number and vitals were recorded on a piece of paper and later sent to the data room to be entered when electricity was available. As a result, a lot of laboratory tests were not done as it was difficult to determine if they were due or had a result available. Due to the large number of patients having a visit on a particular day when there was no electricity to use the E-first system, HCWs were overwhelmed and demotivated to conduct a laborious task of trying to retrieve their files from the containers where they were stored. For our study participants in the HBD and AC models, we had stored their files in the study office and therefore it was easier to retrieve their files and fill out ART forms or slips of papers which could be inserted in their files and regular patient data updates on the files by the study staff made it easier to determine whether a patient was due for a laboratory test or not. Although implementing partners had provided an electrical generator to serve as a backup for power outages, this was only used for emergency sections of the clinics such as in-patient wards, theatre, and the data room where data was being entered for those patients who data was collected on paper.

V. Patient Mobility

Mobility of patients within the community and outside the community represented a challenge to our trial. Participants who moved/relocated from one zone to another within the community and not offering the intervention would result in transitioning to standard of care. Those who moved outside the community but continued to receive care at the clinic would also be transitioned to SoC. For those who moved outside the community and requested a transfer of their care to another HCF, would result in termination from the study. Although this challenge was attributed to the design of the study (unit of randomization being the zones they are living in), it equally represents a challenge to implementation of these models by Ministry of Health as they would need to be able to continue care when patients move within or outside the communities. In addition, it represents logistical implications as resources need to be available to track patients in DSD models who move frequently so that they continue to engage in care.

Some scheduled visits did not occur because participants were not found at home during the visit. Even if a CHiP could not contact a participant 2-3 days prior to a visit, a text message via phone would be sent. When participants were not found home, the CHiP would try to call or leave a message with anyone in the household for the participant to call back. In most cases, participants would be reached, and patients would be visited either later during the day or in the next 5 days. In most cases, a missed visit would be due to patient having relocated either to a different zone which did not offer the intervention or moved out of the community but continues care in the clinic. These participants would be transitioned to standard of care whilst remaining in the study. Across the two models of delivery, we did note a high rate of transfers amongst participants to areas within the study catchment that was not offering the intervention or outside the study catchment area. These participants were transitioned to SoC. A higher rate of transfers was noted in the HBD model (74/127; 58%) compared to AC (29/70; 41.4%). The reason why we noted a higher rate of transfers in the HBD model was because these participants were followed up in their homes so any relocation would be known by the CHiPs. Within the same model, participants also opted out of the model to continue care at the clinic (SoC) (34/127; 26.8%) and of these a few had decided to opt out as they knew they we removing to an area that was not being offered the models of care. Others opted out for reasons unknown. Although the rates of transfer in AC model was lower than HBD, suggesting lower rates of transfer, this number could be underestimated as the CHiPs delivering the club models would not be able to determine if participants moved out of the area or not. Participants could have moved out of their zones to another zone or outside the study catchment area but were unwilling to provide this information for fear of being transitioned to SoC. In the standard of care model, it was not feasible to

determine movements within or outside the study catchment area as they were not followed up by the CHiPs in the community and not a pre-requisite for receiving care in the clinic.

VI. Challenges with monitoring and evaluation

Data collection using the EDC device with SmartCare installation had to be aborted during the first year of the trial. As our trial was amongst the first to pilot the community SmartCare module, we faced challenges in having the data sync from the EDC into the facility database and partners who were piloting this for their community models of ART faced similar challenges. Synchronizing data with the facility database to merge the data collected in the community resulted in patient records being deleted from the main database and despite engaging the program developers funded by PEPFAR, fixing the database servers and installations of programs proved futile. As we were not the only partners implementing this method of capturing data, Ministry of Health with support from PEPFAR partners decided to re-design the community SmartCare module and therefore we decided to stop using the electronic capturing of data during home and club visits and use the paper-based forms. The use of paper-based forms to collect data in the field served as a back-up which was later manually entered into SmartCare database.

Using this method of collecting data was found to be labour intensive, time consuming, high frequency of incomplete records and susceptible to errors. More time was needed to organize the data and extra processing time was required after collecting data in paper-based forms, to convert into electronic format and clean the data prior to analysis. During the study it took around 10-14 days post initial data collection to be double entered in the SSPS software and cleaned and at the end of the study period, an additional 3 months of labour-intensive work was spent on cleaning the data and entering into the SSPS software. As records needed to be retained, there was unnecessary bulk of paper which eventually suffered wear and tear during transportation and storage.

As this trial was comparing outcomes of the two community models of ART delivery with the standard of care, we had to rely on clinical patient records and SmartCare database for the clinical outcomes of all the patients in the cohort. Due to varied completeness and quality of data, acquiring data for patients under standard of care was difficult, limiting internal validation. This incompleteness also meant that for patients in the standard of care, we could not include some of the data with regards to death, LFTU and viral load results in our analysis limiting the robustness of our findings. Due to this incompleteness, we were unable to incorporate certain data on death, LFTU, and viral load values in our analysis for patients receiving standard of care, hence limiting the robustness of our findings. Secondly, misclassification or delayed inclusion of treatment outcomes was likely in the SoC cohort. In determining outcomes such as viral load suppression, LTFU and death, it was a challenge to monitor

this in the SoC cohort as we had to heavily rely on the completeness of the SmartCare data. Our outcomes on VL result, LTFU and death varied between the two intervention models and the SoC and this was mainly due to the incompleteness or misclassification of these indicators in the SmartCare database. For example, we recorded higher number of known deaths in the Community models compared to SoC at the end of the study period (31 versus 2). This was because in the SoC, it is difficult to record death as patients who are more than 120 days late with no known outcomes despite tracking are classified as LTFU. The weak ascertainment and poor implementation of defaulter tracing activities could have inflated our LTFU numbers, and these could have included deaths. Other examples in the SoC cohorts were the high number of LTFU at 24 months into the study period recorded in SmartCare. But upon manual verification with patient files and Pharmacy registers, 50% were incorrectly classified as LTFU as these patients were still in care and had come for a drug pick-up or clinical visit in the last 6 months.

5.10 Discussion

In this chapter, we have demonstrated the feasibility and acceptability of community models of ART delivery in an urban resource-limited setting and offer valuable insights for future efforts to adapt and implement the models of ART delivery for the growing number of PLHIV on ART. Our findings around the feasibility and fidelity of implementing DSD models are comparable with findings across available literature from health care facility and community-based health interventions across SSA. In this study, we observed that using trained CHWs to support PLHIV on ART is feasible and acceptable both by HCW and patients. Several studies have called for their recognition in HIV programmes as they are considered critical enablers for DSD scale-up [154, 163, 212]. Over the last decade or more, this group of cadres have been included in national strategic plans to provide an integral link in HIV support and follow-up between the communities and HCFs which are often constrained by HCWs shortages. As these cadres are well recognized in the communities they work in, their roles in health programmes interventions such as DSD need to be formalized as they currently lack recognition and their scope of practice is vague and lacks standardization[212, 213]. For implementing these models of delivery on a large scale and ensuring sustainability, a lot of work is needed in order to determine who will deliver these models of delivery and how can we sustain them in the longer term in the absence of donor funding and how do we go about strengthening the implementation and sustainability with respect to monitoring and evaluation, human resources, and infrastructure.

As DSD models are scaled up in the hope of improving the quality and efficiency of ART delivery and outcomes, our findings indicated many gaps in the programmatic goals for DSD implementation in

resource-constrained settings over the next few years. From our experience in this study, routine HIV viral load testing was a major bottleneck to both inclusion of more "potential stable" patients into DSD models and adherence monitoring. Patients in these models of ART delivery classified as "stable" may be at risk of treatment failure despite lack of clinical symptoms[214]. HIV viral load testing provides confidence that a patient is adherent to treatment despite infrequent clinical interactions at the health care facility and therefore access to HIV testing and results is considered as an enabler as it both simplifies the "stable" eligibility criteria for model inclusion and reduced follow-up visits[214]. The use of a central laboratory to conduct VL testing for all PLHIV in a district resulted in delays in or losses of results which in turn delayed clinical decision making of patients who were enrolled in these models and the lack of resources, inadequate human resources, and sample transportation to the laboratory were all factors that compromised the coverage of routine viral load monitoring. These challenges have been highlighted in the WHO guidelines[52] which calls for strengthening laboratory network and diagnostic services, establishing national strategic plans and policies for laboratory monitoring, and allocating appropriate resources, including human and financial resources, to ensure the availability of testing services[52].

Another important observation noted was staff involvement and integration of DSD models with the existing health care system are crucial factors for these models to function. Several studies and reviews have shown that integration of the DSD models with the existing health care system and staff involvement are important for patient referrals, clinical assessment and maintaining quality of care [215]. This allows patients in the models of care to be under the responsibility of the health care facility who remain accountable for them [175, 215]. Our observation in implementing these models of care highlighted that patients in the HBD and AC models were not viewed as the responsibility of the health care facility staff. Although the staff were supportive of implementing these models outside the health care facility with a view that it would reduce congestion and long waiting times in the clinic, the fact that this was a two-year study and funded by NGO made them reluctant to take ownership of the two models of ART delivery. Patients in these models of ART delivery were not viewed as the clinics responsibility and therefore reluctant to assist with some of the activities (pre-packaging of drugs, drug scripts and follow up on VL results) without additional staffing and incentives. Another challenge noted in the health care facility was difficulties in engaging staff to support patients in these models of ART delivery due staff rotations within various departments in the clinic and this was predominantly noted in the pharmacy department where new staff would be reluctant to pack drugs and provide scripts.

With regards to monitoring and evaluation of DSD models, the challenges encountered are like what has been reported in previous studies and reviews. Despite the widespread scale-up of DSD models in SSA, M&E systems have not been tailored to these models and there is scarcity of standardized, structured approaches to document patient- and program-level data[216, 217]. Although tools have been developed to capture data, there is need for further simplification and adaptations to capture longitudinal information on eligibility to and engagement with DSD services (proportion enrolled, retained, and virally suppressed). At present M&E data collection is heavily dependent on paper-based tools which are time consuming, error prone and not feasible in our setting. The use of electronic data capturing (EDC) devices for data collection at community-level has been suggested as an alternative although no studies have reported their use. Although in our study, an EDC installed with software to capture data at community level and later sync to the SmartCare database was developed, it proved futile due to the complexity of the existing SmartCare application (software issues, etc.), a lack of confidence among end users, and a lack of meaningful feedback, all of which undermined the application's use. These challenges encountered in our setting where digital services have not yet proliferated have also been observed in studies in Malawi and Uganda with the use of mobile health applications for community-based health interventions[218, 219]. Similarly, a systematic evaluation of the usage of mHealth technology in resource-limited areas highlighted a lack of infrastructure and equipment as a major impediment to mHealth scaling up [219, 220]. These findings in light of our findings show that although using these technologies have the potential to improve the efficiency of monitoring and evaluating DSD models, there is need to invest in and adapt to local materials and resources to avoid these barriers. As we move towards scaling up DSD models in the context of UTT, there is an urgent need to refine the existing M&E systems to collect information essential for both patient and program management.

A potential concern with regards to implementing DSD models in resource-limited settings is stigma which has been reported by some studies as both a barrier and enabler to DSD implementation [221]. Certain delivery methods that reduce frequent clinic interactions have been mentioned as potentially stigma reducing[164, 221-223] and have shown that only 3% of patients refuse to engage in DSD models due to stigma[31, 178] and use of CHWs in HIV care also reduces stigma. Other studies have recently reported the potential impact of stigma in DSD models of care [221, 224]. A qualitative study in Ghana reported PLHIV preferred facility-based care over community-based model due to a strong fear of stigma and discrimination[225], and findings from Malawi and South Africa found that community adherence clubs have little impact on reducing HIV-related stigma[212, 221]. Interestingly our study findings showed that both HBD and AC were seen as models that reduced stigma previously experienced in the clinics and study participants did not perceive CHWs (CHiPs) providing HIV support

and drugs in their homes or club venues as stigmatizing. This positive impact could largely be due to the fact that repeated household visits by CHiPs over a 3-year period of delivering door-to-door combination prevention package solidified the relationship between the CHiPs and the communities [226, 227]. However, the generalizability of our findings to other settings remains to be seen especially in settings that do not have CHWs delivering HIV interventions and this needs to be explored further.

Our study highlights the importance of political support towards implementation of DSD models and their operations, expansion, and sustainability. This includes integration of CHWs, adequate resources, reliable drug supply and continued training of staff based on the DSD model framework [215, 228]. Many countries in sub-Saharan Africa have relied heavily on donor funding to implement DSD services without which their sustainability is threatened. In order to sustain these models of care on a larger scale, there is need to adequately address the challenges of impetrating and sustaining these models of care in the long run. According to Macgregor et al[229], implementing DSD models on a large scale should be a continuous process in the health care system and although found to be cost-effective, there is need for additional resources for rapid scale up and sustainability. Adaptation to the country's context and innovative approaches to overcome challenges must be a high priority. Therefore, political and financial commitments, regulatory frameworks and mechanisms to mentor and supervise CHWs will be urgently required.

Chapter 6: Acceptability and Preferences of Community Models of ART delivery

6.1 Chapter overview

One of the objectives of this thesis includes the acceptability of community models of ART delivery by PLHIV on ART in an urban setting. This chapter adds to our understanding of the current uptake of community models of ART delivery and explores PLHIV ART delivery choices (revealed and stated preferences) when options are given or not. As resource-limited countries scale-up DSD models following the 2021 WHO recommendations, understanding patients' preferences for HIV delivery services is critical to maximizing the uptake and impact of these models. Presented below is the manuscript which has been published in the AIDS and Behaviour journal on 24th July 2021.

6.2. Research paper 3. Acceptability and Preferences of Two Different Community Models of ART Delivery in a High Prevalence Urban Setting in Zambia: Cluster Randomized Trial, Nested in the HPTN 071 (PopART) Study

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
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Author(s) [Please list all named Authors]:	mohammed limbada, Chiti Bwalya, David Macleod, Osborn Shibwela, Sian Floyd, Diana Nzara, Vasty Situmbeko, Richard Hayes, Sarah Fidler, Helen Ayles, the HPTN 071 (PopART) Study Team	(the 'Author')
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ORIGINAL PAPER

Acceptability and Preferences of Two Different Community Models of ART Delivery in a High Prevalence Urban Setting in Zambia: Cluster-Randomized Trial, Nested in the HPTN 071 (PopART) Study

Mohammed Limbada[1] · Chiti Bwalya[1] · David Macleod[3] · Osborn Shibwela[1] · Sian Floyd[3] · Diana Nzara[1] · Vasty Situmbeko[1] · Richard Hayes[3] · Sarah Fidler[2] · Helen Ayles[1,4] on behalf of the HPTN 071 (PopART) Study Team

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Abstract

Community delivery of Antiretroviral therapy (ART) is a novel innovation to increase sustainable ART coverage for People living with HIV (PLHIV) in resource limited settings. Within a nested cluster-randomised sub-study in two urban communities that participated in the HPTN 071 (PopART) trial in Zambia we investigated individual acceptability and preferences for ART delivery models. Stable PLHIV were enrolled in a cluster-randomized trial of three different models of ART: Facility-based delivery (SoC), Home-based delivery (HBD) and Adherence clubs (AC). Consenting individuals were asked to express their stated preference for ART delivery options. Those assigned to the community models of ART delivery arms could choose ("revealed preference") between the assigned arm and facility-based delivery. In total 2489 (99.6%) eligible individuals consented to the study and 95.6% chose community models of ART delivery rather than facility-based delivery when offered a choice. When asked to state their preference of model of ART delivery, 67.6% did not state a preference of one model over another, 22.8% stated a preference for HBD, 5.0% and 4.6% stated a preference for AC and SoC, respectively. Offering PLHIV choices of community models of ART delivery is feasible and acceptable with majority expressing HBD as their stated preferred option.

Keywords HIV · Anti-retroviral therapy · Home-based ART delivery · Adherence clubs · Stated preference

Introduction

By the end of 2016, 36.7 million [30.8–42.9 million] people were living with HIV globally with the vast majority living in low-and middle-income countries [1]. East and Southern Africa are the most affected regions with approximately 19.4 million People living with HIV (PLHIV) accounting for more than half the world's HIV-positive population [1]. As the world commits to reaching the UNAIDS 90-90-90 targets for HIV diagnosis, treatment, and viral suppression

✉ Mohammed Limbada
Mohammed@zambart.org.zm

Chiti Bwalya
Bwalya@zambart.org.zm

David Macleod
David.Macleod@lshtm.ac.uk

Osborn Shibwela
Osborn@zambart.org.zm

Sian Floyd
Sian.Floyd@lshtm.ac.uk

Richard Hayes
Richard.Hayes@lshtm.ac.uk

Sarah Fidler
s.fidler@imperial.ac.uk

Helen Ayles
Helen@zambart.org.zm

1 Zambart House, School of Medicine, University of Zambia, Ridgeway Campus, Off Nationalist Road, P.O. Box 50697, Lusaka, Zambia

2 Imperial College, United Kingdom and Imperial College NIHR BRC, London, UK

3 Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

4 Department of Clinical Research, London School of Hygiene and Tropical Medicine, London, UK

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by 2020 to end the AIDS epidemic by 2030, there has been substantial progress in scaling up Antiretroviral treatment (ART) programs globally. By 2018, more than 2/3 (79%) of all PLHIV knew their status with 23.3 million (62%) PLHIV accessing ART [2].

Zambia has an estimated HIV prevalence of 11.3% in adults with an estimated 1.2 million PLHIV [3], most in urban areas. The government, in close partnership with its PEPFAR implementing partners has made tremendous progress over the last decade towards epidemic control with 63% of Zambians in need of ART receiving it by the end of 2016 [3–6]. Following the adoption of the WHO [8] treatment guidelines there has been an expansion in numbers of people on ART to about 85% of PLWH who know their status [7–10]. In spite of these successes, the ART treatment program in Zambia still faces many challenges. From the demand point of view, the change in guidelines increased the demand for ART services resulting in overcrowding, long waiting times and overburdening of the already fragile health facility system thus increasing the workload and burnout for the few existing health care workers [11, 12]. These challenges compromise service delivery and may lead to ART interruption, poor adherence, ongoing transmission and the development of viral drug resistance and increased mortality [9, 10, 13]. Adherence to treatment and virological suppression are critical for survival and prevention of onward viral transmission and without a change in the current delivery model of ART in Zambia, lifelong ART for all PLHIV is unsustainable. Decentralization of ART services into the community through community-based ART delivery models is one of the WHO recommended strategies to maintain the HIV continuum of care in resource limited settings where the existing formal health systems are unable to cope with increasing numbers of PLHIV on treatment [13].

Community-based models decentralize HIV services leading to improved service delivery by reducing congestion at health facility, maintaining capacity of clinic staff and enhancing access to ART and adherence for PLHIV allowing them to have more power to coordinate their lives between treatment and livelihood options. These models have proven to be effective in a number of settings, empowering patients on ART and communities to take responsibility for their own treatment [14, 15]. In many settings across sub-Saharan Africa (SSA), these models have shown promising outcomes in relation to retention and adherence to treatment and strengthening community engagement by linking community based programs with the existing health care facilities [13, 16–18]. These models are designed for "stable" patients, i.e., those on suppressive ART, to receive HIV services in the community thus reducing frequent clinic and pharmacy visits, transport costs and long waiting times and allowing the health care facility to focus more on patients with advanced disease. The models have been divided into four categories: health care worker-managed group models; client-managed group models; facility-based individual models; and out-of-facility based individual models [19].

The recently ended HPTN 071 (PopART) trial was a community randomized trial conducted in 21 urban communities in Zambia and South Africa investigating whether a community-wide combination HIV prevention package including home-based HIV testing, linkage to care and immediate ART for those who test positive will help reduce HIV incidence [20, 21]. Early data from the PopART intervention in Zambia showed that there were delays in initiation of treatment [21]. Community based approaches to ART delivery have the potential to improve linkage and retention in care and hence help bridge this gap. The design of the PopART intervention, where universal door to door HIV services were provided by trained Community HIV providers (CHiPs), provided us with a unique opportunity to pilot different models of ART delivery with support from the Zambian Ministry of Health. Despite several pilot programs having achieved remarkable success across many settings in sub Saharan Africa [22–24], much about the comparisons between community models of ART delivery and conventional facility-based delivery has been in relation to retention in care and on treatment and the frequency of clinical visits. Very few have compared different models of ART delivery with each other, in particular through soliciting patient preferences for different models of ART delivery [25]. In addition to providing evidence on long term outcomes, cost effectiveness, uptake and acceptability of different models of ART delivery, determining patient preferences towards these models will allow national HIV programs to design and implement models of ART delivery that work best and most appealing to patients in various settings.

To this effect, a three-arm cluster-randomized non-inferiority trial was nested in two of the HPTN 071 (PopART) trial intervention communities with the aim of evaluating clinical outcomes, feasibility and effectiveness of two community models of ART delivery (Adherence clubs and Home-based delivery) for stable HIV+ patients in an urban high HIV prevalence setting in Lusaka, Zambia. In this paper we describe choices ("revealed preferences") and stated preferences of PLHIV for ART delivery models outside the health facility.

Methods

Study Design and Participants

The study was nested in two communities that had been part of the HPTN 071 (PopART) trial. Details of the main HPTN 071 (PopART) trial have been described elsewhere [26]. We conducted a three-arm cluster-randomized non-inferiority

trial to compare virological suppression at 12 months in stable HIV+ patients receiving ART between individuals allocated to receive either ART via community models of ART delivery and those receiving in the facility-based (standard of care). The two Lusaka communities chosen for this substudy resembled other PopART communities in Zambia and reflected the situation with respect to clinic burden HIV prevalence and population migration for many sub-Saharan African countries urban settings in resource limited settings.

The two communities selected for this cluster randomized trial were matched by community size and HIV prevalence (18% and 21% amongst adults aged 18–44). Each community was divided into geographical zones of approximately 500 households (approximately 1400 individuals) and each zone was managed by a pair of trained Community health workers (CHWs). There were 104 zones across the two communities.

All adult HIV+ patients (≥ 18 years) defined as "stable" in accordance with WHO definitions [19] residing in the two urban communities, enrolled for ART in the two primary health care facilities serving the communities, were eligible for inclusion in this nested study. WHO classification for "stable "patients, was (1) Taking first line ART for at least 6 months, (2) Virally suppressed according to national guidelines, and (3) Had no other health conditions requiring the attention of a clinician. An additional eligibility criterion for our study included patients living within the HPTN 071 catchment area and being willing to provide written informed consent.

Randomization

The 104 zones across the two communities were randomly assigned (35:35:34) to one of the three study arms for ART delivery. The three study arms were: Arm 1. Facility-based ART delivery (Standard of care, (SoC) continued collection of ART only at the health care facility, Arm 2. Home-based ART delivery (HBD) where ART was delivered to the participant's home every 3 months by a community health worker (HCW) and Arm 3. Being part of an Adherence club (AC), meeting every 3 months outside of the health care facility and facilitated by a community health worker. In the HBD and AC arms participants were given the choice to continue with ART delivery through the health care facility or to accept the community model of ART delivery route they had been allocated. To achieve balance across the clusters, we stratified randomization by community and further restricted the randomization, first within each community and second across both communities on average values of key outcomes including population size, HIV prevalence which was available at the entire community level only, and proportion of HIV+ patients who attend the local health care facility and distance to the health care facility to ensure overall balance across the study arms.

A public randomization ceremony was held with the community health workers, their supervisors, the primary health care staff, members of the PopART intervention study teams and community advisory boards to allocate the zones to one of the three study arms.

Study Outcomes: Participant's ART Delivery Choices (Revealed Preference) and Stated Preferences

This study explores the participants ART delivery preferences, these have been divided into stated and revealed preferences; stated preferences are those which people say they want and revealed preferences are what they actually choose. The community models of ART intervention were implemented between 3rd May 2017 and 30th April 2019. All eligible patients attending the health care facility were invited to join the study and were asked to consent. Having consented to the study, participants were assigned to a study arm. Those who were assigned to the two community models of ART delivery arms were first asked to choose between the assigned interventions and or continue with facility-based care (SoC), their revealed preference. Participants who were assigned to the facility-based (SoC) arm did not have an option to choose. Subsequently all participant's (including those in the SoC) were asked "*did you have a preferred model of ART delivery out of the three options? If yes, which model of delivery?"*. The response to this question we define as the participant's stated preference and can be one of the four categories: (1) Prefers Facility-based (SoC); (2) Prefers Home Based ART delivery; (3) Prefers Adherence clubs and (4) No preference expressed.

In this paper we describe the revealed preferences made by those in the two community models of ART delivery arms (as to whether they chose facility-based (SoC) or the allocated community model of ART delivery) and the stated preference of all participants about the different models of ART delivery. The stated and revealed preferences were recorded on the enrolment form by the study staff. Participant characteristics with regard to age, sex and years on ART were also collected as part of the general survey during enrolment. All data were entered into an electronic data collection system.

Statistical Analysis

STATA version 13 was used to clean and analyse the data. Descriptive data on the study participants reported preferences were stratified by study arm and presented as medians and interquartile ranges for the continuous variables and proportions for the categorical variables. Of patients who consented to participate in the study, we determined

the proportion who chose the model of delivery assigned to them and the proportion of participants who stated a preference for each model of ART delivery (or no preference). We further conducted analysis by sex, age group, years on ART and trial arm to explore whether there were any associations between these variables and stated preference using Pearson's Chi square test.

An exploratory qualitative study using observations, interviews and Focus group discussions (FGDs) was used to collect qualitative data. Observations of Home based model delivery (HBM) (n = 12) and Adherence club meetings (n = 6), audio-recorded in-depth interviews with a purposively selected sample of PLWH accessing ART through the two models (n = 27) and two FGDs with community health workers administering the models (n = 16) were conducted eight months after the start of the intervention between October and December 2017 and at the end of the study between May and August 2019. Observations provided insights into how community health workers conducted the delivery of ART as well as the micro-social environment surrounding clients. Interviews and FGDs inquired about preferences and experiences of PLWH with accessing ART and acceptability. All discussions ended with participants plotting their overall opinion of the models on a simple visual scale with different facial expressions (emoji's) corresponding to degrees of satisfaction and acceptability.

All audio recordings from FGDs and IDIs were transcribed verbatim and translated to English by the second author. Notes taken during and after the observation were expanded and typed in Word and then later on saved with a unique code representing each participant. All data transcripts including typed notes were imported into Atlas.ti 7 and using the Thematic coding analysis (TCA) approach, all parts of the data transcripts were subjected to iterative coding process by the first author [27, 28]. Analytical categories of related codes and sub codes were then stratified by study site and participant profile. Using Atlas ti 7, code outputs [codes linked to quotations from transcripts and summed up in a theme] were created representing recurrent themes related to factors influencing choice of a model and acceptability and served as a basis for further analysis and interpretation.

Ethics

The study was granted ethical clearance from the University of Zambia Biomedical Research Ethics (UNZABREC) and the London School of Hygiene and Tropical Medicine ethics committee. Prior to approval, this protocol had also been through regulatory review and approved by Division of AIDS (DAIDS) who granted us permission to carry out this study as an ancillary study to HPTN 071 (PopART) and registered at ClinicalTrials.gov. Further approvals were granted by Zambian National Health Research Authority and Ministry of Health. Written informed consent was obtained from all participants.

Results

A total of 2499 eligible participants were identified across the two communities between May and December 2017 who were eligible for inclusion in the trial and of these, 2489 (99.6%) consented to participate, 10 (0.4%) declined consent (Fig. 1). The three study arms were well balanced according to baseline characteristics, However there were fewer participants in the SoC arm. Of the participants who were eligible, the majority were female across all arms (N = 1757, 71%), reflecting the stable patient clinic population on ART. The median age of participants was 40 years (IQR: 33–47) in the SoC and AC arms and 39 years (IQR: 33–46) in the HBD arm. The median years being on ART was 4 years (IQR: 2–7) across all three arms.

Choices of Models of ART Delivery in the Two Community Models of ART Delivery Arms

There were 781 (31.4%) stable participants were assigned to the SoC arm, 852 (34.2%) assigned to HBD arm and 856 (34.4%) to AC arm. Of the participants who were assigned HBD, 27 (3.2%) chose to continue receiving care at the clinic and 48 (5.6%) who were assigned AC chose to continue receiving care from the clinic. Among the participants randomized to the community models of ART delivery arms [HBD and AC], overall, 95.6% chose the community models of ART delivery that they were randomized to receive [96.8% in the HBD arm and 94.4% in the AC arm] (Fig. 1).

Preferences for Models of ART Delivery

Out of the 2489 participants who were asked for their stated preference of ART delivery model, 1682 (67.6%) did not state a preference of model of delivery over any of the others, 568 (22.8%) stated they would prefer home-based delivery, 125 (5.0%) stated they would prefer adherence clubs and 114 (4.6%) stated a preference for facility-based (SoC) (Table 1). Participants in the facility-based (SoC) arm were most likely to state a preference of one mode of ART delivery over another and of those that did state a preference the majority preferred HBD. Overall in the SoC arm, 39% stated no preference, 48% HBD, 12% AC and only 1% preferring SoC. Few individuals in the HBD arm stated a preference of one model of ART delivery over another, with 88% reporting no preference, and among those who did state a preference they preferred SoC over the two community models of ART delivery options. In the AC arm, 73% did not state a

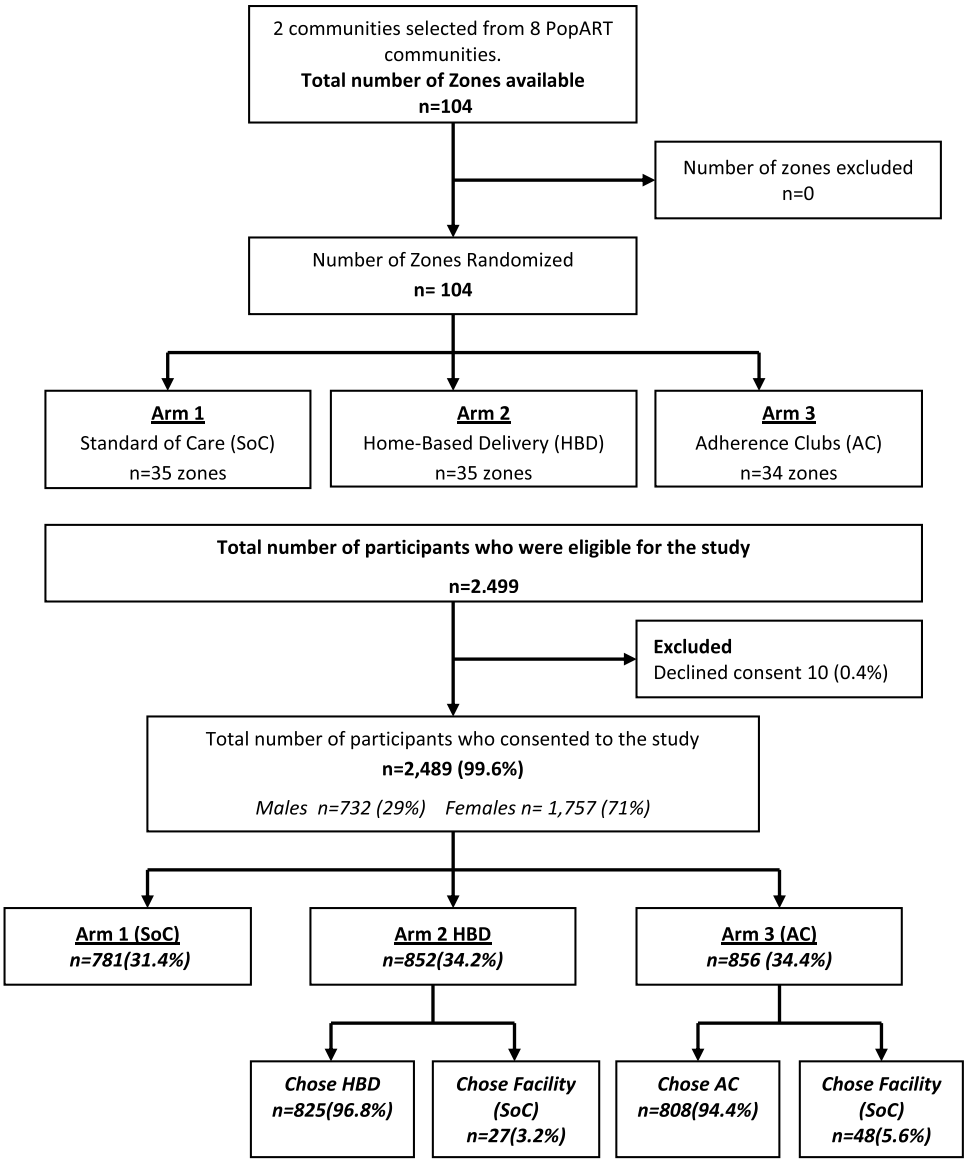

Fig. 1 Uptake and choices across the three study arms. Data are n (%)

preference but amongst those that did there was a clear preference for HBD, with 19% stating this preference (Table 1). We found no evidence of association between stated preference for ART delivery model and any of age, sex or time on ART, but did find strong evidence ($p < 0.001$, $\chi^2(6) = 670.4$) of an association with trial arm (Table 1). Among the 27 participants in the HBD study arm who chose to receive SoC, all 27 stated a preference for SoC when asked. However, in the same arm, an additional 19 participants chose HBD despite their stated preference being for facility-based (SoC). Similarly in the AC arm out of the 48 participants who chose SoC, 46 participants stated a preference for SoC, one a preference for HBD and one had no preference, an additional 11 participants who stated a preference for SoC chose to join AC anyway (Table 2).

Qualitative findings from in depth interviews with 27 study participants, revealed a number of factors that may have influenced participants' preferences for HBD compared with AC and SoC. Congestion at the clinic was reported to be a prominent factor that may have influenced the preference for out of facility models, especially HBD. For all PLHIV interviewed, overcrowding of the ART clinic was the major reason why they preferred HBD. As one male participant reflected: 'The issue of having too many people at the clinic was a real problem that made the waiting worse.' 'Congestion is a real and big problem at the clinic', added another female participant. CHWs also mentioned overcrowding at the clinic was the main reason that made people prefer HBD. In addition, there were a number of other challenges at the clinic that may have influenced the choice of HBD followed by AC. The waiting area at the

Table 1 Participants stated preferences for model of ART delivery and associations between preferences and participant baseline characteristics

	Overall (n = 2489)	No preference	Preferred SoC	Preferred HBD	Preferred AC	P-value*
1. Trial arm		N = 1682 (67.6%)	N = 114 (4.6%)	N = 568 (22.8%)	N = 125 (5.0%)	***P < 0.001***
Standard of care	781	303 (38.8%)	9 (1.2%)	377 (48.3%)	92 (11.8%)	$\chi^2(6) = 670.4$
Home based delivery	852	751 (88.1%)	46 (5.4%)	25 (2.9%)	30 (3.5%)	
Adherence clubs	856	628 (73.4%)	59 (6.9%)	166 (19.4%)	3 (0.4%)	
2. Sex						
Male	732 (29.4%)	489 (66.8%)	43 (5.9%)	157 (21.4%)	43 (5.9%)	***0.101***
Female	1757 (70.6%)	1193 (67.9%)	71 (4.0%)	411 (23.4%)	82 (4.7%)	$\chi^2(3) = 6.2$
3. Age group						
18–24	111	82 (73.9%)	4 (3.6%)	20 (18.0%)	5 (4.5%)	***0.713***
25–34	610	422 (69.2%)	25 (4.1%)	135 (22.1%)	28 (4.6%)	$\chi^2(12) = 8.9$
35–44	992	668 (67.3%)	53 (5.3%)	224 (22.6%)	47 (4.7%)	
45–54	554	360 (65.0%)	26 (4.7%)	134 (24.2%)	34 (6.1%)	
55+	222	150 (67.6%)	6 (2.7%)	55 (24.8%)	11 (4.9%)	
4. Years on ART						
< 1 year	77	47 (61.0%)	8 (10.4%)	16 (20.8%)	6 (7.8%)	***0.189***
1–2 years	671	462 (68.8%)	32 (4.8%)	144 (21.5%)	33 (4.9%)	$\chi^2(9) = 12.5$
3–5 years	829	563 (67.9%)	40 (4.8%)	192 (23.2%)	34 (4.1%)	
> 5 years	912	610 (66.9%)	34 (3.7%)	216 (23.7%)	52 (5.7%)	

Data are n (%)

*Pearson's Chi square test

Table 2 Preferences amongst those who chose the community models of ART delivery versus those who did not

	Home-based delivery arm		Adherence club arm	
Stated preferences	Chose SoC	Chose HBD	Chose SoC	Chose AC
No preference	0	751	1	627
Preferred standard of care	27	19	46	13
Preferred home-based delivery	0	25	1	165
Preferred adherence clubs	0	30	0	3

health facility was said to be very small, with only a few benches that could not accommodate all clients meaning most had to stand in the sun for a very long time while they waited to be attended to. Moreover, the location of these waiting areas was a problem for some patients because they feared being seen by others while they were waiting at the separate ART clinic building.

> " … They say it is not fair that they are separated from the rest of the clinic… I have two clients, for them they even said they have even stopped coming to the clinic. 'When going to get my drugs, the location of clinic makes everyone to see you immediately you enter, and they will know that you have gone to get ARVs". (FGD, CHWs, community 1).

The culture of clinic staff was also cited as reason as to why people preferred the HBD and the AC models. PLHIV complained of harsh treatment by health care workers. Being shouted at and the use of stigmatizing language was a commonly reported experience by PLHIVHs as reported by CHWs:

> "Others felt as if they were not treated with dignity and respect, which caused them to get frustrated. If someone calls you name and you do not respond, you will be shouted at, 'eh, 'we are calling you and you are not answering, did you not hear your name being called'. So, those clients started feeling frustrated. So, when we came in [referring to CHiPs and the Model], they started saying that this was easy" (CHWs, FGD, community 1).

Long waiting time was another contributing factor as PLHIV reported coming to the clinic as early as 05.30am to have access to treatment early and then go for work on time.

> "It was hard because there used to be huge groups of people at the clinic, when you go at 6 AM, you come

back around 14–15PM." (IDI, woman, club member, community 1).

For patients to avoid long queues and receive drugs more quickly, an informal trade between patients and clinic staff, especially lay counsellors, was established. Participants mentioned that for them to skip the queue and be attended to faster, they could pay staff from 10 kwachas ($1) to 50 kwachas ($10), with the amount to be paid being dependent on the economic status of the client. Once this was done, the staff would then find means for a patient to be attended to in the quickest manner possible. This informal trade was perceived as adding to the waiting times for those patients that did not have money to pay the staff. Those that paid could come late and be seen before those that came early. This informal and hidden arrangement was considered to have become part of the organizational routines of the clinic.

"If you wanted to be attended to quickly, just pay a K50. In addition, it has actually become a routine, because for those that pay, they will spend at least an hour and then leave. But for those who don't, they are likely to spend the whole day there" (CHWs FGD, community 2).

The HBD model and, to a large extent, the AC had several advantages over the clinic. Participants described their experiences with the HBD and AC model as the opposite of that of the clinic. They reported the overriding advantage of HBD and AC being the convenience and control that participants were able to retain over their time with respect to their livelihood activities as most of them worked in the informal sector which required them to leave home early in the morning and come back late in the evenings. The community ART models made it possible for them not to have to choose between going to the clinic and going to work. Drugs were delivered at prearranged times through an appointment system, enabling PLHIV to plan their work or business activities around this. The practice of CHWs making and re-confirming appointments with clients allowed them the mobility they required to continue livelihood activities. HBD was considered better than AC because drugs were delivered in the homes and participants did not have to move from their homes to a communal venue unlike the clubs.

Another factor cited by participants was the fact that the models were new HIV initiatives delivered by trusted counsellors that people already knew. The CHWs were well known within the communities and had built relationships of trust with household members during the course of the main trial. When the HBD model was implemented, participants were free to choose it because they knew the people that were supposed to be delivering the intervention as one CHWs reflected:

"They are welcoming, because we've been with them and we have created that rapport from the beginning. So, they know us" (CHWs FGD, community 2).

In all the observed home visits by CHWs, clients seemed very happy with the visit, greeting the CHWs with smiles. During the interviews, participants were asked about their view on the models and asked to plot their overall opinion of the HBD and AC on a simple visual scale with different facial expressions (emoji's) corresponding to the degrees of satisfaction from not at all satisfied to extremely satisfied. The majority of PLHIV gave the model a score of 5/5, indicating they were extremely satisfied with the way the model had fit into their lives. This satisfaction is reflected in the following quote from one of the participants.

"Well, I am very happy with this programme and everything that happens in it. It has reduced the problems I used to face when I used to go to the clinic, making us stand in queues, leaving the clinic late; it has reduced all of that." (IDI, Woman, Community 2).

When comparing the number of study participants that said they were either very satisfied or extremely satisfied with the two models, the HBD had more PLHIV expressing high levels of satisfaction than those that were from AC. A few participants rated the model four out of five indicating they still faced problems with follow-up procedures at the facility whilst others were neutral about the clubs because they felt the clubs should rather meet every 6 months than 3 months to give them enough time for their livelihood activities.

Both HBD and AC were seen as models that reduced the stigma previously experienced at the clinic. Accessing ART from dedicated areas in the local clinic was interwoven with fears about *'being seen accessing ART'* and being recognised as a person with HIV. Establishing the HBD on the back of a door-to-door HIV testing programme and using the same people (CHWs) was mentioned by the majority of PLWH as one major factor that minimized stigma during the home visits. The existence of the prior programme helped veil the delivery of ARVs as everyone identified the CHWs with the HIV testing programme and not with the ART delivery programme.

'My neighbours do not know the reason why they visit me but what they do know is that they move door to door in each and every household checking on people." (IDI, woman, community 2).

Discussion

This manuscript describes the choices and stated preferences of models of ART delivery amongst a group of stable people living with HIV who consented to enrol into a CRT

comparing acceptability and safety of two different models of delivering ART outside of current facility based care with the standard of care. In our study population, over 95% chose the community models of ART delivery rather than facility-based (SoC) when offered a choice (as their "revealed preference"). When asked to express their preference for a mode of ART delivery, over 65% did not state a preference but for those who stated a preference, there was an overwhelming acceptance and enthusiasm for community models of ART delivery options.

Our findings confirm that decentralizing ART care outside the current facility-based care into the communities using community health workers to provide adherence support and pre-packed medications is feasible and acceptable. This is consistent with findings from previous studies which have shown that community-based ART programs can achieve remarkable results in expanding access to treatment and retention in resource limited settings [29] as they overcome many of the challenges patients face such as long waiting times to access medications, frequent clinic trips and transportation costs [30–33]. An analysis of programmatic data by Broad Reach International [34] from 217 facilities in five districts in South Africa between 2016 and 2017, showed rapid uptake of differentiated models of care (facility and out-of-facility based) with approximately 75% of eligible patients accepting and a 10% increase in patients moving to community based models. However, it is unknown whether patients in this analysis were offered a choice between the models and standard of care. Similarly, the HPTN 071 (PopART) trial showed that using Community HIV providers (CHiPs) to provide a door-to-door combination HIV package is well accepted, feasible and effective in coverage of HIV testing and knowledge of status in both adults and adolescents [35, 36]. To-date there is limited data documenting patient choices and preferences towards models of ART delivery in resource-limited settings as well as factors associated with the choices patients make towards non-facility based care although location-related preferences appeared prominent [37], with most patients citing long waiting times, overcrowding and distance as the real reason for their choice. Findings from a recent study in Zambia using discrete choice experiments to ass stable HIV patient's preferences towards differentiated care models demonstrated substantial heterogeneity with the strongest overall preference for reduced clinic visits [25].

Exploring choices and preferences that patients make towards health care in resource limited settings is difficult and there is very limited data on health decision making by patients in these settings. A review of literature has revealed that patient involvement in health care decision making is empowering and has been associated with improved treatment outcomes [38]. Recognition of a patient's knowledge, health care worker- patient relationship, allocation of sufficient time for participation and also factors associated with patient's knowledge, beliefs, physical and cognitive abilities and values can influence patient participation in health care decisions [38]. In resource limited settings, health care workers with constrained resources are unable to offer a choice and instead dictate to the patient who are therefore unused to being asked to express their own choices and usually do not, for fear of being neglected in care. Patients may struggle to choose between health care options as they lack confidence, may not be sure of the options they would prefer or have conflicting priorities [39]. In resource-constrained settings, patient's choices tend to be influenced by structural aspects of the health care service such as availability and accessibility of health care providers, quality of staff, costs of treatment and by processes such as availability of information, continuity of treatment, waiting time and transport costs [40]. This could explain the reason why patients would "choose" the interventions offered to them.

In our study population, over 95% of the participants in the community models of ART delivery arms who were offered a choice between community and facility-based care options chose the former. It may be understandable that barriers such as location, distance to clinic, overcrowding and long waiting times are important factors and whilst these barriers are well known determinants of uptake, acceptability and outcomes [41], reasons for choosing community models of ART delivery may vary. When determining patient preferences, 1/3 of our study population stated a preference towards a model of ART delivery and of these, majority stated a preference for community models of ART delivery (HBD and AC) compared to SoC. A large proportion, 2/3 of the study population did not state a preference towards any of the 3 ART delivery options and whether that reflects a true lack of preference needs to be explored further. Some of the possible explanations as to why our study participants were unwilling to state a preference could be that: (1) They do not perceive themselves as having much autonomy of choice when it comes to health care services; (2) They are not empowered about choice especially in resource-limited and (3) The design of our study where participants were assigned to the study arm before they were asked on their preferences and therefore less likely to state a preference when satisfied with what they had received, for example, only 11.9% of participants in the HBD arm actually stated a preference compared with 61.2% in the Soc arm. In the study arms where participants did not get an option off being in HBD, a higher stated preference towards HBD was observed over the other two options. In both HBD and AC arms, participants were less likely to state preferences towards the modes of ART delivery.

Although several studies have suggested increasing experience of stigma by household members who were receiving follow-up visits by community health workers to link to care

when tested positive [42], it appears that in our study, the high acceptability of community models of care by participants did not perceive community health workers providing HIV support and drug delivery in their homes or community venues as stigmatizing. This could largely be due to the fact that during the HPTN 071 (PopART) trial, repeated home visits by community health workers delivering the door-to-door combination prevention package over the course of 3 years solidified the relationship between CHWs and the communities and could also have changed the communities perception towards these cadres [35, 43]. However, we cannot say how these findings may be generalizable to other settings that do not have community workers delivering HIV interventions.

The study had a number of limitations. First this study was done in an urban setting where patients have never been exposed to community models of ART delivery or other forms of differentiated care offered by the government as part of their health care services, and therefore may not have been able to or could have struggled to determine their preferences towards community models of ART delivery unknown to them. Secondly, the design of our study where participants were asked for their preference only after they were assigned to the study arms could have led to bias. It is possible that had we asked for their preferences prior to them knowing which mode of ART delivery they were being allocated to, we may have found a different outcome.

Our review sheds light for future opportunities to conduct preference studies in resource-limited settings. As HIV programs scale up community models of ART delivery in the context of universal treatment, there is need to further identify patient and provider preferences for community models of care that will improve clinical outcomes.

Conclusion

Offering PLHIV a choice of different models of ART care in high-burden resource limited settings is possible and when offered a choice between facility and community models of ART delivery, the majority of those who expressed a preference stated a preference for home-based ART delivery, the revealed preference when the option was implemented was over 95%. As national programs scale up models of ART delivery in resource- limited settings, acceptability, choices and preferences will be important in order to determine which models to prioritize as they could be significant factors in clinical outcomes and integrity of the models of delivery.

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Author Contributions DN and VS collected most of the data during recruitment. ML, BC and OS collected some of the data and provided overall supervision and technical support to the data collection. ML, OS and DM conducted quantitative data analysis and BC conducted qualitative data analysis. ML wrote up the first draft of this paper. HA, SF, DM and BC reviewed and edited the first draft and substantially reviewed and edited the second draft. HA, SF, DM, RH, SF and HPTN 071 Publication working group reviewed the paper and provided critical input. All authors were involved in the design of the main study, contributed to the writing of the paper, and read and approved the final version.

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Data Availability Research data that underpins analysis outlined in this paper cannot be made available. The dataset contains measurements that may be used to re-identify study participants, due to the number and type of variables captured. Participant and ethical consent for wider sharing was also not obtained, due to the research being performed at a time prior to data sharing becoming the norm. However, the study team invite interested parties to contact them to discuss the research and data collected in further detail.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval The study was approved by the London School of Hygiene and Tropical Medicine, University of Zambia Biomedical Research Ethics Committee and Ministry of Health, Zambia.

Consent to Participate Informed consent was obtained from all individual participants included in the study.

References

1. UNAIDS. Fact sheet - Latest statistics on the status of the AIDS epidemic. 2018. Available from http://www.unaids.org/en/resources/fact-sheet. Accessed 4 Jan 2019.
2. UNAIDS. Fact Sheet December 2019: Global HIV Statistics. 2019. Available from https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf
3. UNAIDS. Country factsheets Zambia 2019. Available from https://www.unaids.org/en/regionscountries/countries/zambia. Accessed 29 Sept 2019.
4. Dovlo D. Using mid-level cadres as substitutes for internationally mobile health professionals in Africa. A desk review. Hum Resour Health. 2006. https://doi.org/10.1186/1478-4491-2-7.
5. UNAIDS. Prevention Gap Report 2016. Available from http://www.unaids.org/sites/default/files/media_asset/2016-prevention-gap-report_en.pdf. Accessed Mar 2020.
6. Piot P, Abdool Karim SS, Hecht R, Legido-Quigley H, Buse K, Stover J, et al. Defeating AIDS—advancing global health. Lancet (London, England). 2015;386(9989):171–218.
7. WHO. Consolidated guidelines on the the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2nd ed. Geneva: WHO; 2016.
8. WHO. Guidelines on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva: WHO; 2015.
9. Fatti G, Shaikh N, Eley B, Grimwood A. Effectiveness of community-based support for pregnant women living with HIV: a cohort study in South Africa. AIDS Care. 2016;28(Suppl 1):114–8.
10. Rueda S, Park-Wyllie LY, Bayoumi A, Tynan AM, Antoniou T, Rourke S, et al. Patient support and education for promoting adherence to highly active antiretroviral therapy for HIV/AIDS. Cochrane Database Syst Rev. 2006. https://doi.org/10.1002/14651858.CD001442.pub2.
11. Topp SM, Chipukuma JM, Giganti M, Mwango LK, Chiko LM, Tambatamba-Chapula B, et al. Strengthening health systems at facility-level: feasibility of integrating antiretroviral therapy into primary health care services in Lusaka, Zambia. PLoS ONE. 2010;5(7):e11522.
12. Bigna JJR, Plottel CS, Koulla-Shiro S. Challenges in initiating antiretroviral therapy for all HIV-infected people regardless of CD4 cell count. Infect Dis Poverty. 2016;5(1):85.
13. WHO. March 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: WHO; 2014.
14. Rasschaert F, Decroo T, Remartinez D, Telfer B, Lessitala F, Biot M, et al. Adapting a community-based ART delivery model to the patients' needs: a mixed methods research in Tete, Mozambique. BMC Public Health. 2014;14:364.
15. Horvath T, Azman H, Kennedy GE, Rutherford GW. Mobile phone text messaging for promoting adherence to antiretroviral therapy in patients with HIV infection. Cochrane Database Syst Rev. 2012. https://doi.org/10.1002/14651858.CD009756.
16. Fatti G, Grimwood A, Bock P. Better antiretroviral therapy outcomes at primary healthcare facilities: an evaluation of three tiers of ART services in four South African provinces. PLoS ONE. 2010;5(9):e12888.
17. Mills EJ, Nachega JB, Bangsberg DR, Singh S, Rachlis B, Wu P, et al. Adherence to HAART: a systematic review of developed and developing nation patient-reported barriers and facilitators. PLoS Med. 2006;3(11):e438.
18. Decroo T, Rasschaert F, Telfer B, Remartinez D, Laga M, Ford N. Community-based antiretroviral therapy programs can overcome barriers to retention of patients and decongest health services in sub-Saharan Africa: a systematic review. Int Health. 2013;5(3):169–79.
19. International AIDS Society (IAS). Differentiated care for HIV: a decision framework for antiretroviral therapy delivery: International AIDS Society; 2016.
20. Hayes R, Ayles H, Beyers N, Sabapathy K, Floyd S, Shanaube K, et al. HPTN 071 (PopART): rationale and design of a cluster-randomised trial of the population impact of an HIV combination prevention intervention including universal testing and treatment - a study protocol for a cluster randomised trial. Trials. 2014;15:57.
21. Hayes R, Floyd S, Schaap A, Shanaube K, Bock P, Sabapathy K, et al. A universal testing and treatment intervention to improve HIV control: one-year results from intervention communities in Zambia in the HPTN 071 (PopART) cluster-randomised trial. PLoS Med. 2017;14(5):e1002292.
22. Rasschaert F, Decroo T, Remartinez D, Telfer B, Lessitala F, Biot M, et al. Adapting a community-based ART delivery model to the patients' needs: a mixed methods research in Tete, Mozambique. BMC Public Health. 2014. https://doi.org/10.1186/1471-2458-14-364.
23. Apondi R, Bunnell R, Awor A, Wamai N, Bikaako-Kajura W, Solberg P, et al. Home-based antiretroviral care is associated with positive social outcomes in a prospective cohort in Uganda (1999). J Acquir Immune Defic Syndr. 1999;44(1):71–6.
24. Khabala KB, Edwards JK, Baruani B, Sirengo M, Musembi P, Kosgei RJ, et al. Medication adherence clubs: a potential solution to managing large numbers of stable patients with multiple chronic diseases in informal settlements. Tropical Med Int Health. 2015;20(10):1265–70.
25. Eshun-Wilson I, Mukumbwa-Mwenechanya M, Kim H-Y, Zannolini A, Mwamba CP, Dowdy D, et al. Differentiated care preferences of stable patients on antiretroviral therapy in Zambia: a discrete choice experiment. JAIDS. 2019;81(5):540–6.
26. Hayes R, Ayles H, Beyers N, Sabapathy K, Floyd S, Shanaube K, et al. HPTN 071 (PopART): rationale and design of a cluster-randomised trial of the population impact of an HIV combination prevention intervention including universal testing and treatment – a study protocol for a cluster randomised trial. Trials. 2014;15(1):57.
27. Mays N, Pope C. Qualitative research in health care. Assessing quality in qualitative research. BMJ. 2000;320(7226):50–2.
28. Nowell LS, Norris JM, White DE, Moules NJ. Thematic analysis: striving to meet the trustworthiness criteria. Int J Qual Methods. 2017;16(1):1609406917733847.
29. Mukherjee JS, Barry D, Weatherford RD, Desai IK, Farmer PE. Community-based ART programs: sustaining adherence and follow-up. Curr HIV/AIDS Rep. 2016;13(6):359–66.
30. Bemelmans M, Baert S, Goemaere E, Wilkinson L, Vandendyck M, van Cutsem G, et al. Community-supported models of care for people on HIV treatment in sub-Saharan Africa. Tropical Med Int Health. 2014;19(8):968–77.
31. Groh K, Audet CM, Baptista A, Sidat M, Vergara A, Vermund SH, et al. Barriers to antiretroviral therapy adherence in rural Mozambique. BMC Public Health. 2011;11:650.
32. Bezabhe WM, Chalmers L, Bereznicki LR, Peterson GM, Bimirew MA, Kassie DM. Barriers and facilitators of adherence to antiretroviral drug therapy and retention in care among adult HIV-positive patients: a qualitative study from Ethiopia. PLoS ONE. 2014;9(5):e97353.
33. Tshuma N, Mosikare O, Yun JA, Alaba OA, Maheedhariah MS, Muloongo K, et al. Acceptability of community-based adherence

clubs among health facility staff in South Africa: a qualitative study. Patient Prefer Adherence. 2017;11:1523–31.
34. D. Joseph Davey CS, T. Luthuli, E. Darkoh, BroadReach. Uptake of HIV differentiated care models for patients on antiretroviral therapy in South Africa. AIDS 2018 [Internet]. 2018. Available from http://programme.aids2018.org/Abstract/Abstract/11930. Accessed Apr 2020.
35. Shanaube K, Schaap A, Chaila MJ, Floyd S, Mackworth-Young C, Hoddinott G, et al. Community intervention improves knowledge of HIV status of adolescents in Zambia: findings from HPTN 071-PopART for youth study. AIDS. 2017;31:S221–32.
36. Shanaube K, Schaap A, Floyd S, Phiri M, Griffith S, Chaila J, et al. What works - reaching universal HIV testing: lessons from HPTN 071 (PopART) trial in Zambia. AIDS. 2017;31(11):1555–64.
37. Myer L, Iyun V, Zerbe A, Phillips TK, Brittain K, Mukonda E, et al. Differentiated models of care for postpartum women on antiretroviral therapy in Cape Town, South Africa: a cohort study. J Int AIDS Soc. 2017;20(S4):21636.
38. Vahdat S, Hamzehgardeshi L, Hessam S, Hamzehgardeshi Z. Patient involvement in health care decision making: a review. Iran Red Crescent Med J. 2014;16(1):e12454.
39. Entwistle VA, Carter SM, Cribb A, McCaffery K. Supporting patient autonomy: the importance of clinician-patient relationships. J Gen Intern Med. 2010;25(7):741–5.
40. Groenewoud S, Van Exel NJ, Bobinac A, Berg M, Huijsman R, Stolk EA. What influences patients' decisions when choosing a health care provider? Measuring preferences of patients with knee arthrosis, chronic depression, or Alzheimer's disease, using discrete choice experiments. Health Serv Res. 2015;50(6):1941–72.
41. Siedner MJ, Lankowski A, Tsai AC, Muzoora C, Martin JN, Hunt PW, et al. GPS-measured distance to clinic, but not self-reported transportation factors, are associated with missed HIV clinic visits in rural Uganda. AIDS. 2013;27(9):1503–8.
42. Masquillier C, Wouters E, Mortelmans D, le Roux BF. The impact of community support initiatives on the stigma experienced by people living with HIV/AIDS in South Africa. AIDS Behav. 2015;19(2):214–26.
43. Ndubani R, Simuyaba M, Bwalya C. Optimism and acceptance of longitudinal community response to an HIV combination prevention package in Zambia, the HPTN 071 (PopART) study. AIDS 2018 [Internet]. 2018. Available from: https://programme.aids2018.org/Abstract/Abstract/5734.

Chapter 7: Primary Results

This Chapter addresses the primary objective of the trial that determines whether patients in community models of ART delivery have a lower or equal ("non-inferior") risk of virological failure compared to those receiving standard of care in an urban resource-limited setting as well as some of the secondary objectives such as mortality and lost-to-follow-up. Presented below is the manuscript for this chapter which has been submitted to the Lancet HIV journal.

7.1 Research Paper 4: Rates of viral suppression in a cohort of stable HIV+ patients in two community models of ART delivery versus facility-based HIV care in Lusaka, Zambia: A cluster-randomized non-inferiority trial nested within the HPTN 071 (PopART) trial.

Abstract

Intro

Methods

Results

Discussion

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

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Student ID Number	lsh 1602448	**Title**	Dr
First Name(s)	Mohammed		
Surname/Family Name	Limbada		
Thesis Title	A compariosn of different community models of Antiretroviral Therapy delivery among stable HIV+ patients in an urban setting, Zambia		
Primary Supervisor	Prof Helen Ayles		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Lancet HIV		
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SECTION E

Student Signature	[redacted]
Date	

Supervisor Signature	[redacted]
Date	

Rates of viral suppression in a cohort of people with stable HIV from two community models of ART delivery versus facility-based HIV care in Lusaka, Zambia: a cluster-randomised, non-inferiority trial nested in the HPTN 071 (PopART) trial

Mohammed Limbada, David Macleod, Vasty Situmbeko, Ellen Muhau, Osborn Shibwela, Bwalya Chiti, Sian Floyd, Albertus J Schaap, Richard Hayes, Sarah Fidler, Helen Ayles, on behalf of the HPTN 071 (PopART) study team

Background Non-facility-based antiretroviral therapy (ART) delivery for people with stable HIV might increase sustainable ART coverage in low-income and middle-income countries. Within the HPTN 071 (PopART) trial, two interventions, home-based delivery (HBD) and adherence clubs (AC), which included groups of 15–30 participants who met at a communal venue, were compared with standard of care (SoC). In this trial we looked at the effectiveness and feasibility of these alternative models of care. Specifically, this trial aimed to assess whether these models of care had similar virological suppression to that of SoC 12 months after enrolment.

Methods This was a three-arm, cluster-randomised, non-inferiority trial, done in two urban communities in Lusaka, Zambia included in the HPTN 071 trial. The two communities were split into zones, which were randomly assigned (1:1:1) to the three treatment strategies: 35 zones to the SoC group, 35 zones to the HBD group, and 34 zones to the AC group. ART and adherence support were delivered once every 3 months at home for the HBD group, in groups of 15–30 people in the AC group, or in the clinic for the SoC group. Adults with HIV who were receiving first-line ART for at least 6 months, virally suppressed using national HIV guidelines in the last 12 months, had no other health conditions requiring the clinicians attention, live in the study catchment area, and provided written informed consent, were eligible for inclusion. The primary endpoint was viral suppression at 12 months (with a 6 month final measurement window [ie, 9–15 months]), defined as less than 1000 HIV RNA copies per mL, with a non-inferiority margin of 5%.

Findings Between May 5 and Dec 19, 2017, 9900 individuals were screened for inclusion, of whom 2489 (25·1%) participants were enrolled into the trial: 781 (31%) in the SoC group, 852 (34%) in the HBD group, and 856 (34%) in the AC group. A higher proportion of participants had viral load measurements in the primary outcome window in the HBD (581 [61%]of 852 participants) and AC (485 [57%] of 856 participants) groups than in the SoC (390 [50%] of 781 patients) group (p=0·0021). Of the 1096 missing observations, 152 (13·8%) were attributable to either deaths (25 [16%] participants), relocations (37 [24%] participants), or lost to follow-up (90 [59%]); 690 (63·0%) participants had viral load results outside the window period; and 254 (23·2%) did not have a viral load result. The prevalence of viral suppression was estimated to be 98·3% (95% CI 96·6 to 99·7) in the SoC group, 98·7% (97·5 to 99·6) in the HBD group, and 99·2% (98·4 to 99·8) in the AC group. This gave an estimated risk difference of 0·3% (95% CI –1·5 to 2·4) for the HBD group compared with the SoC group and 0·9% (–0·8 to 2·8) for the AC group compared with the SoC group. There was strong evidence (p<0·0001) that both community ART models were non-inferior to the SoC group (p<0·0001).

Interpretation Community models of ART delivery were as effective as facility-based care in terms of viral suppression.

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Zambart, Lusaka, Zambia (M Limbada MSc, V Situmbeko MPH, E Muhau BPharm, O Shibwela MSc, B Chiti MPH, S Floyd MSC, A J Schaap MSc, Prof H Ayles FMedSci); **Department of Infectious Disease Epidemiology** (D Macleod PhD, A J Schaap, Prof R Hayes) **and Department of Clinical Research** (Prof H Ayles PhD), **London School of Hygiene & Tropical Medicine, London, UK; Imperial College and Imperial college National Institute for Health Research Biomedical Research Centre, London, UK** (Prof S Fidler PhD)

Correspondence to: Dr Mohammed Limbada, Zambart, Lusaka 10101, Zambia **mohammed@zambart.org.zm**

Introduction

Globally, about 38 million people have HIV, of whom 25·7 million live in sub-Saharan Africa.[1] Despite the unprecedented scale-up of antiretroviral therapy (ART) coverage in the so-called treat all era, there are concerns over the sustainability of lifelong ART for all people with HIV due to the restricted capacity of the health-care systems.[2,3]

Lifelong ART, sustained engagement in care, and adherence to ART are crucial for the UNAIDS 95-95-95

Research in context

Evidence before this study

Although community models of antiretroviral therapy (ART) delivery have shown promising outcomes in relation to retention in care and ART adherence, there is little of evidence on whether these models will be feasible in urban, resource-limited settings and how these non-facility based models of ART delivery perform in terms of viral suppression compared with standard of care. We searched the MEDLINE, Embase, and Global health databases from Jan 1, 2010, to Aug 21, 2019, using the search terms "ART"or "Antiretroviral therapy" AND "non-health facility based care" AND "sub-Saharan Africa". All studies measuring at least one of the following outcomes were included: viral suppression, lost to follow-up, retention, and mortality. Several systematic reviews published have shown that community HIV programmes increase both affordability and accessibility to ART with favourable clinical outcomes in terms of optimal ART adherence, virological suppression, all-cause mortality, and loss to follow-up. However only a few of these studies have compared these models of ART delivery with conventional health-care facility or with one another, making it difficult to draw conclusions regarding the effect of the models on patient clinical outcomes. To date only a few randomised trials have reported virological suppression as an outcome measure when compared with the health-care facility for people with HIV in low-income and middle-income countries in sub-Saharan Africa. For the outcome of viral suppression, these trials have showed no evidence of a difference in viral suppression between community models of ART delivery and standard of care with an overall estimated risk difference of 1% (95% CI –1 to 4). Observational studies have also shown results broadly consistent with the randomised trials, although slightly more favourable towards community models of ART delivery, with risk differences ranging from 4% to 6%. These studies have also highlighted the need for additional studies to rigorously compare clinical outcomes between the different models of ART delivery.

Added value to this study

This study adds evidence to the growing literature that suggests non-inferiority of community models of ART delivery in people with stable HIV on ART in high HIV burden, low-income and middle-income countries in sub-Saharan Africa for key outcome measures of viral suppression, death, or loss to follow-up compared with current standard of care. Our findings reinforce previous assertions that decentralising ART services outside the health-care facilities into the communities using trained community health-care workers supporting drug delivery and adherence support is feasible, acceptable, and as effective as health facility-based care in ensuring viral suppression 1 year after enrolment. Our trial showed similar or better clinical and virological outcomes to other trials that compared different models of ART delivery to conventional health facility-based care. The proportion of people with HIV on ART who were virally suppressed in our three study groups was more than 95%, in line with the new UNAIDS target and compares favourably with data from multiple previous trials and cohort studies. This trial also identified challenges with regard to programmatic priorities for differentiated service delivery implementation in sub-Saharan Africa in the coming years with respect to viral load testing and monitoring and evaluation of differentiated service delivery models embedded in routine HIV service delivery.

Implications of all the available evidence

Our study has shown that community models of ART delivery are an effective strategy because they can complement health-care facility-based care with regards to clinical outcomes and enhance patients' ability to manage HIV. These findings support national HIV programmes scaling up differentiated service delivery models in low-income and middle-income countries in an effort to expand ART eligibility and access in the context of universal treatment. As national ART programmes strive to achieve the UNAIDS 95-95-95 targets by 2030, our findings have important clinical and public health implications for low-income and middle-income countries in that these differentiated service delivery models can overcome the challenges to ART access and retention in the midst of the weak public health infrastructure and human resource crisis. Policy makers should consider piloting, evaluating, and scaling more ambitious antiretroviral community delivery programmes that can reach higher proportions of people receiving ART.

targets. Although few studies have evaluated the effect of universal treatment on long-term retention, studies published since 2019 have shown that 12 months retention following universal treatment is below that required for viral suppression, highlighting the need for targeted interventions to ensure long-term sustainability.[4,5]

Many national programmes are scaling up alternative service delivery approaches, known as differentiated service delivery models, to cope with the growing number of people with HIV on treatment.[6] A range of differentiated service delivery models focusing on people with stable disease have been successfully implemented in sub-Saharan Africa allowing them to engage in care through on-going adherence support and dispensation of prepacked medications by community health workers.[7,8] They differ from conventional HIV care in the type of services provided, location and frequency of contact with the health-care system, and the type of provider involved.[2,9] These models of delivery have increasingly been recognised as safe and effective alternatives to the current standard health-care facility[10,11] and have shown promising outcomes in relation to ART adherence, viral load suppression, retention in care, loss to follow-up, and all-cause mortality, in addition to decongesting

health-care facilities.[12,13] However, very few have compared differentiated service delivery models to facility health care or to one another, making it difficult to draw strong conclusions on the models' effectiveness on various patient outcomes.[2]

The HPTN 071 (PopART) trial,[14] a community randomised trial done in 21 urban communities in Zambia and South Africa, provided evidence that a combination prevention intervention, including universal testing and treatment, can reduce HIV incidence at population level. Here, we report results from a cluster randomised, non-inferiority trial nested within the HPTN 071 (PopART) trial comparing two different community models of ART delivery with the current standard of care (SoC) in an urban setting in Zambia to gather evidence on the effectiveness of these models in relation to clinical and virological outcomes in people with HIV to guide policy makers on which models to roll out in the context of universal treatment.

Methods

Study design and participants

This three-arm, cluster-randomised, non-inferiority trial was nested within the HPTN 071 (PopART) trial. Details of the main HPTN 071 (PopART) trial have been described previously.[15] Our nested study was done in a catchment population of two primary health-care facilities (with an estimated population coverage of 100 000 people per community) in Lusaka, Zambia. Each community had one public health-care facility and was divided into geographical zones (clusters) that included approximately 500 households (approximately 1400 individuals ≥16 years old). Each zone was managed by a pair of trained community HIV care providers who provided home-based HIV testing and linkage and support services. The two communities were purposely selected for this nested study because they were both randomly assigned to the PopART intervention groups, with community HIV care providers already employed to deliver HIV combination prevention package, and resembled other urban settings in Zambia and sub-Saharan Africa with respect to clinic burden HIV prevalence and population migration.

At the time of the study design (June, 2016), the two communities had an HIV prevalence of approximately 20% in adults (aged 18–44 years), with an estimated 70% of all people with HIV accessing ART. The study population included adults with HIV (≥18 years) enrolled in HIV care at the two primary health-care facilities who had stable disease. These individuals had to be on first line ART for at least 6 months with an HIV viral load of less than 1000 copies RNA/mL within the preceding 12 months, in accordance with the WHO classification. Additional eligibility criterion included living within the study catchment area and willingness to provide written informed consent. The study was approved by the University of Zambia Biomedical Research Ethics committee, Lusaka, Zambia and London School of Hygiene & Tropical Medicine ethics committee, London, UK. Permission to carry out this ancillary study was also granted by the Division of AIDS at the National Institute of Health and the Zambia National Health Research Authority, Lusaka, Zambia.

Randomisation and masking

The unit of random assignment was a community HIV care provider zone and random allocation of zones was done before the start of this study. To achieve balance across the zones or clusters, we stratified randomisation by community and restricted the randomisation within each community on average values of key outcomes: population size, HIV prevalence, proportion of people with HIV who attend the health-care facility, and distance to the health-care facility, to ensure overall balance across the study groups. A list of 10 000 random assignments meeting the restriction criteria was created for each community, numbered 0000 to 9999. Random assignment was done publicly in both communities to select the final allocation of community HIV care provider zones to the study groups. A total of 104 community HIV care provider zones across both communities were randomly assigned (1:1:1) to one of three groups. Group 1 continue ART at the facility-based standard of care (SoC group; 35 zones); group 2 had a choice of home-based ART delivery (HBD group; 35 zones); and group 3 had a choice of being in an adherence club (AC group; 34 zones); participants in the HBD and AC groups could chose to remain in facility-based SoC. As a cluster-randomised trial of a strategy to deliver HIV care service to people with HIV within a cluster, masking of participants, community HIV care providers, and study staff was not feasible.

Procedures

The study recruited participants from May 5 to Dec 19, 2017; follow-up continued until April 30, 2019. People with HIV attending the ART clinic were offered information about the study and their files were screened for study eligibility. Participants without a viral load result in the preceding 12 months had a blood sample collected and were asked to come back after 1 month to be rescreened for eligibility. Eligible participants were escorted to the study nurse for written informed consent. Consenting participants had their zone of residence confirmed and, based on their residential zone, were assigned to one of the study groups. They were then given the option to take up the assigned intervention or continue receiving care at the facility.[16] Participants assigned to the SoC group continued to receive care at the health-care facility according to national guidelines (appendix p 1).

See Online for appendix

In zones randomly assigned to the HBD group, a pair of community HIV care providers visited the participants in their homes once every 3 months to provide adherence support, symptom screening using a simple checklist, and dispensed prepacked drugs. In the AC group, each zone had one club consisting of 15–30 participants who met

once every 3 months at an agreed communal venue for adherence support, symptom screening, and prepacked medications delivered by a community HIV care provider pair. In both intervention groups, participants returned to the clinic at 6 and 12 months for a clinical review, ART refill, and laboratory monitoring as per national guidelines (appendix p 1). The ART supply was dispensed for 3 months at all visits and throughout the study period, all participants received the fixed-dose ART combination of tenofovir disoproxil fumarate, lamivudine or emtricitabine, and efavirenz. There were no financial incentives to participate in the study.

Clinical and follow-up visits in the intervention groups are outlined in appendix (p 1). Participants in both intervention groups were reminded of their scheduled visits by recording the dates on their care card and a text message reminder was sent to their mobile phones a week before their scheduled meeting by the community HIV care providers. In the HBD group, participants not found at home at the time of the visit were followed up by the community HIV care provider via a telephone call or text message to reschedule their home visit within a period of 5 days, provided they had adequate drug supply. In the AC group, participants who were not present during the club meeting were also followed up via a telephone call and text message and asked to come to the clinic for drug refill. During these home visits and club meetings, the community HIV care providers used study forms for standardised monitoring that included adherence counselling guidelines and a symptom screening checklist for tuberculosis and sexually transmitted infections. Participants assigned to the SoC group continued to receive standard HIV care at the facility and did not have any interaction with the study staff. Participants who missed scheduled visits or were lost to care were followed up by the clinic using routine tracing procedures (including documented follow-up home visits and telephone calls to clients and emergency contacts).

All participants had their viral loads tested at the ministry of health's designated central laboratory, Lusaka, Zambia. The study team collaborated closely with the health-care facilities to ensure that results were returned on time, and part-time volunteer workers assisted with entering viral load results into participant files. At each clinical, home, or club visit, study personnel and community HIV care providers emphasised the importance and advantages of viral load testing, described how to interpret results, and reminded participants of their upcoming visit and viral load test. Because participants were not necessarily enrolled at the time of their annual viral load measurement, some adjustment of the timing of viral load test were made to ensure that all fell within 9–15 months of enrolment. At every clinical visit, the study nurse would check when participants were due for a viral load test and order a test if needed. Participants in the intervention groups who became ill or required additional clinical services (detectable viral load >1000 copies per mL) or had symptoms suggestive of other medical conditions (eg, tuberculosis) were transitioned to clinic-based care for follow-up.

Participants in the intervention groups had their medical records kept up to date by the study staff. Data for all participants were periodically extracted from their files and the routine electronic monitoring system (SmartCare, Zambian Ministry of Health, Lusaka, Zambia) to collect clinical information, such as date of ART initiation, ART dispensing intervals, and laboratory results (viral load and CD4). Furthermore, data entered into study designed forms at each home or club visit (eg, attendance registers, drug scripts, event forms, and programme diaries) were used to measure the outcomes and processes of the study objectives, monitor the implementation of the interventions and record key contextual factors. At the end of the study, all the participants in the intervention groups were transitioned to SoC.

Outcomes

The primary endpoint was the proportion of participants with virological suppression at 12 months (with a 3 month reporting cutoff window [ie, 9–15 months]) after study enrolment. Virological suppression was defined as no more than 1000 HIV RNA copies per mL; viral load measurements were done at a designated Ministry of Health laboratory with COBAS TaqMan HIV-1 version 2·0 assay (Roche, Basel, Switzerland) at 6 months and 12 months after ART initiation and annually thereafter. If no primary outcome measurement was taken within the 3 month window then the primary outcome was considered to be missing.

The prespecified secondary endpoints were, first, the proportion of participants who were virally suppressed at 20–24 months after enrolment (as measured by last viral load result taken between 20 and 24 months after enrolment). Second, the proportion of participants lost to follow-up 12 months after enrolment, defined as having no contact more than 90 days after last missed scheduled appointment with unknown outcomes or the proportion of participants who were no longer retained on treatment with unknown outcomes after study enrolment. Participants who transferred out of the health-care facility were not considered lost to follow-up but terminated from the study; other reasons for study termination included death, lost to follow-up, and study withdrawal. Third, the proportion of participants who had died 12 months after enrolment due to any cause. Lastly, the proportion of participants retained on treatment 12 months after enrolment (defined as a documented drug pick up between 9 and 12 months after enrolment). Participants who moved to another zone with a different intervention or outside the study catchment area but continued to receive care at the health-care facility were considered retained in care. Additionally, the study recorded retention in the allocated

model of care defined as the proportion of people retained in their originally allocated group. For this outcome, participants were considered non-retained in the models of care if they transitioned back to SoC for any reason, including comorbidities, lost to follow-up, death, opting out of the intervention, or withdrawal. In both intervention groups, death was recorded as reported by the community HIV care providers who delivered the

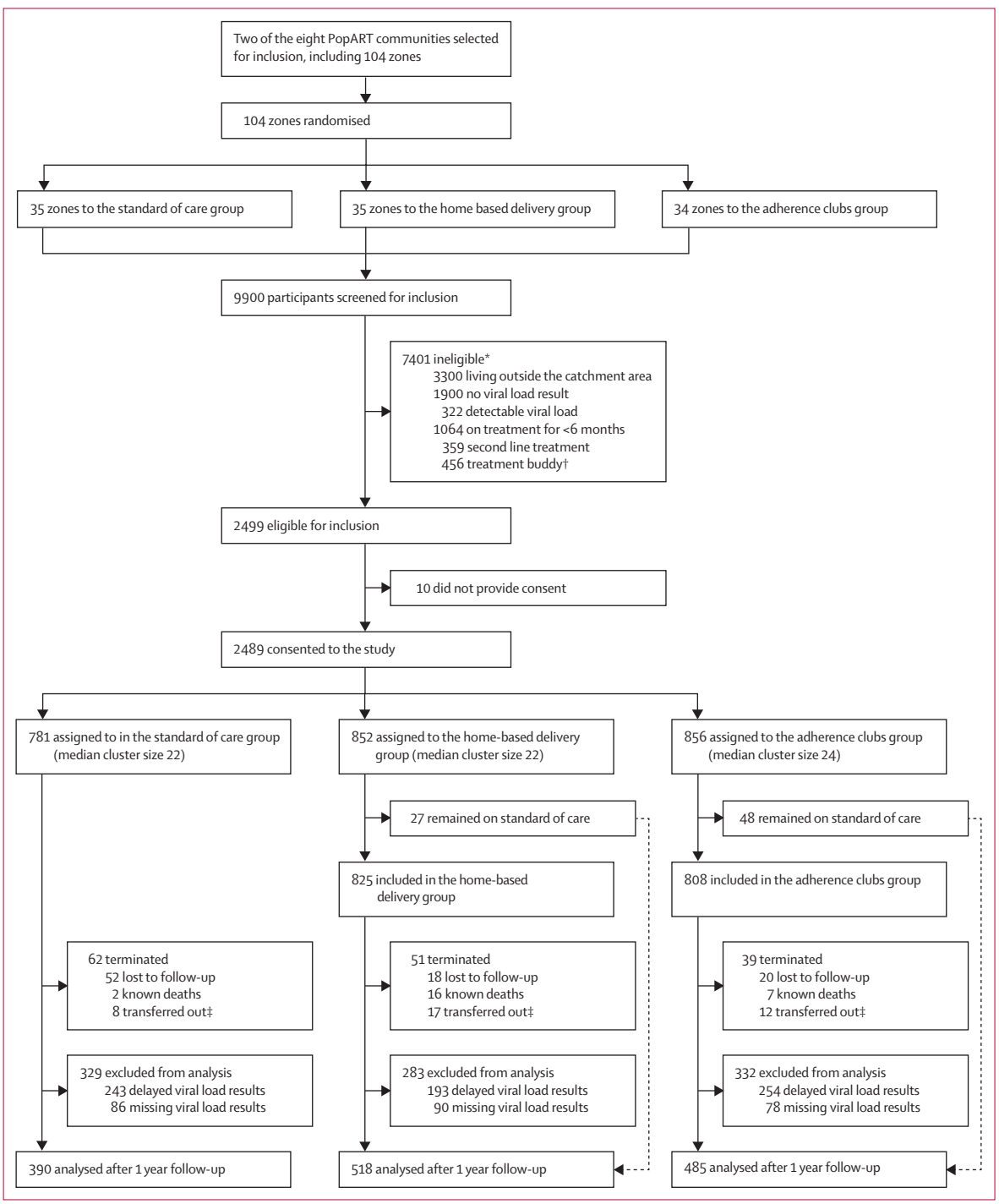

Figure 1: **Trial profile**
Community one had 54 zones and community two had 50 Zones. *Based on crude estimates. †Treatment buddies are also known as treatment supporters; they support treatment (eg, by picking up drug refills if an individual with HIV cannot come to the clinic; treatment buddies were not included in our investigation. ‡Patients transferred out of the community and sought care in another health care facility.

	Standard of care group (n=781)	Home-based delivery group (n=852)	Adherence clubs group (n=856)
Communities			
Community 1	365 (47%)	418 (50%)	370 (43%)
Community 2	416 (53%)	434 (51%)	486 (57%)
Sex			
Male	226 (29%)	247 (29%)	259 (30%)
Female	555 (71%)	605 (71%)	597 (70%)
Age groups (years)			
18–24	32 (4%)	43 (5%)	36 (4%)
25–34	190 (24%)	216 (25%)	204 (24%)
35–44	312 (40%)	342 (40%)	338 (39%)
45–54	175 (22%)	190 (22%)	189 (22%)
≥55	72 (9%)	61 (7%)	89 (10%)
Median age (years)	40 (34–47)	39 (33–46)	40 (34–47)
Years on ART			
<1 year	23 (3%)	30 (4%)	24 (3%)
1–2 years	214 (27%)	223 (26%)	233 (27%)
3–5 years	262 (34%)	285 (34%)	281 (33%)
≥6 years	282 (36%)	314 (37%)	318 (37%)
Median years on ART	4 (2–7)	4 (2–7)	4 (2–7)

Data are n (%) or median (IQR). Data are for the modified intention-to-treat analysis. ART=antiretroviral therapy.

Table 1: **Baseline clinical characteristics of participants in the intervention and control arms**

interventions, whereas in the SoC group deaths were recorded from either SmartCare database or participant clinic records. All primary and secondary outcomes were assessed according to the intention-to-treat principle. No clinical adverse events were anticipated; social harms were reported using social harm forms.

Statistical analysis

On the basis of the data derived from the HPTN 071 (PopART) trial, the number of adults with HIV who were receiving ART averaged approximately 50 per zone, with a harmonic mean of approximately 36 per zone.[16] Assuming that 80% of the eligible adults who agreed to participate in the study, were not lost to follow-up, and had a primary endpoint measurement the number of study participants per zone would be 30. Our study power calculations using this assumption, given 104 zones randomly assigned to the three groups, gave an estimated overall sample size of 3120 participants, approximately 1040 per group. We assumed that of the study participants in the SoC group the proportion who were not virally suppressed 12 months after enrolment to the study would be between 10 and 15%.[16] We defined the non-inferiority margin to be 5%, based on clinical judgement as to what would be a meaningful increase in non-suppression and by similar trials.[17–19] Assuming the coefficient of variation (k) to be 0·3, the estimated study power was 91% to show that the HBD and AC groups were not inferior to the SoC group. The value of k was based on an estimate range of cluster prevalence from 4% to 16%, and the corresponding intracluster coefficient was 0·01. The power calculations used the formula for cluster-randomised, non-inferiority trials by Hayes and Moulton.[20]

Data analysis was done following the methods outlined by Hayes and Moulton.[20] For our primary analysis, the prevalence of viral suppression in each zone within each group was estimated and the mean of the zone-specific values was calculated for each group, along with its corresponding 95% CI. Given the high prevalence of viral suppression in the primary outcome, the CI for the prevalence estimates were obtained with bootstrap methods (ie, taking 100 000 samples of size N from the zone means, calculating the mean from each of these samples, and taking the 2·5 and 97·5 percentiles). The difference in the prevalence between the groups provided the risk difference. The evidence for a difference was assessed using a one-sample t-test, with a non-inferiority margin of 5%. Because of the high prevalence of the primary outcome, bootstrap SEs were used for estimating the 95% CI of the risk difference. The proportion of bootstrap samples that showed a risk difference of more than 5% (favouring SoC groups) provided the p value for testing this hypothesis of non-inferiority. Cluster-level analysis was done to provide estimates of prevalence differences. Because results were frequently absent or delayed, with a turnaround time of 4–12 weeks, a high proportion of individuals did not receive a viral load measurement within the prespecified window. Therefore, a post-hoc sensitivity analyses of the primary outcome were done, widening the window initially to 9–18 months and then to 9–24 months. Due to the large amount of missing viral load data, an additional sensitivity analysis was done (not pre-specified in the protocol) to provide the worst case scenario in which those without a viral load result were categorised as unsuppressed. The trial was registered with ClinicalTrials.gov, NCT03025165.

Role of the funding source

The funders had no role in the study design, data collection, data analysis, and interpretation, or writing of the report.

Results

Between May 5 and Dec 19, 2017, a total of 9900 participants were screened for eligibility in the health-care facilities across both communities. 2499 (25·2%) people with stable HIV were identified as eligible for inclusion, of whom 2489 (99·6%) consented to participate (figure 1). 1757 (70·6%) participants were female, which reflects the population of individuals on ART with stable HIV (table 1). 781 (31·4%) participants were assigned to the SoC group, 852 (34·2%) to the HBD group, and 856 (34·4%) to the AC group. 27 (3%) of 852 participants in the HBD group and 48 (6%) of 856 participants in the AC group chose to continue receiving care at the clinic.

The median age of participants was 40 years (IQR 33–47) and the median duration on ART was 4 years (IQR 2–7).

1393 (56·0%) of the 2489 participants included across all three groups had a viral load result available for analysis within the 9–15 month window used for the primary outcome of viral suppression at 12 months. A higher proportion of participants had a viral load measurement in the HBD (518 [61%] of 852 participants) and AC (485 [57%] of 856 participants) groups than in the SoC group (390 [50%] of 781 participants; table 2). Of those with a viral load measurement available in the primary endpoint window, across all three groups 16 (1·1%) of 1393 were not virally suppressed. The median viral load for those who were unsuppressed was 12 870 RNA copies per mL (IQR 2175 to 28 221). Viral load suppression was estimated to be 98·3% (95% CI 96·6 to 99·7) in the SoC group compared with 98·7% (97·5 to 99·6) in the HBD group and 99·2% (98·4 to 99·8) in the AC group. The intracluster correlation coefficient was 0·01 (95% 0·00 to 0·04). This resulted in an estimated risk of viral load suppression being 0·3% (95% CI –1·5 to 2·4) for the HBD group compared with the SoC group and 0·9% (–0·8 to 2·8) for the AC group compared with the SoC group (figure 2). The lower bound of the two-sided 95% CI for both the risk differences were more than the non-inferiority margin of –5%. There was strong evidence (p<0·0001) that both the HBD and AC interventions were non-inferior to SoC, using our predefined non-inferiority margin of 5%.

Of the 1096 (44%) participants without a viral load in the primary endpoint window, 25 (2·3%) had died, 37 (3·4%) transferred out of the community, and 90 (8·2%) were lost to follow-up. Of the remaining 944 participants who did not have a viral load data recorded in the primary endpoint window, had not died, had not been transferred out of the community, and were not lost-to-follow-up, 690 (73%) had a viral load measurement taken between 15 months and 24 months (giving a total of 2083 [83·7%] participants who had a viral load result between 9 and 24 months) and 254 (10·2%) never had a viral load result, but were not lost to follow-up, had not transferred, and were not known to have died. Reasons for not having a viral load result included not having had a viral load test done, missing results, delayed processing of viral load samples, and delayed entry of viral load results into participant files and Smartcare database.

Post-hoc sensitivity analyses were done to allow the inclusion of some participants with viral load data available outside of the predefined primary endpoint window (9–15 months). First, the window was widened to allow an observation of viral load between 9 and 18 months, resulting in 1723 (69·2%) participants being included in the analysis. A second expansion of the window to 24 months resulted in the inclusion of 2083 (83·7%) participants. Across all scenarios, the proportion of participants who were virally suppressed remained very high (>98% in all groups) with strong evidence (p<0·0001) of non-inferiority (appendix p 2).

The proportion of participants retained and known to be virally suppressed at 12 months was compared in all participants across all three groups, excluding the 37 participants who were known to have transferred out of the community. The mean cluster prevalence was 50·3% (SD 14·2%) in the SoC group, 57·1% (SD 17·7%)

	Participants with viral load result	Participants with viral load >1000 copies per mL (IQR 2175–18 221)	Estimated prevalence of viral suppression* (%; 95% CI)	Risk difference *vs* standard of care†
9–15 months (primary outcome)				
Standard of care group	390/781 (50%)	6/390 (2%)	98·3% (96·6 to 99·7)	..
Home-based delivery group	518/852 (61%)	6/518 (1%)	98·7% (97·5 to 99·6)	0·3% (–1·5 to 2·4)
Adherence clubs group	485/856 (57%)	4/485 (1%)	99·2% (98·4 to 99·8)	0·9% (–0·8 to 2·8)
9–18 months				
Standard of care group	526/781 (67%)	8/526 (2%)	98·0% (96·3 to 99·5)	..
Home-based delivery group	621/852 (73%)	10/621 (2%)	98·3% (97·3 to 99·3)	0·3% (–1·5 to 2·3)
Adherence clubs group	576/856 (67%)	7/576 (1%)	98·8% (97·9 to 99·6)	0·8% (–0·9 to 2·7)
9–24 months				
Standard of care group	633/781 (81%)	8/633 (1%)	98·4% (97·0 to 99·6)	..
Home-based delivery group	711/852 (83%)	13/711 (2%)	98·2% (97·2 to 98·2)	–0·2% (–1·7 to 1·5)
Adherence clubs group	739/856 (86%)	10/739 (1%)	98·6% (97·7 to 99·3)	0·2% (–1·3 to 1·8)
20–24 months				
Standard of care group	123/781 (16%)	2/123 (2%)	99·2% (98·0 to 100)	..
Home-based delivery group	197/852 (23%)	3/197 (2%)	98·9% (97·7 to 100)	–0·3% (–1·9 to 1·3)
Adherence clubs group	379/856 (44%)	6/379 (2%)	98·7% (97·7 to 99·6)	–0·5% (–1·9 to 1·0)

Data are n/N (%). *Estimated prevalence based on mean of zone (cluster) prevalence's; virological suppression was defined according to the Zambian standard of care guidelines: less than 1000 HIV RNA copies per mL (based on the parameters of any assay performed through routine laboratory monitoring). †Is the difference in the risk of virological failure between the intervention and standard of care.

Table 2: **Viral suppression at different time points**

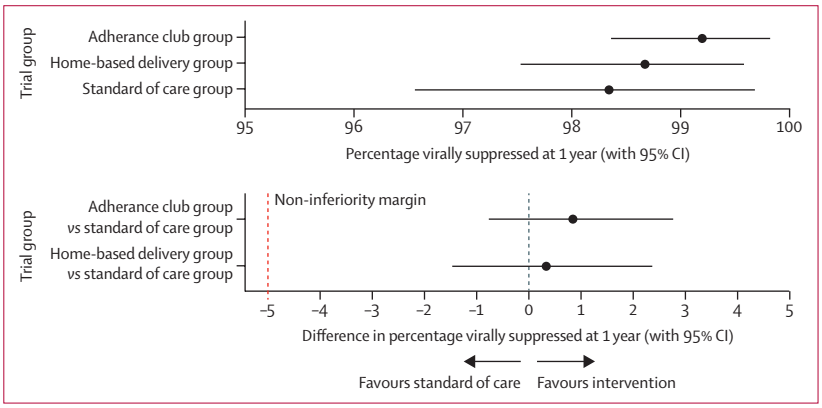

Figure 2: **Comparison of standard of care with home-based delivery and adherence clubs**
(A) Estimated viral suppression in the three treatment groups. (B) Risk difference of viral suppression between the standard of care group and the two intervention groups.

	Standard of care group (n=781)	Home-based delivery group (n=852)	Adherence clubs group (n=856)
Loss to follow-up			
Loss to follow-up at 12 months	72 (9%)	28 (3%)	28 (3%)
Risk difference *vs* standard of care group	..	−6·4% (−9·3 to −3·5)	−6·7% (−9·7 to −3·8)
Loss to follow-up at 24 months	127 (16%)	51 (6%)	46 (5%)
Risk difference *vs* standard of care group	..	−10·9% (−14·3 to −7·6)	−11·8% (−15·3 to −8·3)
Mortality			
Known died at 12 months	2 (<1%)	18 (2%)	8 (1%)
Known died at 24 months	2 (<1%)	19 (2%)	12 (1%)
Combined death and lost to follow-up	129 (17%)	70 (8%)	58 (7%)

Data are n (%) or % (95% CI). *Information obtained on the cause of death was mostly non-specific.

Table 3: **Lost to follow-up and mortality across the study groups**

	Standard of care group (n=781)	Home-based delivery group (n=852)	Adherence clubs group (n=856)
Chose the model assigned	781 (100%)	825 (97%)	808 (94%)
Retained in care at 12 months*	646 (83%)	745 (87%)	776 (91%)
Retained in the model of care at 12 months†	..	733 (88%)	754 (93%)
Transitioned back to standard of care within the first year after enrolment	..	92 (11%)	54 (7%)
Reasons for transition			
Moved out or relocated out of the zone or community‡	..	53/92 (58%)	26/54 (48%)
Opted out of the model	..	24/92 (26%)	19/54 (35%)
Staff decision	..	15/92 (16%)	9/54 (16%)

Data are n (%) or n/N (%). *Defined as participants who had a drug refill within the 120 days in the run up to 12 months after enrolment (ie, between 245 and 365 days after enrolment). †Participants who were still receiving care via the intervention models and had not transitioned to standard of care. ‡Moved out of the zone into another zone offering a different intervention or out of the community but still receiving care at the same health care facility.

Table 4: **Retention in allocated model of antiretroviral delivery**

in the AC group, and 62·3% (13·9%) in the HBD group (appendix p 3). The HBD intervention resulted in higher known viral suppression than SoC, with an estimated risk difference of 12·0% (95% CI 5·3 to 18·7; p=0·00066); although the AC intervention was also better than SoC the difference was not statistically different (risk difference 6·7% [95% CI −0·9 to 14·4]; p=0·085). In both the HBD and AC groups there was very strong evidence (p<0·0001) of non-inferiority against the 5% non-inferiority margin.

For our secondary endpoint of viral suppression in those who had a viral load result 20–24 months after enrolment, more viral load results were obtained in the AC group (44·3%) than in the HBD (23·1%) or SoC arms (15·7%). Viral suppression was estimated to be 99·2% (95% CI 98·0–100·0) in the SoC group compared with 98·9% (97·7–100·0) in the HBD group and 98·7% (97·7–99·6) in the AC group (table 2). This resulted in the estimated risk of viral suppression being slightly lower in both the HBD group and the AC group compared with the SoC group, but still well above the non-inferiority threshold of −5% (p<0·0001).

Deaths at 12 months are reported in table 3. In the entire follow-up period of 24 months, 33 (1·3%) of 2489 participants were known to have died: two (<1%) of 781 in the SoC group, 19 (2%)of 852 in the HBD group, and 12 (1%) of 856 in the AC group (table 3). Information obtained on the cause of death was mostly non-specific. In the HBD group, of the 19 participants who died, three died due to HIV-related causes, seven due to non-HIV related causes, and nine due to unknown cause. In the AC group, one died due to HIV related cause, four due to non-HIV related causes, and seven due to unknown causes. Of the two participants who died in the SoC group, neither were known to be due to HIV-related causes.

By the end of the study, 224 participants were lost to follow-up: 127 (57%) from the SoC group 51 (23%) from the HBD group, and 46 (21%) from the AC group. 2167 (87·1%) of 2489 participants who were retained in care at 12 months. Retention in care was highest in the AC group (776 [91%]), followed by the HBD group (745 [87%]), and last the SoC group (776 [83%]). 92 (11%) of 825 participants in the HBD group and 54 (7%) of 808 participants in the AC group were transitioned to SoC within the first year (table 4). 733 (89%) of 825 participants were retained in the HBD group at 12 months and 754 (93%) of 808 participants were retained in the AC group (table 4). Five (0·5%) participants developed tuberculosis (four in the AC group and one in the HBD group). Throughout the study period, there were no reports of adverse events or social harms.

Discussion

This cluster-randomised, non-inferiority trial done in a high HIV prevalence setting in Zambia provides evidence that two community models of ART delivery were non-inferior to the current standard of care in terms of viral suppression 1 year and 2 years after enrolment. The proportion of participants with viral suppression in our three study groups was more than 95%, which compares favourably with results from other published studies and is higher than we had anticipated, partly due to the eligibility requirement of being virally suppressed within the 12 months before trial enrolment and because the median time on ART in all three arms was 4 years. Although only 55% of individuals had a viral load result during the predefined window period, sensitivity analysis including 85% of the data gave the same result.

Our study adds to the growing body of literature that streamlined services for people with stable HIV, delivered by trained community health workers to support adherence and drug delivery, is as effective as care in health-care facilities in ensuring ART adherence and viral suppression. Randomised studies from Tanzania, Uganda, and Kenya have all shown that home-based ART delivery can achieve similar or higher viral suppression and retention rates than conventional facility-based care.[18,19,21]

Regarding adherence clubs, our findings support randomised studies from South Africa, in which 12 month viral suppression rates were similar between adherence clubs and the health-care facilities.[22,23] However, in most of these published studies, it was difficult to ascertain the viral load coverage because the authors did not specifically describe what percentage of participants did not have a viral load available for analysis. Studies from Lesotho and Zimbabwe on multi-month dispensing and community adherence groups found no difference in viral suppression rates between community models and facility care, despite the limitations of the study from Zimbabwe in viral load results availability, which were similar to ours.[12,24] The findings of our study were also consistent with our systematic review, published in 2021, which found no evidence of differences in viral suppression between patients assigned to various forms of differentiated service delivery models and the health-care facility.[25]

In line with previous studies, retention in both intervention groups was high despite the high patient mobility in urban settings.[14] We found no evidence of a difference in all-cause mortality rates between those assigned to the HBD group and those assigned to the AC group, although comparison of mortality rates to the SoC group was probably subject to ascertainment bias because we relied on routine clinical data, in which deaths outside the clinic are poorly recorded and information obtained on the cause of death mostly non-specific.[10] Lost to follow-up rates in the health-care facility were significantly higher compared with both the HBD and AC groups, but this difference could have been an overestimation because death was poorly recorded, or participants could have transferred without the knowledge of the health-care facility (also known as silent transfer), with others discontinuing therapy.[18,21,23,26] Like many programmes in sub-Saharan Africa reporting lost to follow-up, ascertaining the actual outcomes of people who were lost to follow-up who could frequently not be traced was difficult.[27]

Our findings highlight the suboptimal routine viral load monitoring for people with HIV in low-income and middle-income countries. In our trial and a randomised study in Lesotho,[12] non-availability of viral load results due to prolonged testing turnaround time and missing results resulted in a significant proportion of participants being ineligible for differentiated service delivery inclusion. Nearly half of our study participants were excluded from the primary analysis, and, in comparison with the standard of care, viral load coverage in both community ART models was around 5–10% better because of the viral load demand created by the study team. Although viral load testing capacity has increased in low-income and middle-income countries, insufficient testing, inadequate personnel, inefficient cold chain transportation, and weak sample referral mechanisms continue to prevent people with HIV from getting these tests.[9,28] People with an unsuppressed viral load need to be followed up by peer educators, but this approach has not been robust, and patients are more likely to be informed of their results at the next clinic appointment. There is need to strengthen laboratory services by creating an efficient feedback system, developing guidelines, and providing ongoing training and support to health-care workers about the importance of viral load monitoring and considering alternative viral load technologies, such as point-of-care viral load tests. Additionally, demand for viral load testing must be created by empowering patients to understand the significance of the test, participate in their treatment decisions, and benefit from the use of their results.[29]

During the study, ART stock-outs occurred due to health system issues or supply chain flaws, resulting in 1–2 months ART refills instead of 3 months. This might have effected adherence in the SoC group because more frequent pharmacy visits were required, underlining the need for alternative drug delivery mechanisms in low-income and middle-income countries.

Our study had several strengths in that it used a robust, cluster-randomised design to explore participant outcomes of different ART delivery models and compare them with the health-care facilities in a real-world urban setting, providing evidence that could be generalised to other in low-income and middle-income countries. The use of routine clinical and laboratory data helped prevent this study from influencing participant clinical outcomes. This study showed the acceptability of community health workers to deliver ART, despite potential stigma concerns, this might be because the repeated home visits over 3 years during the main HPTN 071 (PopART) trial solidified their relationship with the communities which could, in turn, have helped overcome many of the challenges people with HIV face in accessing care.[30–33]

The study had several limitations. First, there could have been ascertainment bias for some outcomes, because we knew what occurred to participants in the intervention groups but not in the SoC group, restricting our ability to draw specific comparisons regarding deaths and opportunistic infections. Second, delayed viral load data excluded many potential eligible individuals from the study. The number of participants with a viral load result in the primary endpoint window was substantially lower than predicted and was lower in the SoC group than in the HBD and AC groups. This difference could have introduced bias into the results if the reason for a missing viral load was associated with viral suppression. However, the sensitivity analysis that allowed us to include many of the delayed viral load results gave us a similar result to the primary outcome. Third, we had lower recruitment in the SoC group. This imbalance might have occurred due to participant awareness of the interventions in their residential zones, leading them to visit the clinic outside their scheduled appointments to be screened for study inclusion. This might have led to overestimating viral suppression in the intervention groups. Fourth, compared with the SoC group, lost to follow-up rates were lower in the intervention groups. However, it is unlikely that those

who were lost to follow-up had a higher prevalence of virological suppression than those who were not lost to follow-up, implying that increased lost to follow-up rates in the SoC group makes our comparison more conservative. Fifth, our assumption on prevalence on non-suppression was too high and despite not recruiting our target sample size, the study power was retained by the lower level of non-suppression. Finally, because participants had to be clinically stable, they were probably highly adherent. This calls into doubt their representativeness of all people with HIV and the generalisability of the results. Whereas, people who struggle with adherence and appointment keeping might benefit the most from flexible models of care and should be included in such trials.

Our study has shown that differentiated service delivery models are feasible, acceptable, and do not compromise clinical outcomes for people with stable HIV. They can overcome barriers to ART access despite the weak public health infrastructure, restricted human resources, and the day-to-day realities of living with HIV. They might even be more suited for people with less stable HIV who face difficulties attending the clinic for work, family, or stigma reasons, and offer more individualised care and peer support for newly diagnosed individuals. To fully assess the effectiveness of the models in practice, more research or programmatic evaluations are required to understand their implications long-term (5–10 years follow-up), and which factors have the greatest influence or effect on the models' effectiveness need to be determined. Exploration of annual clinic visits for people with stable HIV, in which viral load testing can be done outside the clinic, might have a beneficial effect on the cost, cost-effectiveness, and acceptability of HIV interventions on a larger scale.

In conclusion, community models of ART delivery were as effective as facility-based care in terms of viral suppression in this urban setting in Zambia. However, in settings with poor viral load resources, such frequent viral load monitoring in people receiving ART with stable HIV might not be optimal compared with efforts to enhance retention on ART or viral load monitoring in populations at higher risk of non-suppression.

Contributors

ML, HA, SFi, and RH designed the trial in consultation with the HPTN 071 protocol team. DM, SFl, and AJS designed the statistical framework of the trial and were involved in the randomisation. ML, OS and DM verified the data. ML and DM analysed the data. ML led the intervention implementation with involvement from BC, VS, EM, and OS. ML wrote the first draft of this manuscript and all authors contributed equally to the trial and reviewed and approved the final manuscript.

Declaration of interests

HA reports grants from The Bill & Melinda Gates Foundation, National Institutes of Allergy and Infectious Diseases (NIAID), National Institute of Mental Health (NIMH), National Institute on Drug Abuse (NIDA), International Initiative for Impact Evaluation (3ie), and the US President's Emergency Plan for AIDS Relief (PEPFAR) during the study; is a member of the technical review panel for the Global Fund to Fight AIDS, Tuberculosis, and Malaria; and reports honoraria payment from global fund outside the submitted work. SFi reports grants from The Bill & Melinda Gates Foundation, NIAID, NIMH, NIDA, and 3ie during the study; is affiliated with the clinical trial HIVCORE006, St Marys Development Trust board, SHM Foundation charitable trust board; and SFi reports consulting fees from Immunocore, outside the submitted work. SFl and DM reports grants from The Bill & Melinda Gates Foundation, NIAID, NIMH, NIDA, and 3ie during the study. All other authors declare no competing interests.

Data sharing

Research data that underpins analysis outlined in this paper cannot be made available. The dataset contains measurements that can be used to reidentify study participants, due to the number and type of variables captured. Participant and ethical consent for wider sharing was also not obtained, due to the research being done before data sharing became the norm. However, the study team invite interested parties to contact the corresponding author to discuss the research and data collected in more detail.

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References

1 UNAIDS. Fact Sheet 2021. 2021. https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf (accessed Jan 24, 2018).

2 Long L, Kuchukhidze S, Pascoe S, et al. Differentiated service delivery models for antiretroviral treatment of HIV in sub-Saharan Africa: a rapid systematic review. AMBIT Project Report Number 04. Boston, MA: Boston University and HE²RO, 2020.

3 Kagee A, Remien RH, Berkman A, Hoffman S, Campos L, Swartz L. Structural barriers to ART adherence in Southern Africa: challenges and potential ways forward. *Global Public Health* 2011; **6:** 83–97.

4 Patricia Chauke et al. Lost to follow up rate in the first year of ART in adults initiated in a universal test and treat programme: a retrospective cohort study in Ekurhuleni District, South Africa. *Pan Afr Med J* 2020; **37:** 198.

5 Alhaj M, Amberbir A, Singogo E, et al. Retention on antiretroviral therapy during Universal Test and Treat implementation in Zomba district, Malawi: a retrospective cohort study. *J Int AIDS Soc* 2019; **22:** e25239.

6 WHO. Key considerations for differentiated antiretroviral therapy delivery for specific populations: children, adolescents, pregnant and breastfeeding women and key populations. Geneva: World Health Organization, 2017.

7 Pasipamire L, Nesbitt RC, Ndlovu S, et al. Retention on ART and predictors of disengagement from care in several alternative community-centred ART refill models in rural Swaziland. *J Int AIDS Soc* 2018; **21:** e25183.

8 Rasschaert F, Decroo T, Remartinez D, et al. Adapting a community-based ART delivery model to the patients' needs: a mixed methods research in Tete, Mozambique. BMC Public Health; 2014; **14:** 364.

9 WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2nd edn. Geneva: World Health Organization, 2016.

10 Nachega JB, Adetokunboh O, Uthman OA, et al. Community-based interventions to improve and sustain antiretroviral therapy adherence, retention in HIV care and clinical outcomes in low- and middle-income countries for achieving the UNAIDS 90-90-90 targets. *Curr HIV/AIDS Reports* 2016; **13:** 241–55.

11 Decroo T, Rasschaert F, Telfer B, Remartinez D, Laga M, Ford N. Community-based antiretroviral therapy programs can overcome barriers to retention of patients and decongest health services in sub-Saharan Africa: a systematic review. *Int Health* 2013; **5:** 169–79.

12 Tukei BB, Fatti G, Tiam A, et al. Twelve-month outcomes of community-based differentiated models of multimonth dispensing of ART among stable hiv-infected adults in Lesotho: a cluster-randomized noninferiority trial. *J Acquir Immune Defic Syndr* 2020; **85:** 280–91.

13 Hoffman RM, Moyo C, Balakasi KT, et al. Multimonth dispensing of up to 6 months of antiretroviral therapy in Malawi and Zambia (INTERVAL): a cluster-randomised, non-blinded, non-inferiority trial. *Lancet Global Health* 2021; **9:** e628–38.

14 Hayes RJ, Donnell D, Floyd S, et al. Effect of universal testing and treatment on HIV incidence—HPTN 071 (PopART). *NEJM* 2019; **381:** 207–18.

15 Hayes R, Ayles H, Beyers N, et al. HPTN 071 (PopART): rationale and design of a cluster-randomised trial of the population impact of an HIV combination prevention intervention including universal testing and treatment—a study protocol for a cluster randomised trial. *Trials* 2014; **15:** 57.

16 Limbada M, Bwalya C, Macleod D, et al. A comparison of different community models of antiretroviral therapy delivery with the standard of care among stable HIV+ patients: rationale and design of a non-inferiority cluster randomized trial, nested in the HPTN 071 (PopART) study. *Trials* 2021; **22:** 52.

17 Geldsetzer P, Francis JM, Ulenga N, et al. The impact of community health worker-led home delivery of antiretroviral therapy on virological suppression: a non-inferiority cluster-randomized health systems trial in Dar es Salaam, Tanzania. *BMC Health Services Res* 2017; **17:** 160.

18 Geldsetzer P, Francis JM, Sando D, et al. Community delivery of antiretroviral drugs: a non-inferiority cluster-randomized pragmatic trial in Dar es Salaam, Tanzania. *PLoS Med* 2018; **15:** e1002659.

19 Jaffar S, Amuron B, Foster S. Rates of virological failure in patients treated in a home-based versus a facility-based HIV-care model in Jinja, southeast Uganda: a cluster-randomized equivalence trial. *Lancet* 2009; **374:** 2080–89.

20 Hayes RJ, Moulton LH. Cluster randomised trials. Boca Raton, FL: Chapman and Hall, 2009.

21 Selke HM, Kimaiyo S, Sidle JE, et al. Task-shifting of antiretroviral delivery from health care workers to persons living with HIV/AIDS: clinical outcomes of a community-based program in Kenya. *J Acquir Immune Defic Syndr* 2010; **55:** 483–90.

22 Fox MP, Pascoe S, Huber AN, et al. Adherence clubs and decentralized medication delivery to support patient retention and sustained viral suppression in care: results from a cluster-randomized evaluation of differentiated ART delivery models in South Africa. *PLoS Med* 2019; **16:** e1002874.

23 Hanrahan CF, Schwartz SR, Mudavanhu M, et al. The impact of community- versus clinic-based adherence clubs on loss from care and viral suppression for antiretroviral therapy patients: findings from a pragmatic randomized controlled trial in South Africa. *PLoS Med* 2019; **16:** e1002808.

24 Fatti G, Ngorima-Mabhena N, Mothibi E, et al. Outcomes of three- versus six-monthly dispensing of antiretroviral treatment (ART) for stable HIV patients in community ART refill groups: a cluster-randomized trial in Zimbabwe. *J Acquir Immune Defic Syndr* 2020; **84:** 162–72.

25 Limbada M, Zijlstra G, Macleod D, Ayles H, Fidler S. A systematic review of the effectiveness of non- health facility based care delivery of antiretroviral therapy for people living with HIV in sub-Saharan Africa measured by viral suppression, mortality and retention on ART. *BMC Public Health* 2021; **21:** 1110.

26 Woodd S, Grosskurth H, Levin J, et al. Home-based versus clinic-based care for patients starting antiretroviral therapy with low CD4+ cell counts: findings from a cluster-randomized trial. *AIDS* 2014; **28:** 569–76.

27 Holmes CB, Sikazwe I, Sikombe K, et al. Estimated mortality on HIV treatment among active patients and patients lost to follow-up in 4 provinces of Zambia: findings from a multistage sampling-based survey. *PLoS Med* 2018; **15:** e1002489.

28 Roberts T, Cohn J, Bonner K, Hargreaves S. Scale-up of routine viral load testing in resource-poor settings: current and future implementation challenges. *Clin Infect Dis* 2016; **62:** 1043–48.

29 Killingo BM, Taro TB, Mosime WN. Community-driven demand creation for the use of routine viral load testing: a model to scale up routine viral load testing. *J Int AIDS Soc* 2017; **20** (suppl 7): e25009.

30 Mukumbang FC, Orth Z, van Wyk B. What do the implementation outcome variables tell us about the scaling-up of the antiretroviral treatment adherence clubs in South Africa? A document review. *Health Res Policy and Syst* 2019; **17:** 28.

31 Roy M, Bolton-Moore C, Sikazwe I, et al. Participation in adherence clubs and on-time drug pickup among HIV-infected adults in Zambia: a matched-pair cluster randomized trial. *PLoS Med* 2020; **17:** e1003116.

32 Bemelmans M, Baert S, Goemaere E, et al. Community-supported models of care for people on HIV treatment in sub-Saharan Africa. *Tropical Med Int Health* 2014; **19:** 968–77.

33 Tshuma N, Mosikare O, Yun JA, et al. Acceptability of community-based adherence clubs among health facility staff in South Africa: a qualitative study. *Patient Prefer Adherence* 2017; **11:** 1523–31.

7.2. Supplementary information

THE LANCET
HIV

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Limbada M, Macleod D, Situmbeko V, et al. Rates of viral suppression in a cohort of people with stable HIV from two community models of ART delivery versus facility-based HIV care in Lusaka, Zambia: a cluster-randomised, non-inferiority trial nested in the HPTN 071 (PopART) trial. *Lancet HIV* 2021; published online Nov 26. http://dx.doi.org/10.1016/S2352-3018(21)00242-3.

Appendices

Appendix 1: Broad overview of the three ART delivery models.

	When	What	By Whom	Where
Model				
Standard of Care (SoC)	Month 0 (enrolment)	Clinical consultation, screening for eligibility*, consent to participate in study* Drug: ART x 90 days	Clinician**	ART clinic
	Months 3, 6, 9 and 12	**Clinical visit:** Clinical consultation, adherence support[!], laboratory monitoring (VL testing) [ǂ] **Drugs**: ART refill for 90 days***		
Home-Based Delivery (HBD)	Month 0 (enrolment)	Clinical consultation, screening for eligibility*, consent to participate in study * **Drug:** ART x 90 days	Clinician **	ART clinic
	Months 3 and 9	Adherence support Symptom screening for TB, STI Provision of Health education & provision of condoms **Drugs**: Dispensation of 3-monthly pre-packed drugs Patients with symptoms referred to clinic	CHiP (community HIV care provider)	Participants Home
	Months 6 and 12	**Clinical visit:** clinical consultation, adherence support[!], **Laboratory:** VL sample collection[ǂǂ] **Drugs:** ART refill x 90 days VL > 1000 or symptom screening positive – participant down referred to SoC [¥]	Clinician **	ART clinic
Adherence clubs (AC)	Month 0 (enrolment)	Clinical consultation, screening for eligibility*, consent to participate in study * **Drug:** ART x 90 days Club venue and meeting date provided	Clinician**	ART clinic
	Months 3 and 9	**Club meeting consisting of 15-30 participants** Adherence support Symptom screening for TB, STI Provision of Health education & provision of condoms **Drugs**: Dispensation of 3-monthly pre-packed drugs Patients with symptoms referred to clinic	CHiP (community HIV care provider)	Community venue (church halls, school classrooms)
	Months 6 and 12	**Clinical visit:** clinical consultation, adherence support[!], **Laboratory:** VL sample collection[ǂǂ] **Drugs:** ART refill x 90 days VL > 1000 or symptom screening positive – participant down referred to SoC [¥]	Clinician**	ART clinic

*Screening for eligibility and consenting was done by research nurse in the health care facility

**clinician includes physicians, clinical officers and nurses

*** ART refills in the SoC varied from 1-3 monthly supplies depending on drug stocks

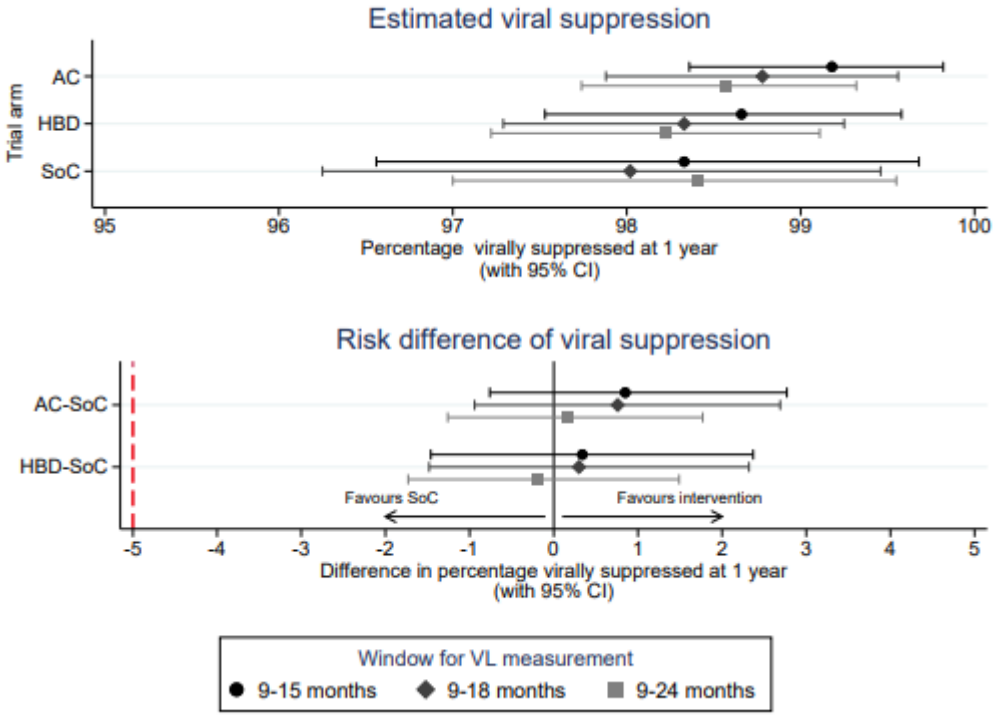
! adherence support in the SoC was done either by the clinician or adherence support workers

ǂ VL testing in the SoC would be done at either one of the 4 visits depending on their annual due date

ǂǂ VL testing in intervention arms were done either at the 6 month or 12 month clinical visit if that visit was close to or corresponded to their scheduled VL testing date.

¥ patients in the intervention arms with VL > 1000 copies were notified of their results either during their clinical visit or even called prior to their clinical or community visit to be seen by the clinician at the HCF.

Appendix 2 : Sensitivity analysis showing estimated and risk difference of viral suppression over time among all patients.



Appendix 3. Composite outcomes (known viral suppression)

	Enrolled and did not transfer out	Known virally suppressed at 12-months*	Estimated prevalence of known viral suppression†	Risk difference vs SoC
Standard of Care	773	384 (49·7%)	50·3% (45·5%, 55·2%)	
Home Based Delivery	835	512 (61·3%)	62·3% (57·6%, 67·1%)	12·0% (5·3%, 18·7%)
Adherence Clubs	844	481 (57·0%)	57·1% (50·9%, 63·2%)	6·7% (-0·9%, 14·4%)

Data are n/N (%).

*Percentages are as per the raw data (the window period 9-15 months after enrolment)

† Means of cluster prevalence by zone

Appendix 4. Risk difference of viral suppression stratified by sex, age group and years on ART.

	Enrolled (N)	No. of those with VL result	VL>1000 copies/ml	Estimated prevalence of viral suppression	Risk difference vs SoC
Men					
Standard of Care	226	102 (45·1%)	2	98·2% [95·0%, 100%]	
Home-Based Delivery	247	147 (59·5%)	4	96·5% [92·5%, 99·6%]	-1·72% [-6·30%, 2·86%]
Adherence Clubs	259	148 (57·1%)	3	98·4% [96·4%, 100%]	0·19% [-3·17%, 3·56%]
Women					
Standard of Care	555	288 (51·9%)	4	98·4% [96·2%, 100%]	
Home-Based Delivery	605	371 (61·3%)	2	99·5% [98·8%, 100%]	1·15% [-0·59%, 3·47%]
Adherence Clubs	597	337 (56·4%)	1	99·7% [99·1%, 100%]	1·31% [-0·37%, 3·55%]
Aged under 40					
Standard of Care	370	182 (49·2%)	4	97·7% [95·2%, 99·7%]	
Home-Based Delivery	434	253 (58·3%)	3	98·9% [97·4%, 100%]	1·21% [-1·28%, 3·95%]
Adherence Clubs	422	226 (53·6%)	0	100% [N/A]*	2·32% [0·34%, 4·76%]
Aged 40+					
Standard of Care	411	208 (50·6%)	2	99·2% [97·8%, 100%]	
Home-Based Delivery	418	265 (63·4%)	3	98·9% [97·5%, 100%]	-0·30% [-2·03%, 1·47%]
Adherence Clubs	434	259 (59·7%)	4	98.5% [97·0%, 99·7%]	-0.67% [-2·49%, 1·22%]
On ART less than 3 years					
Standard of Care	238	119 (50·0%)	4	94·0% [86·2%, 99·2%]	
Home-Based Delivery	253	164 (64·8%)	3	98·2% [96·0%, 100%]	4·12% [-1·66%, 12·2%]
Adherence Clubs	257	136 (52·9%)	2	98·8% [96·9%, 100%]	4·72% [-0·89%, 12·8%]
On ART 3+ years					
Standard of Care	543	271 (49·9%)	2	99·3% [98·2%, 100%]	
Home-Based Delivery	599	354 (59·1%)	3	99·0% [97·8%, 100%]	-0·3% [-1·89%, 1·17%]
Adherence Clubs	599	349 (58·3%)	2	99·2% [97·9%, 100%]	-0·1% [-1·62%, 1·35%]

Data are n (%).*Unable to calculate confidence interval due to no events in AC arm.

Chapter 8. Discussion

8.1 Outline of the chapter

This chapter summarizes the key findings of this research to compare different community models of ART delivery for stable HIV+ patients in an urban setting. Findings of each research component of this thesis have been discussed comprehensively in each of the four research papers and linking chapters. This final chapter summarizes the key findings across the study's primary and secondary objectives and the factors that influence the development and implementation of community models of ART delivery in an urban setting. The study's strengths and limitations will be analysed, and recommendations for future research, policy, programs, and services will be made based on the thesis findings.

8.2 Summary of the key findings

The research undertaken for this PhD compared two community-based ART delivery approaches to existing facility-based standard care in an urban resource-limited setting in Zambia. The findings of this study should be applicable to a wide range of urban and peri-urban settings in Sub-Saharan Africa, where DSD models are being scaled up to handle the growing population of PLHIV on ART. Key research questions relevant to policy makers prior to the consideration of alternative approaches to sustaining ART for all PLWH are, safety, feasibility and acceptability, all of which have been carefully addressed in this PhD.

The critical findings of this research are:

1. A review of current literature demonstrates that non health facility-based care (nHFBC) models are a safe alternative to the current standard of care in resource-limited settings in sub-Saharan Africa in terms of mortality, viral suppression, and retention in care.
2. Community models of ART delivery have been shown to be acceptable in a high burden HIV urban setting with inadequate human resources and infrastructures, with the majority expressing a preference for these models of care.
3. Both community models of ART delivery tested in this research are as effective as facility-based care in terms of viral load suppression.
4. Implementing community models of ART delivery in an urban resource-limited setting is feasible but can be affected by health systems challenges which includes lack of access to viral load testing

and results, inadequate latitude for prescribing drugs, and inadequate funding to support retention and supervision of community health workers.

8.2.1 Review of current literature has shown non-health facility based care (nHFBC) models have promising outcomes and a safe alternative to the current standard of care in resource-limited settings in sub-Saharan Africa.

The systematic review of literature (Chapter 3) found evidence that decentralizing HIV services into the community via non-health facility based care (nHFBC) models has promising outcomes and is a safe alternative to conventional standard of care in resource-limited settings[230]. The review suggested that levels of VLS and mortality are similar in both nHFBC and health facility-based care (HFBC) groups. The pooled risk difference of VLS amongst the four RCTs showed no evidence of a difference in VLS between nHFBC and HFBC, with a point estimate of VLS 1% higher in HFBC [95% CI -1% lower to 4% higher]. Three of the four observational studies reporting VLS were broadly consistent with the RCTs, although they were slightly more favorable towards nHFBC, with risk difference ranging from 4-6%. The pooled hazard ratio of mortality amongst 2 RCTs and 4 observational cohort studies showed no evidence of a difference in mortality between nHFBC and HFBC with an overall estimated hazard ratio of 1.01 [95% CI 0.88, 1.16]. Similarly, with regards to retention and LTFU, articles in our review showed comparable or slightly better outcomes amongst nHFBC when compared to HFBC. Although no formal quantitative analysis was performed on these outcomes due to the very different definitions between papers, it was observed that the outcomes appeared similar between HFBC and nHFBC. Our findings are in line with previously published systematic review by Decroo et al that summarized evidence that community based programs can make treatment more accessible and affordable, as well as enhance adherence and long-term retention of patients on ART [178].

Our systematic review had several limitations, and this included the small number of studies that reported ART delivery through nHFBC models, heterogeneity of the models ranging from their diversity, definitions, outcomes assessed and evaluation methods. Another limitation was that only two-thirds of the articles in our review compared nHFBC to conventional health facility-based care making data available for analysis limited and inclusion in the meta-analysis imperfect, limiting the strength of our conclusions on the various outcomes. The diversity of these nHFBC models, as well as their study designs, could have resulted in observation and confounding bias when comparing them. Significant selection bias was introduced as only stable patients were included in the studies.

Despite the promising outcomes, further studies are needed to fully understand longer clinical outcomes and cost effectiveness of nHFBC and how these models can be placed into the context of existing healthcare systems.

8.2.2 Community models of ART delivery have been shown to be acceptable in a high burden HIV urban setting with inadequate human resources and infrastructures, with the majority expressing a preference for these models of care.

Our study findings confirmed that decentralizing ART outside the current facility-based care into the communities using community health workers (in our case, the CHiPs) to provide adherence support and pre-packed medications is feasible and acceptable (Chapter 6 of this thesis). Over 95% of eligible patients consented to participate in the study demonstrating a general acceptance and enthusiasm towards these innovative models of ART delivery[231]. Several studies have reported stigma as either a barrier or enabler in the uptake of differentiated models of care based outside the health care facility [221]. DSD models that reduced frequency of visits and time spent collecting ART drugs have been mentioned as potentially stigma reducing as patients felt they were less likely to be seen at the clinics or being noticed for their frequent trips to the clinic [164, 221-223]. Other studies have reported DSD models outside the HCF, such as adherence clubs, as stigmatizing as patients feared public disclosure of their HIV status [221, 224]. Despite earlier studies having reported that only 3% of patients refuse to engage in DSD models due to stigma [178, 232], recent qualitative studies from Ghana, Malawi and South Africa have reported that DSD models outside the HCF have a limited impact on reducing HIV-related stigma and may be a barrier to patient uptake[212, 221, 225]. Interestingly, our findings showed that both HBD and AC models, utilizing CHWs to provide adherence support and medications, are well accepted and preferred by many PLHIV who do not perceive these models of delivery as stigmatizing. However, our findings could largely be due to the fact that repeated home visits by CHWs (in our study, the CHiPs) over a 3-year period during the door-to-door combination prevention package solidified the relationship between the CHWs and the communities.

Our findings on acceptability of community models of ART delivery is similar to findings from other settings where models such as AC demonstrated high acceptability both by patients and HCWs[233, 234] as these models are capable of overcoming many of the challenges patients face such as long waiting times to access medications, frequent clinical trips and transportations costs[163, 176, 235] In addition, these models have also shown to be acceptable and preferred by HCW as they are perceived to reduce congestion in the clinics and alleviate staff shortages and workload[176]. This study was the first to determine preferences stable PLHIV make when offered a choice between community models of ART delivery and conventional facility-based care. To date there is limited data documenting patient preferences for one DSD model over another, as a head-to-head comparison. Several studies have reported patient satisfaction with DSD services as high as 81% [236] although there is no comparative data to suggest if patient satisfaction with DSD models was higher than with health care facility. Although a small number of studies have reported preferences towards specific DSD models, the

majority expressed a preference for individual models and facility-based models [multi-month scripting, fast-track and appointment spacing] compared to group models [Table 8.1] [236, 237].

Our findings showed that over 95% of PLHIV who were offered a choice between facility-based care and community models of ART delivery (HBD and AC) chose the latter (as their "revealed preference"). When asked for their preferences out of all three options, only 1/3 of our study population stated a preference and of these the majority stated a preference for the community models of ART delivery (HBD and AC) compared to SoC. A large proportion, 2/3 of the study population did not state a preference towards any of the three options provided and whether that reflects a true lack of preference needs to be explored further. Some explanations as to why the majority of our study participants did not state a preference could be that in resource limited settings, patients are not empowered about choice and do not perceive themselves as having much autonomy within health care services. In addition, our study design could have contributed to this finding as participants were assigned to the study arms before they were asked about their preferences and therefore less likely to state a preference when satisfied with the model of ART delivery assigned. For example, over 60% of participants in the SoC arm stated a preference compared to the HBD arm where only 11.9% stated a preference. Where participants were not given the option of being in an HBD model of delivery (i.e., in the SoC or AC arms), a higher proportion stated preference towards HBD was observed over the other two options[231].

Our study not only demonstrates the growing importance of examining patient preferences for DSD models in order to progress knowledge and explain how HIV services must change to meet the needs of PLHIV, but also offers key lessons for HIV policy and service delivery. Achieving the UNAIDS 95:95:95 target for HIV testing, treatment, and viral suppression is a major goal in the global HIV response, and understanding patient preferences for HIV delivery services, which may differ across population groups and settings, is critical to maximizing the uptake and impact of these models[238]. Retention and adherence to treatment are the major factors that influence DSD model effectiveness, and both are influenced by patient's preferences and satisfaction. To maximize the efficiency and reaching goals of DSD models, a thorough understanding of the barriers to achieve retention and adherence to treatment in these models is required. Using stated preferences as in our study can help understand by providing insights about DSD preferences, key attributes from the DSD models from patient and HCW perspectives, and preferences for DSD models among patients and policy makers. Our findings warrant further research to explore factors that have a bearing on patient preferences towards DSD models in order to determine which models of care to prioritize as they could be significant factors in clinical outcomes and integrity of DSD services.

Table 8.1. Patient Preferences and satisfaction for DSD models in SSA*

Country	Model	Satisfaction metric or model to which DSD is preferred	% Of patients reporting they preferred the DSD model
Facility based individual model			
Kenya [239]	Facility fast track	Compared to community adherence groups (CAGs)	**84.7%**
Out of facility based individual models			
Ghana [240]	Community based refills for key populations	Compared to refills by clinicians	**80%**
Mozambique [241]	Community pharmacies	Compared to health care facility (SoC)	**84.0%**
Tanzania [205]	Home-Based delivery	Compared to SoC	**86.0%**
Uganda [242]	Community-based ART	Compared to SoC	**87.4%**
Client led groups			
Zambia[243]	Community adherence groups	Compared to SoC	**64.2%**

*Modified from AMBIT Project Report Number 1, August 2019. Available at https://sites.bu.edu/ambit/files/2019/09/AMBIT-report-01-patient-benefits-and-costs-Sept-03-2019-v1.1.pdf

8.2.3 Rates of viral suppression in a cohort of stable HIV+ patients in two community models of ART delivery versus facility-based HIV care.

The main findings of the trial are that stable patients receiving care in community models of ART delivery do not have an increased risk of virological failure compared to those receiving standard of care. In this urban African setting, the two community ART delivery modalities (HBD and AC) were non-inferior to the facility-based standard of treatment for viral suppression one year after enrolment. Despite the fact that our study results were based on 55% of patients receiving a viral load test during the pre-defined window period due to several challenges with viral load testing (as described in Chapter 7), our findings of viral suppression of > 95% in all three trial arms were comparable to, if not better than, results reported in several other published trials. According to our systematic review (Chapter 3), seven of the ten studies that demonstrated viral suppression as an endpoint in non-health facility-based care included a comparison to conventional care (3 RCTs and 4 observational cohort studies). There was a remarkably consistent effect of VS (I2 = 0.04 percent) found across the randomized trials, very marginally in favour of community models of ART care, with an overall estimated risk difference of 1% and no statistically significant evidence of a difference in viral suppression between the randomized trials. Rates of VS in each of the two ART delivery models in our study were superior to what was reported in prior studies from Uganda and Tanzania[31, 32], and rates of VS in AC models were similar or better to previously published trials that compared AC to SoC in South Africa[26, 174]. Grimsrud et al. found significantly higher VS in non-facility models of care

(estimated risk difference of 39%), albeit in that paper, patients in the non-facility-based models were classified as “stable on ART” while the comparison group was not.

One of the major challenges encountered in our study and other resource-limited settings in SSA face for individual and public health is the poor access to HIV viral load testing and results (described in Chapter 5). Since 2013, the World Health Organization (WHO) recommended the use of routine HIV viral load testing over CD4 as the “gold standard” to monitor patients response to ART[12]. Adoption of this recommendation was initially slow by national programs, but the last few years have seen funders and national programs supporting and scaling up routine viral load monitoring[211]. Despite the fact that programs in resource-limited settings have adopted the WHO guidelines and modified their HIV treatment guidelines to incorporate routine viral load testing for all PLHIV on ART, these policies have not been widely implemented, resulting in insufficient access to VL testing for PLHIV[244]. Major barriers include high sample volumes, shortages of trained laboratory staff, insufficient testing capacity, cold chain inefficiency in transportation of samples, overburdened HCW, poor training, weak transport and laboratory systems and weak sample referral systems[245]. In these settings, lengthy turnaround times and the loss of samples or results continue to be a problem[245].

As viral load monitoring provides critical information regarding an individual’s health it is critical to strengthen every step of the viral load cascade[211]. In order to mitigate the barriers to the cascade of viral load testing in resource limited settings, there is an urgent need for governments to strengthen the health and laboratory systems in order to: 1. Improve coverage and utilization of VL testing, 2. Improve sample collection and transportation networks to ensure prompt delivery of samples to laboratory and results to patients, 3. Improving the link between laboratory information system and health care facility and 4. Use of alternative viral load technologies such as point of care VL tests should be considered in the future as that could address most of the challenges faced with the current cascade of Viral load testing [245]. In addition, there is also need to improve demand creation for access to HIV viral load testing through HIV treatment education and community mobilization[244] and possibly diversion of resources from routine CD4 testing to VL monitoring for stable patients on ART[246-248]. PLHIV must be empowered to comprehend the significance of HIV VL testing and results, to participate in their care decisions, and to benefit from the use of their results, all of which will increase demand creation[247, 249].

Although retention in care is imperative to sustain an undetectable HIV viral load[146], there is still no standard measure for retention in care as it is complex and difficult to define[138]. Despite the World Health Organization defining retention in HIV care as the continuous engagement of patients in ART care[172], the metrics to ART retention have differed widely. Various measures have been used to

measure retention in care such attending regular follow-up appointments and frequency of visits to the ART clinic. In our study, for all the participants who were still in care at the end of the study period and not known to have transferred out, retention in the two community models of ART delivery was higher than in the facility-based care [92% HBD; 93.2% AC vs 83.4% SoC]. These findings are similar or better than what has been reported in previous studies. The few RCTs that have compared retention between facility-based care and non-facility-based care in SSA have reported community models had comparable rates to those in the facility [26, 32, 179]. Equally, most observational studies also demonstrated similar retention outcomes between community-based models and facility-based models [182, 190, 197] or better outcomes in community-based models [162, 193]. Our findings highlight the necessity of deploying CHWs to provide targeted adherence support and defaulter tracing for enhanced overall ART retention in different ART delivery models. The use of CHW trained to follow-up patients to reduce LTFU have been shown to be beneficial in bringing patients back to care in many SSA settings[250, 251].

With regards to LTFU, the heterogeneity in the definitions of LTFU across various settings has made it difficult to assess differences in LTFU between and within ART programs, therefore obstructing comparability [252]. Programmatically, loss to follow-up refers to patients who are no longer in care and have an unknown outcome, a generic term referring to patients who were on ART who have not returned to the clinic[25, 253, 254]. It represents patients who have died, undocumented (silent) transfer and those who are alive but withdrew from care voluntarily. According to a recent study, death and undocumented transfers were significant among LTFU patients in Sub-Saharan African settings [255]. Our findings showed that community models of ART delivery were associated with lower LTFU rates compared to the HCF, similar to what has been reported in other studies where community-based programs are associated with a decreased risk of LTFU. As highlighted in our systematic review (Chapter 3), most studies in SSA that included LTFU as one of their outcomes when comparing community-based models to HCF showed either comparable or better LTFU rates in community-based models despite the large variations in defining LTFU.

Our study found no evidence of a difference in the rates of all-cause mortality between the two community models of ART delivery (HBD versus AC). We were unable to compare the mortality rates to the health care facility cohort, despite seemingly fewer deaths in the facility cohort, due to the poor recording of deaths in the HCF. The mortality rates in both the HBD and AC models were comparable to those reported by other RCTs and cohort studies in similar settings, where there was no statistically significant difference in the rates of all-cause mortality in patients assigned to community-based ART models versus those assigned to the HCF[27]. Previous studies have suggested that incomplete reporting of mortality and failure to capture most deaths that occur outside the HCF in most programs

across SSA are often considered as LTFU[256]. Recent findings from a study conducted in Zambia's high-volume HIV clinics indicated that deaths are underreported within the country's national HIV program and that mortality rates varied significantly across sites and provinces[256].

Recording patient outcomes on ART are important indicators for successful HIV treatment and effectiveness of HIV programs including differentiated care. Failure to capture indicators during routine monitoring of patients limits the assessment of the impact of HIV services and identification of gaps needed for improvement [256]. In our study, recording routine patient outcomes from the HCF to make a comparison to the interventions was a huge challenge and accounted for a high number of patients in the HCF not having a VL test done within the 9-15 months window period for our primary analysis. The current SmartCare data system used for monitoring patient's health and performance of ART programs in Zambia has major challenges in both completeness and quality of data collected to track patients on ART and this quality seems to be deteriorating over the years as ART programs expand. With the use of both paper-based forms and computer-based entry for data collection, the greatest challenge is incomplete forms and data entry errors which translate to missing data in the SmartCare database[257]. Although the SmartCare system has evolved over the last couple of years transitioning from "Electronic-last" (where data is retrospectively entered into SmartCare from paper-based forms) to introduce a direct entry system for SmartCare called "Electronic-first", no discernible improvements in the completeness or accuracy of data has been observed in high-volume facilities in Lusaka, Zambia[258]. Most of these challenges with regards to monitoring and evaluation of these programs have also been experienced in other resource-limited settings and these include: 1.). funding gaps for staffing and data collection, 2). lack of an effective feedback from the data system leading to disengagement and complacency at operational level, 3). Backlogs in data entry from paper-based into computer-based methods, 4). Power outages putting a strain on computer-based data collection and entry and 5). Lack of standard operating procedures for reporting data. In our findings, we also noted the workload and backlog of entering data into the SmartCare database affected the quality of data entered, observed during our data cleaning process. These findings are equally consistent with literature that that has cited lack of human expertise and financial resources as major implementation of electronic medical recording (EMR) system[259].

Although we have shown from this study that community models of ART delivery were non-inferior to the HCF for viral suppression in an urban resource-limited setting, the availability of viral load testing and results remain a challenge to HIV programmes and could undermine gains from universal treatment.

8.2.4 Community models of ART delivery are feasible and practical to implement in high HIV burden urban settings.

Despite the large-scale implementation of DSD models in various formats in Sub-Saharan African settings and their promising outcomes, there is a dearth of detailed information about DSD model implementation in these settings. Information that is available to policy makers, funders and national HIV programs about how these models are implemented is lacking. In this thesis, we described the strategies utilized during the implementation process in an urban resource-limited setting and the effectiveness of the interventions as a viable and sustainable health service program which could potentially be conducted entirely by the existing health systems and community health workers. Although our interventions (HBD and AC) were in a controlled research setting, process of implementing these interventions and ensuring fidelity and sustainability in a "real-world" setting would require more or less of the approaches that were used. The insights of implementing these interventions throughout this thesis are summarized below.

A. Were the interventions implemented as planned? Lessons learnt.

In general, the community models of ART delivery (HBD and AC) were implemented as planned and scaling-up these models of ART delivery in resource-limited settings is feasible. From our observations, both HBD and AC models were successfully decentralized and, as detailed in chapters 4 and 5, we identified key factors that are either enablers or jeopardizers to the success of implementing community models of ART delivery in an urban setting which could also be generalizable to rural settings (Chapter 5, Table 5.8). The key factors that we identified included:

1. *Involving key stakeholders and communities* during the planning stages in the development of the interventions and throughout the implementation until study completion was critical. This included MoH and implementing partners (IPs), facility health care workers, community health workers, members of the Community Advisory Board (CAB) and patients. This process enabled the interventions to be integrated into the current ART delivery system, promoted and increased the acceptability of the interventions, and garnered support and enthusiasm from both HCWs and CHWs, all of which contributed to the creation of a favorable environment for implementing and sustaining the interventions throughout the course of the study.

2. Effective coordination and communications - Implementing community models of ART delivery within a community, whose members are unfamiliar with this type of intervention requires effective coordination and communication in order to enhance information exchange, improve

transitions of care and ensure patient-centred quality-of-care[260]. This was essential to meet patients' expectations and engage them actively to participate in the interventions. Regular feedback from patients during the delivery of the interventions was sought to evaluate the impact of these interventions and ensure that their preferences and views are taken into consideration. In addition, strong communication between the IPs, HCF and CHiPs were found to be critical in optimizing patients flow in the clinics. For example, the CHiPs in our study were instrumental both in sensitizing and mobilizing patients for the study. They helped by sensitizing the communities and the patients at the clinics about the benefits of this program. As the program became established, patients who were less certain or hesitant began to show enthusiasm towards joining the programs by coming to the clinic to determine if they were eligible. This observation is consistent with other research that show implementation of an intervention can be more successful if it is promoted by individuals who come from or can relate easily to the target population[170, 261, 262]. The importance of effective coordination and communication in implementing health care interventions has also been reported in other studies [170, 175, 260] across resource-limited settings.

3. *Strengthening the healthcare facility capacity* – a competent workforce to ensure successful implementation and patient care is required and therefore a multidisciplinary team of health care staff (Clinicians, nurses, pharmacists, data clerks) and community health workers is needed. Due to inadequate human resources in health care facilities in resource-limited settings, there is need for appropriate staffing to implement these interventions. The existing number of staff and their roles need to be identified to ensure job descriptions are in place for all the staff to understand. Staffing requirements need to be monitored to ensure adequate staff are in place to carry out the implementation and monitoring and evaluation of patients. Clinical and financial requirements were equally essential to the achievement of successful program implementation and this included salaries for CHiPs and research staff, airtime for mobile phones, stationary, furniture, laboratory specimen bottles, clinic staff part-time payments and transportation of supplies to the clubs. ART drug supply had to be reliable and uninterrupted, and it is therefore crucial to have a pharmacist supporting the procurement and distribution of ART in the interventions. Some bottlenecks were encountered such as drug stockouts, routine viral load testing and SmartCare database challenges. However, no reports of unwanted HIV disclosure and ARV trade or misuse, were noted.
4. *On-going supervision and quality control* -The fidelity of our interventions may have been strengthened by the on-going supervision and quality control put in place by the study staff and the use of intervention manuals for each of the two interventions. Quality assurance was assessed

on all source documentations and reports derived from the CHiPs delivering the interventions were used to track the progress of the intervention's activities. The CHiPs conducted a high proportion of the stipulated activities prior and during each club session and home visit such as notifying patients on their upcoming visit through phone calls or physical reminders, adherence support, dispensing pre-packed drugs, symptom screening and making referrals to the clinic for appropriate services. This could be attributed to the clear structurally designed operating manuals tailored to guide them through each visit and the trainings (initial and refresher) that was provided throughout the study. The utilization of study records for monitoring and evaluation on a consistent basis provided as an indirect measure of our program's fidelity. The collection of data using the study forms was a feasible measure (though time consuming and error prone) as the data collected was part of routine program delivery. Forms that were completed were indicative of a successful club or home visit and drugs distributed to the right patient. Periodic visits by the study team accompanying the CHiPs to the club sessions and home visits were conducted to monitor the fidelity of the intervention delivery.

B. Were our Models of ART delivery acceptable?

The acceptability of implementing the two community models of ART delivery is reflected in the proportion of patients who consented to take up the offer of the two community models of ART delivery when offered a choice (described in Chapter 6). Over 90% of participants who were eligible consented to the study and less than 5% of participants opted out of the models of care. From our qualitative analysis, both patients and CHiPs described the HBD and AC model as being acceptable as it reduced frequent trips to the clinics thus saving on transportation costs and time. The AC model had an advantage over the HBD model in that it allowed for resource-based adaptations. Club meetings, for example, could be held in a location convenient for all members or even in a patient's home.

To support the further expansion of DSD models and their integration into health care systems, various studies, including ours, underline the need for additional human and structural resources [229, 233, 234, 263]. Without external funding, there have been concerns by providers with regards to staff burden, data collection challenges, lack of sufficient resources and supply chain inconsistencies. This calls for government funding and formal employment of CHWs to deliver community-based HIV programmes.

Our findings around the fidelity of implementation of community models of ART delivery are comparable with findings across available literature from health facility or community-based health interventions in sub-Saharan Africa. These studies have shown that fidelity of interventions

can be strengthened by on-going supervision and quality control [264]. A process evaluation study conducted to determine the fidelity, acceptability, and feasibility of CHW support to improve HIV treatment outcomes in Zimbabwe (ZENITH trial) found that using clear and structurally designed tools tailored to guide CHWs and in-depth trainings improved the interventions' overall fidelity [265].

C. Key lessons learnt from implementation of community models of ART delivery.

I. *Staff involvement and integration of DSD models with the existing health care systems are crucial both for models to function and maintaining patient's quality of care.* As highlighted in several studies and reviews, this allows patients in the models of care to be under the responsibility of the HCF who remains accountable for them [175, 215]. Although in our study, HCWs were supportive of implementing these models outside the health care facility with a view that it would reduce congestion and long waiting times in the clinic, the fact that this was a two-year study funded by an NGO made them reluctant to take ownership of the two models of ART delivery. Patients in these models of ART delivery were not viewed as the clinics responsibility and therefore reluctant to assist with some of the activities (pre-packaging of drugs, drug scripts and follow up on VL results) without additional staffing and incentives.

II. *More resources are needed to fully exploit the potential benefits of community models of ART delivery in decongesting health care facilities.* A larger number of stable patients need to be transitioned from clinic-based to alternative model-based care and this cannot be achieved with existing resources as the clinics continue being overburdened as PLHIV in need of treatment continue to grow. There is need for additional funding and resources to pay for staffing, trainings, costs of running the models (stationary, transport, phone airtime, dispensation bags), clinical and data capturing time. The large contribution from our study were seen as critical to the existence and operations of these models of care and without further funding for long-term scale-up, these models would not be sustainable putting patients at risk for long term retention and adherence to treatment[263].

III. *Strengthening laboratory network and diagnostic services.* A key lesson learnt was that access to viral load testing and results is considered as an enabler as it simplifies the "stable" eligibility criteria for joining the models and most importantly reduced follow-up visits. The difficulties encountered with routine viral load monitoring necessitate the strengthening of laboratory networks and diagnostic services, establishment of national strategic plans and policies for laboratory monitoring, and the allocation of appropriate resources, including human and financial resources, to ensure the availability of testing services[52].

IV. *Monitoring and Evaluation systems for DSD need to be simplified and standardized.* As highlighted in the discussion in Chapter 5, data collection for monitoring and evaluating DSD models is heavily dependent on paper-based tools (registers etc.) which are time-consuming and not be feasible in our setting. The scarcity of standardized, structured approaches to document patient-level and program-level data[216, 217] limits guidance to programs on how best to collect data. Data capturing tools need further simplification and adaptations. In addition to existing ART records, DSD require supplementary tools to collect information regarding DSD membership and other essential information collected during the community visits (referrals, TB symptoms, treatment interruption etc.) which may necessitate timely follow-up and referrals. In this study, several paper-based forms had to be designed from the time of screening to patient exit and this included screening and eligibility forms to determine eligibility and proportion of patients enrolled in the models of care. The use of electronic devices to record data in our study was difficult due to the excessive complexity, loss of confidence among end-users, and lack of useful feedback, all of which hampered the application's use, particularly in an environment where digital services have not yet proliferated. As we move towards scaling up DSD models in the context of UTT, there is an urgent need to refine the existing M&E systems to collect information essential for both patient and program management.

V. Formal recognition and integration of community or lay health workers in community-based programs are considered as critical enablers for DSD scale-up and operations [163, 212, 215]. This group of cadres provide an integral link in HIV support and follow-up between the communities and health care facilities which are often constrained by a shortage of trained health care workers. In most of the resource-limited settings, lay or CHWs are usually employed by donor funded implementing partners resulting in a lack of cohesion and sustainability[213] As these cadres are well recognized within the communities they work in and conduct community outreach activities, their roles in health program interventions such as DSD needs to be formalized as they currently lack recognition, sustained financing and their scope of practice is vague and lacks standardization[212, 213]. The recognition and standardization of CHWs or lay workers and inclusion in the country's national human resource in the context of scaling up DSD services will be critical as in the absence of formal recognition and donor funding, threaten the sustainability of DSD services. Therefore, political and financial commitments, regulatory frameworks and mechanisms to mentor and supervise CHWs will be urgently required.

Although our cluster-randomized trial evaluated the effects of the pre-specified outcomes which was viral suppression, there is need to conduct a process evaluation alongside our outcomes for such complex interventions to assess their fidelity, feasibility and acceptability. Although our trial did look at acceptability, feasibility and fidelity through qualitative work, an implementation science framework or program theory could have explicitly helped define and frame acceptability, feasibility and fidelity of the two intervention models.

Literature from several studies in sub-Saharan Africa have shown that although public health interventions have been proven to be effective in resource-limited settings, they are not creating the expected impact in other settings where replicating and scaling up these interventions have been challenging[266, 267]. Like our interventions, the implementation process is complex and influenced by contextual factors from both within and outside healthcare interventions which can impede implementation and render interventions ineffective. Prior to implementing DSD models within a new context, it is critical to determine if it can be effective and if any adaptations are needed to enhance their impact on patient outcomes. Understanding this context helps to improve the fit of these innovations and implementation strategies thus improving feasibility, fidelity and acceptability. Details of the implementation process of DSD models are needed for others to evaluate, replicate, improve and scale up these models of care[268].

Implementation science have proposed various frameworks or theories that can be used to improve diffusion of evidence based interventions, adapt innovations to local contexts, better understand the implementation setting, and evaluate the implementation process. The National Institute for Health Research (NIHR) and The Medical Research Council (MRC) have recently launched a new complex intervention research framework which provides an updated definition of complex interventions, highlighting the dynamic relationship between the intervention and its context [269, 270]. The framework divides complex intervention research into four phases: development or identification of the intervention, feasibility, evaluation, and implementation[270]. Each phase has a common set of core elements considering context, developing and refining programme theory, engaging stakeholders, identifying key uncertainties, refining the intervention, and economic considerations. These elements should be considered early and continually revisited throughout the research process, and especially before moving between phases (for example, between feasibility testing and evaluation)[270]. In order to establish the feasibility and acceptability of DSD models, mixed methods approach needs to be adopted and feasibility can be assessed by collecting data on recruitment and retention rates, adherence rates, time required to recruit the target sample size, rates of completion of the intervention and feasibility of data collection methods[271]. Implementation fidelity is the degree to which an intervention is delivered as intended and is critical to successful translation of

evidence-based interventions into practice [272]. Acceptability of the interventions can be assessed both quantitatively and qualitatively. In addition to using consenting to study as an indicator of acceptability, we also used a discreet method to determine participant choices and preferences to models of ART delivery. Participant's data can also be collected through study forms to ascertain visit dates, drugs dispensation, activities conducted during the visits, transfers out from the study catchment area or down referral to clinic care and deaths. An embedded qualitative study will obtain patients' views and experiences of the intervention, including what they perceive to be barriers and facilitators to using it[271].

In addition, economic evaluation should be a core component of all phases of the intervention research to help identify the scope of costs and benefits that matter most to decision makers. Although cost and cost-effectiveness of the two models of ART delivery were not part of my PhD thesis, a prospective economic evaluation, from a provider's perspective, is being undertaken by the economics team at Zambart to comparatively calculate the incremental cost-effectiveness ratio (ICER) in terms of cost per HIV positive individual with suppressed viral and DALY averted for each of the trial intervention arms. Economic evaluation is key to providing evidence on resource requirements for scale up as well as value for money. Cost analysis will provide vital information to stakeholders or managers to judiciously implement health care programs and interventions. Cost-effectiveness analyses will provide key information for policymakers and funders to prudently invest in healthcare for optimal health benefits with available resources. This will be published separately.

8.3 Strengths and Limitations of the study

The strengths and limitations of each of the research components are discussed in each of their chapters. In this section I will discuss and expand some of the main strengths and weaknesses.

8.3.1 Study strengths

1. This study was a cluster-randomized trial with a non-inferiority design, and to our knowledge, was amongst the first in an urban resource-limited high HIV burden setting that rigorously compared clinical and virological outcomes of patients participating in community models of ART delivery to current facility-based ART delivery as standard of care. CRTs are regarded as the gold standard for the evaluation of health interventions and allow both the direct and indirect effects of an intervention to be captured. This study was rigorously designed to determine the overall effect of implementing community models of ART delivery in resource-limited settings. Providing policymakers and HIV programs with evidence on patient outcomes, acceptability and feasibility of community models of ART delivery and the potential solutions to the integration of these

models of ART delivery into the existing health care system will accelerate policy adoption and scale-up in the context of universal treatment in an effort to minimize the barriers to accessing care and treatment.

2. The use of routine clinical and laboratory data helped prevent this study having influence on clinical outcomes such as viral suppression, retention and mortality. Our study supported the existing government HIV program. We studied treatment outcomes under "real world" situations as an operational research incorporated into the existing ART program.
3. The study provided us with information about patient's choices and preferences for one model of ART delivery over another.
4. This trial was nested in the main HPTN 071 (PopART) trial. The CHiP database provided us with an extensive and accurate data on uptake measures that enhanced our ability to monitor and measure the impact of the interventions. Leveraging the main trials investment, trained staff, data systems and community engagement represented us a unique opportunity to extend the roles of the CHiPs and clinic staff to evaluate this novel innovation.
5. The study was conducted in an urban setting, where health system challenges are similar in urban settings of Zambia and other resource-limited settings. Therefore, our findings could be more applicable to similar urban settings and may even be generalizable to rural settings.

8.3.2 Limitations

1. The clusters ("zones") allocated to the interventions were limited to the study catchment area which were defined within the main HPTN 071 trial. Therefore, recruitment of potential patients into the study was limited to those living within the study catchment only. In addition, the study zones were previously part of the main HPTN 071 (PopART) trial so the communities were familiar with the services provided by the community health workers and this may not reflect how well their services would be accepted in a different setting.
2. As is the case with the majority of operational research studies, we had limited influence over what occurred in the standard of care (control) arm. In Zambia, the current standard of treatment for HIV continues to evolve as recommendations change and alternative diverse models of ART delivery are implemented. For instance, implementation of fast-track and 6-monthly drug dispensation which were offered to some of our patients in the standard of care arm. The shift from E-last to E-first in data collection in the standard of care arm made it very difficult to track routine indicators such as VL results on time.
3. The use of routine data for measuring outcomes such as viral suppression, LTFU and mortality were challenging as most of these results were either missing, delayed or yet to be updated in

the facility health care database and clinical records, and for some of these outcomes like death and LTFU, we could not make a comparison between the intervention models and the standard of care.

4. As highlighted in the thesis chapters, there were more female than male participants recruited in the study reflecting the current stable patient clinic population in the clinic and more participants were recruited in the intervention arms as compared to the standard of care arm. This imbalance in the arms could have arisen from the fact that patients in the community were likely to have known the interventions their zones were allocated to because of ongoing sensitizations about the study, prompting them to come to the clinic outside of their scheduled visit dates to be screened for inclusion in the models of care. If these led to more patients in the intervention arms, it could have led to overestimating viral suppression in those arms. Finally, there were many participants who had a missing viral load result at 9-15 months after study entry, a window used for our primary analysis but who subsequently had a viral load result between 15 and 24 months.
5. We could have observed "courtesy or social desirability" bias as a potential limitation in eliciting the choices and preferences towards these models of delivery. Such bias is common in settings where patients might not reveal their true attitudes and reluctant to express negative opinions of services.
6. The delayed viral load data excluded many potential eligible individuals from the study. The number of participants with a viral load result in the primary endpoint window was substantially lower than predicted and was lower in the SoC group than in the HBD and AC groups. This difference could have introduced bias into the results if the reason for a missing viral load result was associated with viral suppression. However, the sensitivity analyses that allowed us to include many of the delayed VL results gave a similar result to the primary outcome.
7. As patients in the SoC arm were still receiving some "intervention" (i.e., they were having CHiP visits in in the main trial) and enhanced viral load access and support compared with non-PopART communities, they might have been doing better than patients not getting the CHiPs visit, diluting the difference we observed because there might have been an even bigger difference if we had been able to compare it with non-PopART communities ("real" SoC). These effects might work in the same direction (i.e., either enhancing the difference, or narrowing it) or they might work in opposite directions.
8. Limitations may have also resulted from the sort of patients or CHWs interviewed for qualitative analysis, as they only evoked views of stable HIV patients in ART delivery models, which may differ from those not in delivery models or not yet in HIV care. Given time and resources, eliciting views from patients not in the models of care and the general community would be meaningful

as they might have different views regarding the models of care. Stable patients may have already had exposure to task shifting (Nurse-based ART initiation and lay worker adherence support) in the health care facilities prior to the interventions, which could influence their perception of home based and Adherence clubs' models of delivery.

8.4 key lessons learned from this PhD process.

The last four years have been a period of intense learning and contemplation since beginning my PhD. The following are the lessons I learned from the time the study was designed to the time the study was completed:

- **Need for patience, flexibility and adaptations in complex situations** when conducting a research study. As with most studies there are a number of delays ranging from development of study protocols, approvals and time required to implement the activities.
- **Frequent communications with field staff and health care workers** are critical to understand challenges they face in delivering the interventions and the ability to lead and problem-solve to minimize the challenges for the study's integrity. Understanding the challenges that employee's encounter can help us improve how we support them and what we expect from them.
- **Understanding the data collection and cleaning process**. A key lesson learned from this study was the data collection technique. Using paper-based forms to collect data and integrate with the existing database is quite tedious and prone to errors therefore requiring stringent quality control measures on the already burdened study staff. Using the electronic database (SmartCare) is equally challenging due to incomplete and missing data and took the staff over 5 months to clean the datasets. A lesson learnt from this for future studies is to develop tools that collect minimal but vital data that can also be linked with the SmartCare database not only to serve as a purpose for entering data but also investigate irregularities in data.

8.5 Findings in the context of research

Although several sources have described favourable patient clinical outcomes in differentiated models of care, very few have compared these models of ART delivery to conventional standard of care or one another. Additionally, the available literature on these studies and reports revealed considerable heterogeneity in their study designs, definitions and assessment of clinical outcomes, as well as evaluation methods, making it difficult to draw firm conclusions about the impact of these models on various outcomes[273]. Our findings on viral suppression and mortality in Chapter 7 aligns with findings from previous studies that DSD models can achieve comparable or even better outcomes to health facility-based care, thereby supporting evidence to scale up these models of care.

The distinction between DSD model uptake and coverage is critical in our understanding of effective and sustainable DSD models in resource-limited settings. Coverage is defined as the proportion of eligible patients enrolled in a DSD model, whereas uptake is the proportion of patients who enrolled in a DSD model when given the opportunity to do so[274]. Very few sources have reported uptake and coverage in this manner. According to a gray literature review (AMBIT project) on DSD services in sub-Saharan Africa[274], uptake and coverage of DSD models are poorly evaluated due to a lack of accepted definitions to standardize numerators and denominators, as well as a lack of knowledge about the true number of sites in these settings that offer DSD services. In this study, we have shown uptake of community models of ART delivery in our study by offering patients who were randomized to the intervention arms a choice to continue receiving care in the clinic or take up the DSD model. Our findings show that when offered a choice between HCF and DSD, over 95% take up the DSD model, an indication that these models are well acceptable in urban settings despite major concerns such as stigma which is considered a major barrier to taking up these models of care outside the health care facility.

With regards to patient preferences towards DSD models in resource-limited settings, there is limited data to determine which models of care patients prefer. The majority of the studies have only reported satisfaction levels with DSD models being high, albeit no comparative data to whether satisfaction levels were higher than with health care facility standard of care or one model over another. A possible explanation is that the majority of research gathered from publications is prone to bias, as models that do not achieve high levels of patient and provider satisfaction and patients who depart models prior to evaluation are likely to be underrepresented in the research. Due to a lack of head-to-head comparisons in which patients can chose which model to enrol in, patient preferences and choices are virtually non-existent in the existing literature, with the exception of a few studies demonstrating that patients prefer individual models to group models[237]. Our study which did a head-to-head

comparison in eliciting choices and preferences between community models of ART delivery and standard of care showed that over 95% of patients chose the alternative model of delivery over the standard of care when offered a choice between the two. This finding is important as national programs scale up differentiated service delivery, patients' preferences will be critical to determine which models to prioritize as they could be significant factors in the clinical outcomes and integrity of these models.

8.6 Implications for scaling up DSD models in resource-limited settings.

Our study adds to the growing body of evidence to support implementation of differentiated service delivery as an innovative strategy to support the HIV care continuum and achieve viral suppression among PLHIV on ART in urban high HIV prevalence settings in SSA. By evaluating two community ART models delivered in a real-world and resource-limited high HIV burden urban setting, we shed light on a variety of policy and programming implications for future scale-up efforts.

Our findings suggest that the full potential of DSD models in reducing workloads and decongestion in the health care facilities in urban settings has not yet been realized. Although models outside the HCF are feasible to implement, there is need to sustain and optimize the efficiencies promised by DSD services through:

1. Implementing policies that recognize and regulate the roles of community health workers as part of the health-care system. The rising need for such cadres in resource-limited settings is currently offset by several limitations such as recognizing them as formal workers in the health care system, prescription and dispensation regulations and poor supervision and remunerations. Failure to address this, there is a high risk of service interruption in the long run and therefore in the context of scaling up DSD models.

2. Strengthening and prioritizing the demands that come along with scaling up DSD models. On the supply side, logistics related to ART supply chain (drug procurement, supply chain and pharmacy management) need to be strengthened as scale up dramatically increases the demands for ART medications. Weaknesses in the supply chain can result in stockouts interrupting the services and therefore be critically monitored and reported. Additionally, the duration of drug supply should be tailored to the patient's needs, and refills should be kept to a minimum to ease the load on both patients and health care systems. This requires a change in policies to facilitate the decentralization of dispensing into the communities. Although these policies have been put in place in some countries like Zambia, the poor supply chain hinders its implementation. The recent switch in ART regimen from single combination pill – Tenofovir (TDF), Lamivudine (3TC)

and Efavirenz (EFV) to TDF, 3TC and Dolutegravir which is not yet a fixed dose combination for all adult PLHIV could potentially complicate the logistics in dispensing for longer durations and follow-ups within the model's dynamics. On the demand-side, our findings emphasize access to viral load monitoring as stable ART patients may be at risk of treatment failure despite the absence of clinical symptoms. The fact that stable patients in DSD models will interact less frequently with the health care facility, routine viral load monitoring will provide confidence and re-assurance that patients in these models of care are adherent to treatment. The use of VL testing will reduce frequent clinical visits and also allow programs to simplify eligibility criteria for enrolment into DSD models.

3. Identifying factors associated with uptake and retention in DSD models. Although DSD models have shown to have a wide variety of benefits, there are substantial number of patients who may still prefer to remain in the current health care facility for various reasons such as stigma, disclosure etc. Stigma has not been well explored in the context of DSD and although our study showed stigma not having an impact in the uptake of DSD models. A greater understanding of the patient-level characteristics that influence uptake and retention in these models is required, as are the complex and diverse preferences of patients when scaling up DSD models using suitable planning and programming techniques.
4. Aligning HIV service delivery within the evolving context of resource limited settings. Several factors in resource-limited settings can favour or threaten the sustainability of DSD models. This includes the economic situation, political environment, patient education levels and geographical factors. At present the high unemployment rates, poor education quality, inadequate infrastructure and human resources and overstretched public health system comprises the standard quality of care [224]. Poverty levels are highest in the rural areas compared to urban areas and this mirrors the availability of HCWs in these settings likely to threaten the sustainability of HBD and AC compared to community adherence groups which are known to work better in these settings as shown from studies in Mozambique, Malawi and Lesotho[161, 167, 212, 215]. Adherence clubs and Home-Based ART delivery are more likely to be eligible for urban and peri-urban settings given the evidence from recent publications in South Africa, Uganda and Tanzania which are speculative of how these models would operate in such settings [32, 175, 232, 263]. However, the mobility of patients in urban settings which was observed in our study has the potential to impede the smooth running of these models of care.
5. Within the context of national and global epidemics which can cause severe disruptions to the health systems, economic activities and movement of people may hinder PLHIV from going to the clinics to collect their ART leading to treatment interruptions. The current Covid-19

pandemic is no exception where countries have put in measures to mitigate the spread of disease by restricting unnecessary movements, gatherings and encouraging people to socially distance themselves. National ART programs need to realign their HIV service delivery to ensure that PLHIV continue to receive their ARVs. Several countries including Zambia have been implementing multi-month scripting (MMD) prior but with the pandemic have made the eligibility criteria flexible by dispensing MMD to PLHIV without a viral load result.

From our experience in the study, the Cholera epidemic in 2018 which was considered a national emergency resulted in curfews in the study population setting as a way to mitigate the spread of the disease and the HCFs in the two study sites were the cholera admission centres. Although our club and HBD meetings were considered a high risk to both CHWs and patients, we worked with the authorities to continue the interventions and use them as a platform to minimize patient interaction with the HCF, promote key health messages (hand washing and personal hygiene), distribution of chlorine for drinking water and administration of oral cholera vaccine to study participants and their families during the home and club visits. All these activities were conducted by CHWs highlighting their importance in an epidemic.

Overall, our research indicates that large-scale implementation of DSD models is unlikely to follow a linear path as outlined in the current national implementation tool guide, necessitating policymakers to offer alternative approaches that better reflect the complex and changing nature of DSD models and create new opportunities for understanding and scaling up health service[275].

8.7 Recommendations for programming and research

To reinforce the delivery of ART at scale, the current 2021 WHO guidelines promotes a public health approach by using simplified and standardized ART that supports decentralization of care, task shifting and community ART delivery and more efficient procurement and supply management[276]. shifting and community ART delivery and more efficient procurement and supply management [276]. Since 2016, several countries in SSA have adopted and scaled up differentiated service delivery as part of their national policy. Our research has clearly identified community-based ART delivery models as a safe alternative to the current standard of care, and factors ranging from the patient and community to the health-care system environment influence the development and implementation of these models of care through their influence on those prerequisites. Based on our results, the following are recommended to Policy makers and researchers in the implementation of DSD models on a larger scale in the context of universal treatment:

1. An urgent call for policy makers, donors and program managers in health facilities to provide leadership support and adequate planning to ensure success of these models of delivery. The planning of scaling up DSD models should be to create an enabling environment that will support health care workers to take ownership of these models. The lack of supportive policies, regulatory frameworks, absence of key stakeholder involvement, inadequate supportive supervision, inefficient referral systems, lack of human resources and funding should be given special attention.
2. Advocacy for community health workers. Recognizing CHWs as formalized health workers need to be taken into considerations as they are key in delivering and sustaining these models of ART delivery in the communities. Policies and guidelines over CHW trainings, supervision and enumeration need to be put in place by national governments in their budgets.
3. Improving demand creation- both health care workers and PLHIV need to understand the benefits associated with being enrolled in DSD models. There is need to improve the knowledge and motivation of both HCWs and PLHIV through mentorship, community engagement and stigma reduction activities which are critical to optimizing uptake and efficiencies of DSD models. In addition, Viral load monitoring which is the gateway to enrolment into DSD models need to be scaled up and be easily accessible. Key areas that need to be strengthened to ensure that PLHIV in care and in DSD models have routine access to VL testing and results include:
    - Strengthening the sample transport chain from health care facilities to the laboratory
    - Putting in place SOPs for VL monitoring and results – creating an efficient feedback system
    - Continuous trainings for HCWs to understand the importance and benefits of VL monitoring and management of patients with detectable viral loads.
    - Education and counselling to empower PLHIV about the benefits of routine VL monitoring so that they advocate for VL testing.
4. For monitoring and evaluating DSD efficiencies and health outcomes, the following need to be addressed:
    - Data collection tools need to be simplified and standardized across all formats of DSD models.
    - The SmartCare system should be able to link data collected at community level to clinic level to evaluate the impact of the DSD models across different meeting points (i.e., clinical visits and community visits).
    - Frequent reporting and feedback of data collected should be made available at facility, district and provincial level so that key partners and other relevant stakeholders have a better understanding of the success and challenges of implementing DSD models.

5. The need to support implementation of mobile health or electronic health interventions to improve data collection, follow-ups and prompt reminders for patients.

Directions for future research includes:

- Rigorously evaluating clinical outcomes (VS, LTFU, Mortality and retention), with comparisons to different DSD models and health care facilities to fully understand the implications of these models of care especially on a longer-term follow-up under routine care settings. It is critical to know what happens to clinical outcomes after entry into DSD models 3, 5 or 10 years later.
- Identification of patient and provider preferences towards DSD models that will improve their efficiencies, ART retention and sustainability. Further research is warranted to understand the broad acknowledgement in literature regarding the complexities of patient preferences towards DSD models and whether socioeconomic status and settings (rural or urban) have an influence on patients' choices and preferences towards DSD models.
- Identifying the factors that have the greatest influence or effect on the effectiveness of DSD models in practice. At the moment, it is unclear which factors have the greatest impact and how they influence the development and implementation of DSD models in practice in resource-limited settings. Our findings on identifying factors that may act as barriers or enablers in developing and implementing DSD models may serve as the foundation for future research.
- Evaluation of DSD models for key populations (as they have been and continue being socially isolated and not having confidence in the current health system for fear of stigmatization). Much remains to be learned about how effectively and for whom different types of models work, as well as whether they can be scaled up to reach key populations. There is need to determine which models can mitigate the barriers to accessing HIV services, engaging and retaining them in care.
- Currently there is a growing recognition of the need to adapt DSD services for unstable patients (those with advanced HIV disease, high viral load, and co-morbidities) and policy guidelines have been put in place for differentiating care for unstable patients. As the current scale-up of DSD models focuses on stable patients who are more experienced and have already achieved viral suppression under the current standard of care, there is need to determine how best we can identify, establish and strengthen referrals for unstable patients to accessing HIV services in a timely manner.
- Qualitative studies to understand the impact of stigma in the implementation and sustainability of DSD models to determine effective stigma-reduction interventions prior to

implementation of DSD models. Further research on relevant provider and patient views on the various formats of DSD models is required to advise policymakers on the optimal approach to DSD in their specific context.

- Integrating DSD models into the existing public health care system in the event that donor financing is no longer available. Currently the implementation of DSD models in SSA has been possible as resources have been available from donor support for human resources, salaries and technical assistance. What happens to the implementation and sustainability of these models of care once donor funding is no longer available?
- Currently there is scarce information available on the costs and benefits of DSD for HIV treatment for both patient and the health systems and therefore further research is warranted for which DSD models are cost-effective to patients and HIV programmes for wider scale implementation as this will help guide the choice of DSD approach by national programs.
- Evidence supporting approaches to integrating reproductive health services and injectable ART agents with DSD models is limited. There is need for research to identify approaches to integrate these services into DSD models that could lead to better uptake of these services (e.g., contraception, cervical cancer screening, vaccination and injectable 6-monthly treatment of Lenacapavir). There is a potential for these alternative approaches that might fit better into these DSD models and need for implementation research to evaluate the feasibility and acceptability of these different strategies of integration into DSD models of care.

8.8 The current status of DSD scale-up in SSA

Since our analysis, several studies in SSA have reported the beneficial outcomes in the HIV cascade amongst PLHIV in various DSD models, including improved ART uptake, adherence and suppression of viral load[276]. With regards to Adherence clubs and home delivery models, summary of evidence from published data up until October 2020 highlights improved client outcomes and suggest these models can also benefit specific client populations including children, adolescents, pregnant women and key populations[277]. Several countries in Africa have adopted various formats of DSD models in their national policy and these include Adherence clubs, community adherence groups (CAGS), Multi-month dispensation (MMD), fast-track ART refills and home ART delivery. Programmatic evaluations of these models have shown outcomes similar to our findings and qualitative analysis of DSD models have also demonstrated these models being able to decongest the clinics and reduce patient waiting times[277]. Although qualitative research in some locations, like as Zambia, has identified various

health system difficulties, including insufficient ARV supplies and the inability to conduct routine monitoring tests due to stock-outs and delays[277, 278].

Although all the studies were highly heterogeneous and evidence insufficient to determine which type of DSD model was associated with better or superior outcomes than the other, this has prompted the WHO to update its guidelines in April 2021 recommending DSD for HIV treatment and care. Prior to the release of these guidelines over 20 countries in Africa with technical support from the International Centre for AIDS Care and Treatment Programs (ICAP) have now scaled up DSD services for PLHIV. Through ICAP, the HIV Coverage, Quality and Impact Network (CQUIN) has dedicated to expanding and improving DSD services and this has been achieved through partnership with ministries of health, implementing partners, civil societies, academic institutions and donor agencies to scale up DSD services according to each country's needs. Through this network, countries exchange best practices, pilot innovations, knowledge generation, and creation of tools and resources for scaling up DSD services[279].

In addition to recommending DSD for HIV treatment and care, the 2021 WHO guideline have also changed its recommendation to the following:

1. Expanding the eligibility criteria to PLHIV on second-and third line ART regimen with suppressed viral load
2. Adapting DSD services for those with advanced HIV disease, high viral load, and co-morbidities.
3. Consider specific populations. DSD should be tailored to meet the needs of children, adolescents, pregnant and breastfeeding mothers, and other vulnerable populations.
4. Initiation ART outside the health care facility and support for same-day ART initiation, reducing frequency of clinical visits to twice a year, providing ART refills lasting 3-6 months (preferably every 6 months if feasible), and service integration as a way of reducing visit frequency and making DSD a cost-saving intervention. However, evidence is needed on outcomes associated with less frequent visits and drug refills beyond 6 months for various populations.

The current Covid-19 pandemic has and is still causing severe disruptions to the health systems, economic activities, and movement of people (prohibition of gatherings). These restrictions may potentially disrupt PLHIV accessing treatment as they are unable to go to the clinic to collect their medications. In order to support HIV treatment for PLHIV and reduce the risk of SARS-CoV2 exposure at the clinics, national ART programs made significant policy adaptations to their HIV treatment services to protect PLHIV and HCW by:

- Scaling up DSD services to allow PLHIV on ART to access longer ART refills (also known as MMD or multi-month dispensation) to reduce frequency of visits to the clinic. Countries such as Zambia, Uganda and Eswatini have expanded MMD access from 3 months to 6 months. In South Africa, ART script length was extended to 12 months[239].
- Reducing the DSD eligibility criteria to increase access to DSD models including for newly initiated ART patients. In some countries, one of the eligibility criteria for DSD models such as viral load suppression has been waivered for people on ART[239, 279]. In Ethiopia, policy changes were made to include pregnant and breastfeeding women and virally suppressed children above 2 years into DSD models.
- Expansion of clinic hours and fast-track services as well as scaling up out-of-facility models such as community dispensation points.
- Other modifications include the cancellation or restructuring of group models such as adherence clubs and community adherence groups in order to enhance social distancing.
- Expansion of community-based models such as home ART delivery either through community pharmacy to patient homes or health facility pharmacy to patient homes using CHWs.

Although countries have rapidly changed the design and delivery of HIV treatment, the full impact of these adaptations on patient health outcomes and health systems and whether these adaptations will be sustained beyond the pandemic is yet to be known. As countries have adopted swiftly to the less intense models such as MMD, it remains to be seen whether DSD models outside the health care facility will be scaled up in the near future. There will be need to critically monitor and evaluate patient outcomes accessing DSD models versus those in routine care during the covid pandemic as well as those accessing expanded DSD models understand the risks and benefits. Further research is warranted to answer these questions.

8.9 DSD – The way forward

Although DSD models have primarily focused on stable patients, where "stability" has been difficult to define, and may inadvertently fail to provide community-based care to those who may benefit the most from it (e.g., adolescents and men), the time has now come to shift our focus beyond stable patients as we have shown from this and other trials that it is safe and well accepted amongst patients deemed to be at low risk of severe disease. Key populations have been underrepresented in HIV testing and treatment programs, and decentralizing ART services among key populations may enhance access to care and retention in HIV treatment programs. Several studies have found that adolescents have the highest rates of attrition from HIV treatment and care, whereas men lag behind in attaining

viral suppression and are less likely to seek care, owing to gender norms and stigma [280, 281]. A recent study in South Africa and Uganda found that community-based ART delivery, including HIV testing and same-day ART initiation, increases viral suppression among PLHIV with detectable VL, particularly among men, when compared to HCF-based services[280]. This suggests that streamlined services, such as HIV testing and ART initiation, can reduce barriers to care and increase the proportion of PLHIV who begin ART and achieve viral suppression. The Zvandiri program in Zimbabwe also provided evidence that peer-supported community-based differentiated service delivery can substantially improve HIV virological suppression in adolescents with HIV and should be scaled up to reduce their high rates of morbidity and mortality[281]. These studies have indicated that community-based DSD models that incorporate HIV testing and ART initiation are an effective strategy that may be scaled up to address the gaps in linkage to care and viral suppression overall, and in men in particular. Although this client-centred strategy will necessitate service adaptations, such as expanding to new delivery platforms, cost may not be a limiting factor given the increased health improvements found with a high proportion of PLHIV obtaining viral suppression.

It is also time to seize the opportunity to integrate DSD with other services including sexual reproductive health (family planning, cervical cancer screening), chronic non-communicable diseases (NCDs), Pre-exposure prophylaxis (PreP) and TB prevention and treatment services. The poor quality of care for NCDs and other health services may undermine the investments made to strengthen HIV programs. Integration of these services with DSD may reduce unnecessary burdens on the health system and recipients of care. However there are several barriers to integrating DSD with other health care services and these include lack of resources to pay for non-HIV services, lack of centralized support of NCDs and lack of health insurance. This calls for opportunities for:

- TB treatment programs to be integrated into DSD for PLHIV.
- Family planning for women living with HIV where women living with HIV who manage their own ART may be a receptive audience for multi-month refills of oral contraceptives or longer acting self-administered contraceptives.
- Integration of PreP with DSD services
- Integration of chronic NCDs such as hypertension and diabetes among PLHIV.
- With lack of funding to formalize CHWs in the near future, there is need to explore other models of ART delivery that can be sustainable such as exploring point-of-care (PoC) tests and use of vending machines to distribute HIV self-testing (HIVST) kits, PreP, condoms and even ART and determine how they work for key populations.

8.10 Conclusion

Community models of ART delivery as a form of differentiated HIV care are innovative strategies to maintain and address the barriers to the HIV continuum of care in the context of universal treatment as the numbers of PLHIV on treatment continue to grow in resource-limited settings.

Our findings contribute to the growing body of research supporting WHO recommendations for scaling up differentiated models of ART delivery in resource-limited settings in order to improve ART adherence and retention. This was one of the few trials that evaluated two ART delivery models to the existing facility-based standard of care in an urban setting. Our study found that decentralizing ART delivery outside of the health care facility by engaging trained community health workers to assist with drug distribution and adherence support was just as effective as facility-based care. The findings on viral suppression rates are similar with past studies in which the risk difference of viral suppression in the two types of care was comparable or somewhat better than in facility-based treatment in resource-limited settings.

This trial also highlighted the importance of the context in which the two models of ART delivery, are implemented in resource-limited urban settings. The study has revealed numerous factors that enable or jeopardize the implementation of DSD models within the health care system, patient and community, policy and funding and wider health systems. These factors have been found to have serious implications calling for a wider multidisciplinary team to address the factors if DSD models are to be developed effectively and sustainably. Notably, this study also identified human resource support and patient and stakeholder acceptance of community health workers as criteria for the creation and implementation of DSD models.

The major strength of this trial was that it was conducted in a real-world setting, which means that our interventions may be implemented in similar contexts. The trial's limitations included various problems for the health-care system, such as routine laboratory monitoring and monitoring and evaluating different delivery models.

The models of ART delivery in our study were well-accepted and supported by PLHIV. However, additional research is required to rigorously evaluate clinical outcomes with appropriate comparisons in order to fully grasp the long-term consequences of DSD models for HIV management.

Chapter 9 References

1. Muiruri C, Omar HR, Bartlett JA. Antiretroviral Treatment in Resource-Limited Settings. In: Hope TJ, Richman DD, Stevenson M, editors. Encyclopedia of AIDS. New York, NY: Springer New York; 2018. p. 113-22.
2. Deeks SG, Lewin SR, Havlir DV. The end of AIDS: HIV infection as a chronic disease. Lancet (London, England). 2013;382(9903):1525-33.
3. Group TTAS. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. New England Journal of Medicine. 2015;373(9):808-22.
4. Lundgren JD, Babiker AG, Gordin F, Emery S, Grund B, Sharma S, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. The New England journal of medicine. 2015;373(9):795-807.
5. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. The New England journal of medicine. 2011;365.
6. World Health Organization. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. 2015. http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/. Accessed 13 Mar 2019.
7. Braitstein P, Brinkhof MW, Dabis F, Schechter M, Boulle A, Miotti P, et al. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. Lancet (London, England). 2006;367(9513):817-24.
8. Keiser O, Orrell C, Egger M, Wood R, Brinkhof MWG, Furrer H, et al. Public-Health and Individual Approaches to Antiretroviral Therapy: Township South Africa and Switzerland Compared. PLoS medicine. 2008;5(7):e148.
9. Médecins Sans Frontières. (2013). Reaching Closer to Home:Progress implementing community-based and other adherence strategies supporting people on HIV treatment Experiences from DRC, Lesotho, Malawi, Mozambique, South Africa & Zimbabwe. MSF Analysis & Advocacy Unit (AAU) Brussels with Southern Africa Medical Unit (SAMU), Cape Town, South Africa: [Online] Available at : www.samumsf.org.
10. Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, et al. Viral Load and Heterosexual Transmission of Human Immunodeficiency Virus Type 1. New England Journal of Medicine. 2000;342(13):921-9.
11. HIV/AIDS. National Institute of Allergy and Infectious Diseases [Internet]. 2020 [cited 2020Jun5]. Available from: https://www.niaid.nih.gov/diseases-conditions/hivaids.
12. WHO. Consolidated Guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva2013.
13. Joint United Nations Programme on HIV/AIDS. 90-90-90:an ambitious treatment target to help end the AIDS epidemic. Geneva: UNAIDS 2014.
14. UNAIDS. UNAIDS Fast-track: ending the AIDS epidemic by 2030. Geneva; 2014.
15. Brazier E, Maruri F, Duda SN, Tymejczyk O, Wester CW, Somi G, et al. Implementation of "Treat-all" at adult HIV care and treatment sites in the Global IeDEA Consortium: results from the Site Assessment Survey. Journal of the International AIDS Society. 2019;22(7):e25331.
16. Long L, Kuchukhidze S, Pascoe S, Nichols B, Cele R, Govathson C, Huber A, Flynn D, Rosen S. Differentiated service delivery models for antiretroviral treatment of HIV in sub-Saharan Africa: a rapid systematic review. AMBIT Project Report Number 04. Boston:Boston university and HE^{2}RO, 2020.
17. Sanjana P, Torpey K, Schwarzwalder A, Simumba C, Kasonde P, Nyirenda L, et al. Task-shifting HIV counselling and testing services in Zambia: the role of lay counsellors. Hum Resour Health. 2009;7(1):44.
18. Zachariah R, Teck R, Buhendwa L, Labana S, Chinji C, Humblet P, et al. How can the community contribute in the fight against HIV/AIDS and tuberculosis? An example from a rural district in Malawi. Trans R Soc Trop Med Hyg. 2006;100(2):167-75.

19. Hirschhorn LR, Oguda L, Fullem A, Dreesch N, Wilson P. Estimating health workforce needs for antiretroviral therapy in resource-limited settings. Human Resources for Health. 2006;4(1):1.
20. El-Sadr WM, Lundgren J, Neaton JD, Gordin F, Abrams D, Arduino RC, et al. CD4+ count-guided interruption of antiretroviral treatment. The New England journal of medicine. 2006;355(22):2283-96.
21. Grimsrud A, Barnabas RV, Ehrenkranz P, Ford N. Evidence for scale up: the differentiated care research agenda. Journal of the International AIDS Society. 2017;20(Suppl 4):22024.
22. International AIDS Society (IAS). Differentiated care for HIV: a decision framework for antiretroviral therapy delivery: International AIDS Society; 2016.
23. Geiske Zijlstra MLJEHASF. A literature review of the effectiveness of programs delivering antiretroviral therapy in non-facility based setting in sub-Saharan Africa.
24. Limbada M, Bwalya C, Macleod D, Floyd S, Schaap A, Situmbeko V, et al. A comparison of different community models of antiretroviral therapy delivery with the standard of care among stable HIV+ patients: rationale and design of a non-inferiority cluster randomized trial, nested in the HPTN 071 (PopART) study. Trials. 2021;22(1):52.
25. Grimsrud A. Loss to follow-up from South Africa's antiretroviral treatment programme: Trends, risk factors, and models of care to improve retention. University of Cape Town. 2015.
26. Fox MP, Pascoe S, Huber AN, Murphy J, Phokojoe M, Gorgens M, et al. Adherence clubs and decentralized medication delivery to support patient retention and sustained viral suppression in care: Results from a cluster-randomized evaluation of differentiated ART delivery models in South Africa. PLoS medicine. 2019;16(7):e1002874.
27. Nachega JB, Adetokunboh O, Uthman OA, Knowlton AW, Altice FL, Schechter M, et al. Community-Based Interventions to Improve and Sustain Antiretroviral Therapy Adherence, Retention in HIV Care and Clinical Outcomes in Low- and Middle-Income Countries for Achieving the UNAIDS 90-90-90 Targets. Current HIV/AIDS reports. 2016;13(5):241-55.
28. Khabala KB, Edwards JK, Baruani B, Sirengo M, Musembi P, Kosgei RJ, et al. Medication Adherence Clubs: A potential solution to managing large numbers of stable patients with multiple chronic diseases in informal settlements. Tropical Medicine and International Health. 2015;20(10):1265-70.
29. Grimsrud A, Lesosky M, Kalombo C, Bekker LG, Myer L. Implementation and Operational Research: Community-Based Adherence Clubs for the Management of Stable Antiretroviral Therapy Patients in Cape Town, South Africa: A Cohort Study. Journal of acquired immune deficiency syndromes (1999). 2016;71(1):e16-23.
30. Tsondai PR, Wilkinson LS, Grimsrud A, Mdlalo PT, Ullauri A, Boulle A. High rates of retention and viral suppression in the scale-up of antiretroviral therapy adherence clubs in Cape Town, South Africa. Journal of the International AIDS Society. 2017;20(Suppl 4):21649.
31. Jaffar S, Amuron B, Foster S, Birungi J, Levin J, Namara G, et al. Rates of virological failure in patients treated in a home-based versus a facility-based HIV-care model in Jinja, southeast Uganda: a cluster-randomised equivalence trial. Lancet (London, England). 2010;374.
32. Geldsetzer P, Francis JM, Sando D, Asmus G, Lema IA, Mboggo E, et al. Community delivery of antiretroviral drugs: A non-inferiority cluster-randomized pragmatic trial in Dar es Salaam, Tanzania. PLoS medicine. 2018;15(9):e1002659.
33. Morris MB, Chapula BT, Chi BH, Mwango A, Chi HF, Mwanza J, et al. Use of task-shifting to rapidly scale-up HIV treatment services: experiences from Lusaka, Zambia. BMC health services research. 2009;9:5.
34. Ministry of Health. National Human Resources for Health Strategic Plan 2011 – 2015 Zambia2011 [Available from: http://www.moh.gov.zm/docs/hrsp.pdf.
35. Gottlieb MS, Schroff R, Schanker HM, Weisman JD, Fan PT, Wolf RA, et al. Pneumocystis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. The New England journal of medicine. 1981;305(24):1425-31.

36. Barré-Sinoussi F, Ross AL, Delfraissy JF. Past, present and future: 30 years of HIV research. Nat Rev Microbiol. 2013;11(12):877-83.
37. Wainberg MA, Jeang K-T. 25 years of HIV-1 research – progress and perspectives. BMC Medicine. 2008;6(1):31.
38. UNAIDS. Fact sheet - Latest statistics on the status of the AIDS epidemic. 2018. [Available from: http://www.unaids.org/en/resources/fact-sheet]. Accessed 4 Jan 2019.
39. UNAIDS. Fact Sheet December 2019: Global HIV Statistics. 2019 [cited 13th January 2020]; Available from:https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf.
40. *Global HIV and AIDS statistics.* Avert.org; 2020. Available at https://www.avert.org/global-hiv-and-aids-statistics (accessed June 2020).
41. UNAIDS. *UNAIDS data 2019*. Geneva, Switzerland: UNAIDS; Available from: https://www.unaids.org/en/resources/documents/2019/2019-UNAIDS-data [accessed June 2020].
42. Kharsany ABM, Karim QA. HIV Infection and AIDS in Sub-Saharan Africa: Current Status, Challenges and Opportunities. The open AIDS journal. 2016;10:34-48.
43. The HIV Life Cycle Understanding HIV/AIDS [Internet]. 2019 [cited 2020Jul24]. Available from: https://aidsinfo.nih.gov/understanding-hiv-aids/fact-sheets/19/73/the-hiv-life-cycle.
44. The science of HIV and AIDS - overview [Internet]. Avert. 2019 [cited 2020Jul24]. Available from: https://www.avert.org/professionals/hiv-science/overview.
45. Antiretroviral Drug Discovery and Development. National Institute of Allergy and Infectious Diseases. U.S. Department of Health and Human Services; [cited 2020Jun5]. Available from: https://www.niaid.nih.gov/diseases-conditions/antiretroviral-drug-development.
46. Fischl MA, Richman DD, Grieco MH, Gottlieb MS, Volberding PA, Laskin OL, et al. The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial. The New England journal of medicine. 1987;317(4):185-91.
47. Sharma M, Ying R, Tarr G, Barnabas R. Systematic review and meta-analysis of community and facility-based HIV testing to address linkage to care gaps in sub-Saharan Africa. Nature. 2015;528(7580):S77-85.
48. Ford N, Meintjes G, Vitoria M, Greene G, Chiller T. The evolving role of CD4 cell counts in HIV care. Current opinion in HIV and AIDS. 2017;12:1.
49. Eholié SP, Badje A, Kouame GM, N'Takpe J-B, Moh R, Danel C, et al. Antiretroviral treatment regardless of CD4 count: the universal answer to a contextual question. AIDS research and therapy. 2016;13:27-.
50. Song A, Liu X, Huang X, Meyers K, Oh D-Y, Hou J, et al. From CD4-Based Initiation to Treating All HIV-Infected Adults Immediately: An Evidence-Based Meta-analysis. Frontiers in Immunology. 2018;9(212).
51. Anglemyer A, Rutherford GW, Easterbrook PJ, Horvath T, Vitória M, Jan M, et al. Early initiation of antiretroviral therapy in HIV-infected adults and adolescents: a systematic review. Aids. 2014;28 Suppl 2:S105-18.
52. WHO. Consolidated guidelines on the the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2nd ed2016.
53. Strategies for Management of Antiretroviral Therapy Study G, Emery S, Neuhaus JA, Phillips AN, Babiker A, Cohen CJ, et al. Major clinical outcomes in antiretroviral therapy (ART)-naive participants and in those not receiving ART at baseline in the SMART study. The Journal of infectious diseases. 2008;197(8):1133-44.
54. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. New England Journal of Medicine. 2015;373(9):795-807.
55. TEMPRANO ANRS Study Group. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. The New England journal of medicine. 2015;373(9):808-22.
56. Grinsztejn B, Hosseinipour MC, Ribaudo HJ, Swindells S, Eron J, Chen YQ, et al. Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection:

results from the phase 3 HPTN 052 randomised controlled trial. The Lancet Infectious diseases. 2014;14(4):281-90.
57. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Antiretroviral Therapy for the Prevention of HIV-1 Transmission. New England Journal of Medicine. 2016;375(9):830-9.
58. Hull MW, Montaner JSG. HIV treatment as prevention: the key to an AIDS-free generation. J Food Drug Anal. 2013;21(4):S95-S101.
59. Piot P, Abdool Karim SS, Hecht R, Legido-Quigley H, Buse K, Stover J, et al. Defeating AIDS--advancing global health. Lancet (London, England). 2015;386(9989):171-218.
60. WHO. Programmatic update: antiretroviral treatment as prevention (TASP) of HIV and TB: executive summary. Geneva: World Health Organization; 2012.
61. Brault MA, Spiegelman D, Hargreaves J, Nash D, Vermund SH. Treatment as Prevention: Concepts and Challenges for Reducing HIV Incidence. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2019;82:S104-S12.
62. Sabapathy, K; (2017) Factors associated with the uptake of HIV testing and treatment in the first year of the HPTN 071 (PopART) intervention. PhD thesis, London School of Hygiene & Tropical Medicine. DOI: https://doi.org/10.17037/PUBS.04645535
63. Rodger AJ, Cambiano V, Bruun T, Vernazza P, Collins S, van Lunzen J, et al. Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy. Jama. 2016;316(2):171-81.
64. HIV treatment as prevention--it works. Lancet (London, England). 2011;377(9779):1719.
65. Herbeck J, Tanser F. Community viral load as an index of HIV transmission potential. The Lancet HIV. 2016;3(4):e152-e4.
66. UNAIDS. 90–90–90 - An ambitious treatment target to help end the AIDS epidemic. 2017. Available at https://www.unaids.org/en/resources/documents/2017/90-90-90.
67. Gardner EM, McLees MP, Steiner JF, del Rio C, Burman WJ. The Spectrum of Engagement in HIV Care and its Relevance to Test-and-Treat Strategies for Prevention of HIV Infection. Clinical Infectious Diseases. 2011;52(6):793-800.
68. McNairy ML, El-Sadr WM. The HIV care continuum: no partial credit given. Aids. 2012;26(14):1735-8.
69. Kilmarx, H., & Mutasa-Apollo, H. (2013). Patching a leaky pipe: the cascade of HIV care. Current Opinion in HIV and AIDS, 8(1), 59–64. https://doi.org/10.1097/COH.0b013e32835b806e.
70. Joint United Nations Programme on HIV/AIDS. The gap report: beginning of the end of the AIDS epidemic. Geneva. 2014 [accessed 17 June 2020]. Available from: http://www.unaids.org/sites/default/files/media_asset/UNAIDS_Gap_report_en.pdf.
71. Hayes R, Floyd S, Schaap A, Shanaube K, Bock P, Sabapathy K, et al. A universal testing and treatment intervention to improve HIV control: One-year results from intervention communities in Zambia in the HPTN 071 (PopART) cluster-randomised trial. PLoS medicine. 2017;14(5):e1002292.
72. Hayes R, Sabapathy K, Fidler S. Universal testing and treatment as an HIV prevention strategy: research questions and methods. Current HIV research. 2011;9.
73. Attia S, Egger M, Müller M, Zwahlen M, Low N. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. AIDS. 2009;23(11):1397-404.
74. Iwuji CC, Orne-Gliemann J, Larmarange J, Okesola N, Tanser F, Thiebaut R, et al. Uptake of Home-Based HIV Testing, Linkage to Care, and Community Attitudes about ART in Rural KwaZulu-Natal, South Africa: Descriptive Results from the First Phase of the ANRS 12249 TasP Cluster-Randomised Trial. PLoS medicine. 2016;13(8):e1002107.
75. Dodd PJ, Garnett GP, Hallett TB. Examining the promise of HIV elimination by 'test and treat' in hyperendemic settings. AIDS. 2010;24(5):729-35.
76. Gray RH, Kigozi G, Serwadda D, Makumbi F, Watya S, Nalugoda F, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. Lancet (London, England). 2007;369(9562):657-66.

77. Bailey RC, Moses S, Parker CB, Agot K, Maclean I, Krieger JN, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. Lancet (London, England). 2007;369(9562):643-56.
78. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. PLoS medicine. 2005;2(11):e298.
79. Hallett TB, Singh K, Smith JA, White RG, Abu-Raddad LJ, Garnett GP. Understanding the impact of male circumcision interventions on the spread of HIV in southern Africa. PLoS One 2008; 3:e2212.
80. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, Paris R, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. The New England journal of medicine. 2009;361(23):2209-20.
81. Montaner JS, Hogg R, Wood E, Kerr T, Tyndall M, Levy AR, Harrigan PR. The case for expanding access to highly active antiretroviral therapy to curb the growth of the HIV epidemic. Lancet 2006; 368:531–536.
82. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. Lancet 2009; 373:48–57.
83. Dieffenbach CW, Fauci AS. Universal Voluntary Testing and Treatment for Prevention of HIV Transmission. JAMA. 2009;301(22):2380-2.
84. Garnett GP, Baggaley RF. Treating our way out of the HIV pandemic: could we, would we, should we? Lancet (London, England). 2009;373(9657):9-11.
85. Lima VD, Johnston K, Hogg RS, Levy AR, Harrigan PR, Anema A, et al. Expanded access to highly active antiretroviral therapy: a potentially powerful strategy to curb the growth of the HIV epidemic. J Infect Dis. 2008;198(1):59-67.
86. Perriat D, Balzer L, Hayes R, Lockman S, Walsh F, Ayles H, et al. Comparative assessment of five trials of universal HIV testing and treatment in sub-Saharan Africa. Journal of the International AIDS Society. 2018;21(1):e25048.
87. Bärnighausen T, Eyal N, Wikler D. HIV Treatment-as-Prevention Research at a Crossroads. PLoS medicine. 2014;11(6):e1001654.
88. Perriat D. Integration and generalization of “Universal Test and Treat” strategies for HIV in sub-Saharan Africa : The ANRS 12249 TasP Trial and beyond 2017.
89. Havlir D, Lockman S, Ayles H, Larmarange J, Chamie G, Gaolathe T, et al. What do the Universal Test and Treat trials tell us about the path to HIV epidemic control? Journal of the International AIDS Society. 2020;23(2):e25455-e.
90. Iwuji CC, Orne-Gliemann J, Tanser F, Boyer S, Lessells RJ, Lert F, et al. Evaluation of the impact of immediate versus WHO recommendations-guided antiretroviral therapy initiation on HIV incidence: the ANRS 12249 TasP (Treatment as Prevention) trial in Hlabisa sub-district, KwaZulu-Natal, South Africa: study protocol for a cluster randomised controlled trial. Trials. 2013;14:230.
91. Floyd S, Shanaube K, Yang B, Schaap A, Griffith S, Phiri M, et al. HIV testing and treatment coverage achieved after 4 years across 14 urban and peri-urban communities in Zambia and South Africa: An analysis of findings from the HPTN 071 (PopART) trial. PLoS medicine. 2020;17(4):e1003067.
92. Chamie G, Kamya MR, Petersen ML, Havlir DV. Reaching 90-90-90 in rural communities in East Africa: lessons from the Sustainable East Africa Research in Community Health Trial. Current opinion in HIV and AIDS. 2019;14(6):449-54.
93. BCCP. Botswana Combination Prevention Project. 2015 [cited 2020 Jun 21]. Available from https://clinicaltrials.gov/ct2/show/NCT01965470.
94. Walsh FJ, Bärnighausen T, Delva W, Fleming Y, Khumalo G, Lejeune CL, et al. Impact of early initiation versus national standard of care of antiretroviral therapy in Swaziland's public sector health system: study protocol for a stepped-wedge randomized trial. Trials. 2017;18(1):383.

95. Hayes R, Ayles H, Beyers N, Sabapathy K, Floyd S, Shanaube K, et al. HPTN 071 (PopART): rationale and design of a cluster-randomised trial of the population impact of an HIV combination prevention intervention including universal testing and treatment - a study protocol for a cluster randomised trial. Trials. 2014;15:57.
96. Plazy M, Farouki KE, Iwuji C, Okesola N, Orne-Gliemann J, Larmarange J, et al. Access to HIV care in the context of universal test and treat: challenges within the ANRS 12249 TasP cluster-randomized trial in rural South Africa. Journal of the International AIDS Society. 2016;19(1):20913-.
97. Iwuji CC, Orne-Gliemann J, Larmarange J, Balestre E, Thiebaut R, Tanser F, et al. Universal test and treat and the HIV epidemic in rural South Africa: a phase 4, open-label, community cluster randomised trial. The Lancet HIV. 2018;5(3):e116-e25.
98. Larmarange J, Diallo MH, McGrath N, et al. The impact of population dynamics on the population HIV care cascade: results from the ANRS 12249 Treatment as Prevention trial in rural KwaZulu-Natal (South Africa). J Int AIDS Soc. 2018;21(suppl 4):e25128.
99. Balzer LB, Ayieko J, Kwarisiima D, Chamie G, Charlebois ED, Schwab J, et al. Far from MCAR: Obtaining Population-level Estimates of HIV Viral Suppression. Epidemiology. 2020;31(5):620-7.
100. Rasschaert F, Decroo T, Remartinez D, Telfer B, Lessitala F, Biot M, et al. Adapting a community-based ART delivery model to the patients' needs: a mixed methods research in Tete, Mozambique. BioMed Central; 2014. p. 364.
101. Makhema J, Wirth KE, Pretorius Holme M, Gaolathe T, Mmalane M, Kadima E, et al. Universal Testing, Expanded Treatment, and Incidence of HIV Infection in Botswana. The New England journal of medicine. 2019;381(3):230-42.
102. Rueda S, Park-Wyllie LY, Bayoumi A, Tynan AM, Antoniou T, Rourke S, et al. Patient support and education for promoting adherence to highly active antiretroviral therapy for HIV/AIDS. The Cochrane Library. 2006.
103. MaxART: Early Access to ART for All in Swaziland (MaxART). 2016. [cited 22 jun 2020]. Available at https://clinicaltrials.gov/ct2/show/NCT02909218.
104. S. Khan DS, F. Walsh, S. Mazibuko, M. Pasi, B. Chai, R. Reis, K. Mlambo, W. Delva, G. Khumalo, M. Zwane, Y. Fleming, E. Mafara, A. Hettema, C. Lejeune, T. Bärnighausen, V. Okello. Universal test and treat (UTT) versus standard of care for access to antiretroviral therapy in HIV clients: The MaxART stepped-wedge randomized controlled health systems trial in Swaziland. AIDS 2018; Amsterdam2018.
105. Hayes RJ, Donnell D, Floyd S, Mandla N, Bwalya J, Sabapathy K, et al. Effect of Universal Testing and Treatment on HIV Incidence — HPTN 071 (PopART). New England Journal of Medicine. 2019;381(3):207-18.
106. Impact of Universal Testing and Treatment in Zambia and South Africa: HPTN071(POPART). CROI; Seattle2019.
107. Nash D, Yotebieng M, Sohn AH. Treating all people living with HIV in sub-Saharan Africa: a new era calling for new approaches. Journal of virus eradication. 2018;4(Suppl 2):1-4.
108. World Health Organisation. Scaling up Antiretroviral Therapy in resource-limited settings. Geneva, Switzerland: 2002. [Google Scholar].
109. Vitoria M, Vella S, Ford N. Scaling up antiretroviral therapy in resource-limited settings: adapting guidance to meet the challenges. Current opinion in HIV and AIDS. 2013;8(1):12-8.
110. Tymejczyk O, Brazier E, Yiannoutsos CT, Vinikoor M, van Lettow M, Nalugoda F, et al. Changes in rapid HIV treatment initiation after national “treat all” policy adoption in 6 sub-Saharan African countries: Regression discontinuity analysis. PLoS medicine. 2019;16(6):e1002822.
111. Herce ME, Chi BH, Liao RC, Hoffmann CJ. Re-thinking Linkage to Care in the Era of Universal Test and Treat: Insights from Implementation and Behavioral Science for Achieving the Second 90. AIDS and Behavior. 2019;23(2):120-8.
112. UNAIDS.FACT SHEET -WORLD AIDS DAY 2019 [Accessed 11th June, 2020]. Available at https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf.

113. Grimsrud A, Cornell M, Schomaker M, Fox MP, Orrell C, Prozesky H, et al. CD4 count at antiretroviral therapy initiation and the risk of loss to follow-up: results from a multicentre cohort study. J Epidemiol Community Health. 2016;70(6):549-55.
114. Kay ES, Batey DS, Mugavero MJ. The HIV treatment cascade and care continuum: updates, goals, and recommendations for the future. AIDS Research and Therapy. 2016;13(1):35.
115. Gueler A, Vanobberghen F, Rice B, Egger M, Mugglin C. The HIV Care Cascade from HIV diagnosis to viral suppression in sub-Saharan Africa: a systematic review and meta-regression analysis protocol. Systematic Reviews. 2017;6(1):172.
116. McNairy ML, Lamb MR, Abrams EJ, Elul B, Sahabo R, Hawken MP, et al. Use of a Comprehensive HIV Care Cascade for Evaluating HIV Program Performance: Findings From 4 Sub-Saharan African Countries. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2015;70(2):e44-e51.
117. Scanlon ML, Vreeman RC. Current strategies for improving access and adherence to antiretroviral therapies in resource-limited settings. HIV/AIDS (Auckland, NZ). 2013;5:1-17.
118. Wanyenze RK, Hahn JA, Liechty CA, Ragland K, Ronald A, Mayanja-Kizza H, et al. Linkage to HIV care and survival following inpatient HIV counseling and testing. AIDS and behavior. 2011;15(4):751-60.
119. Bassett IV, Regan S, Chetty S, Giddy J, Uhler LM, Holst H, et al. Who starts antiretroviral therapy in Durban, South Africa?... not everyone who should. AIDS (London, England). 2010;24 Suppl 1(Suppl 1):S37-S44.
120. UNAIDS. Global Report: UNAIDS Report on the Global AIDS Epidemic. 2012.
121. Hall HI, Halverson J, Wilson DP, et al. Late diagnosis and entry to care after diagnosis of human immunodeficiency virus infection: a country comparison. Palaniyar N, ed. PLoS One. 2013;8(11):e77763. doi:10.1371/journal.pone.0077763.
122. ICAP Approach to Differentiated Service Delivery. Retrieved 16 Sep 2019 from: https://cquin.icap.columbia.edu/resources/icap-approach-to-differentiated-service-delivery/.
123. Mugglin C, Estill J, Wandeler G, Bender N, Egger M, Gsponer T, et al. Loss to programme between HIV diagnosis and initiation of antiretroviral therapy in sub-Saharan Africa: systematic review and meta-analysis. Tropical medicine & international health : TM & IH. 2012;17(12):1509-20.
124. UNAIDS. UNAIDS Report on the Global AIDS Epidemic 2013 Global Report; 2013.
125. Seeley J, Bond V, Yang B, Floyd S, MacLeod D, Viljoen L, et al. Understanding the Time Needed to Link to Care and Start ART in Seven HPTN 071 (PopART) Study Communities in Zambia and South Africa. AIDS Behav. 2019;23(4):929-46.
126. Floyd S, Ayles H, Schaap A, Shanaube K, MacLeod D, Phiri M, et al. Towards 90-90: Findings after two years of the HPTN 071 (PopART) cluster-randomized trial of a universal testing-and-treatment intervention in Zambia. PloS one. 2018;13(8):e0197904.
127. Sanga ES, Mukumbang FC, Mushi AK, Lerebo W, Zarowsky C. Understanding factors influencing linkage to HIV care in a rural setting, Mbeya, Tanzania: qualitative findings of a mixed methods study. BMC public health. 2019;19(1):383.
128. Nsigaye R, Wringe A, Roura M, Kalluvya S, Urassa M, Busza J, et al. From HIV diagnosis to treatment: evaluation of a referral system to promote and monitor access to antiretroviral therapy in rural Tanzania. Journal of the International AIDS Society. 2009;12(1):31-.
129. Govindasamy D, Meghij J, Kebede Negussi E, Clare Baggaley R, Ford N, Kranzer K. Interventions to improve or facilitate linkage to or retention in pre-ART (HIV) care and initiation of ART in low- and middle-income settings--a systematic review. Journal of the International AIDS Society. 2014;17:19032.
130. Genberg BL, Lee Y, Rogers WH, Wilson IB. Four types of barriers to adherence of antiretroviral therapy are associated with decreased adherence over time. AIDS and behavior. 2015;19(1):85-92.

131. Tomori C, Kennedy CE, Brahmbhatt H, Wagman JA, Mbwambo JK, Likindikoki S, et al. Barriers and facilitators of retention in HIV care and treatment services in Iringa, Tanzania: the importance of socioeconomic and sociocultural factors. AIDS Care. 2014;26(7):907-13.
132. Nhassengo P, Cataldo F, Magaço A, Hoffman RM, Nerua L, Saide M, et al. Barriers and facilitators to the uptake of Test and Treat in Mozambique: A qualitative study on patient and provider perceptions. PloS one. 2018;13(12):e0205919-e.
133. Katz IT, Dietrich J, Tshabalala G, Essien T, Rough K, Wright AA, et al. Understanding treatment refusal among adults presenting for HIV-testing in Soweto, South Africa: a qualitative study. AIDS Behav. 2015;19(4):704-14.
134. Govindasamy D, Ford N, Kranzer K. Risk factors, barriers and facilitators for linkage to antiretroviral therapy care: a systematic review. Aids. 2012;26(16):2059-67.
135. Mbonye M, Seeley J, Ssembajja F, Birungi J, Jaffar S. Adherence to Antiretroviral Therapy in Jinja, Uganda: A Six-Year Follow-Up Study. PloS one. 2013;8(10):e78243.
136. WHO. Retention in HIV programmes: Defining the challenges and identifying solutions; Meeting report (13-15 September 2011, Geneva, Switzerland). 2012.
137. Iroezindu MO. Disparities in the magnitude of human immunodeficiency virus-related opportunistic infections between high and low/middle-income countries: Is highly active antiretroviral therapy changing the trend?. Ann Med Health Sci Res 2016;6:4-18.
138. Mugavero MJ, Westfall AO, Zinski A, Davila J, Drainoni M-L, Gardner LI, et al. Measuring Retention in HIV Care: The Elusive Gold Standard. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2012;61(5):574-80.
139. Umeokonkwo CD, Onoka CA, Agu PA, Ossai EN, Balogun MS, Ogbonnaya LU. Retention in care and adherence to HIV and AIDS treatment in Anambra State Nigeria. BMC Infectious Diseases. 2019;19(1):654.
140. Patel A, Hirschhorn L, Fullem A, Ojikutu B, Oser R. Adult Adherence to Treatment and Retention in Care. Arlington, VA USAID | AIDSTAR-ONE project, Task Order I. 2010.
141. Babatunde O, Ojo OJ, Atoyebi OA, Ekpo DS, Ogundana AO, Olaniyan TO, et al. Seven year review of retention in HIV care and treatment in federal medical centre Ido-Ekiti. Pan Afr Med J. 2015;22:139.
142. Retention in Care | Treatment, Care, and Prevention for People with HIV | Clinicians | HIV | CDC. [online] Available at: https://www.cdc.gov/hiv/clinicians/treatment/care-retention.html [Accessed 6 Dec. 2019].
143. Elul B, Lamb MR, Lahuerta M, Abacassamo F, Ahoua L, Kujawski SA, et al. A combination intervention strategy to improve linkage to and retention in HIV care following diagnosis in Mozambique: A cluster-randomized study. PLoS medicine. 2017;14(11):e1002433.
144. Boeke CE, Nabitaka V, Rowan A, Guerra K, Kabbale A, Asire B, et al. Assessing linkage to and retention in care among HIV patients in Uganda and identifying opportunities for health systems strengthening: a descriptive study. BMC Infect Dis. 2018;18(1):138.
145. Fox MP, Rosen S. Retention of Adult Patients on Antiretroviral Therapy in Low- and Middle-Income Countries: Systematic Review and Meta-analysis 2008–2013. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2015;69(1).
146. Fox MP, Rosen S. Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007–2009: systematic review. Tropical Medicine & International Health. 2010;15(s1):1-15.
147. Haas AD, Zaniewski E, Anderegg N, Ford N, Fox MP, Vinikoor M, et al. Retention and mortality on antiretroviral therapy in sub-Saharan Africa: collaborative analyses of HIV treatment programmes. Journal of the International AIDS Society. 2018;21(2).
148. Zurcher K, Mooser A, Anderegg N, Tymejczyk O, Couvillon MJ, Nash D, et al. Outcomes of HIV-positive patients lost to follow-up in African treatment programmes. Tropical medicine & international health : TM & IH. 2017;22(4):375-87.

149. Brinkhof MWG, Dabis F, Myer L, Bangsberg DR, Boulle A, Nash D, et al. Early loss of HIV-infected patients on potent antiretroviral therapy programmes in lower-income countries. Bulletin of the World Health Organization. 2008;86(7):559-67.
150. Lifson AR, Demissie W, Tadesse A, Ketema K, May R, Yakob B, et al. Barriers to Retention in Care as Perceived by Persons Living with HIV in Rural Ethiopia:Focus Group Results and Recommended Strategies. Journal of the International Association of Providers of AIDS Care (JIAPAC). 2013;12(1):32-8.
151. Kagee A, Remien RH, Berkman A, Hoffman S, Campos L, Swartz L. Structural barriers to ART adherence in Southern Africa: challenges and potential ways forward. Global public health. 2011;6(1):83-97.
152. Lankowski AJ, Siedner MJ, Bangsberg DR, Tsai AC. Impact of Geographic and Transportation-Related Barriers on HIV Outcomes in Sub-Saharan Africa: A Systematic Review. AIDS and behavior. 2014;18(7):1199-223.
153. Geng EH, Nash D, Kambugu A, Zhang Y, Braitstein P, Christopoulos KA, et al. Retention in Care Among HIV-Infected Patients in Resource-Limited Settings: Emerging Insights and New Directions. Current HIV/AIDS reports. 2010;7(4):234-44.
154. WHO. March 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva2014.
155. Ehrenkranz P, Grimsrud A, Rabkin M. Differentiated service delivery: navigating the path to scale. Current opinion in HIV and AIDS. 2019;14(1):60-5.
156. WHO. Key considerations for differentiated antiretroviral therapy delivery for specific populations: children, adolescents, pregnant and breastfeeding women and key populations. Geneva: World Health Organization; 2017.
157. Fatti G, Grimwood A, Bock P. Better antiretroviral therapy outcomes at primary healthcare facilities: an evaluation of three tiers of ART services in four South African provinces. PloS one. 2010;5(9):e12888.
158. Mills EJ, Nachega JB, Bangsberg DR, Singh S, Rachlis B, Wu P, et al. Adherence to HAART: a systematic review of developed and developing nation patient-reported barriers and facilitators. PLoS medicine. 2006;3(11).
159. Grimsrud A, Bygrave H, Doherty M, Ehrenkranz P, Ellman T, Ferris R, et al. Reimagining HIV service delivery: the role of differentiated care from prevention to suppression. Journal of the International AIDS Society. 2016;19(1):21484.
160. Bochner AF, Meacham E, Mhungu N, Manyanga P, Petracca F, Muserere C, et al. The rollout of Community ART Refill Groups in Zimbabwe: a qualitative evaluation. Journal of the International AIDS Society. 2019;22(8):e25393.
161. Decroo T, Koole O, Remartinez D, dos Santos N, Dezembro S, Jofrisse M, et al. Four-year retention and risk factors for attrition among members of community ART groups in Tete, Mozambique. Tropical medicine & international health : TM & IH. 2014;19(5):514-21.
162. Jobarteh K, Shiraishi RW, Malimane I, Samo Gudo P, Decroo T, Auld AF, et al. Community ART Support Groups in Mozambique: The Potential of Patients as Partners in Care. PloS one. 2016;11(12):e0166444.
163. Bemelmans M, Baert S, Goemaere E, Wilkinson L, Vandendyck M, Cutsem G, et al. Community-supported models of care for people on HIV treatment in sub-Saharan Africa. Tropical Med Int Health. 2014;19.
164. Decroo T, Telfer B, Biot M, Maikere J, Dezembro S, Cumba LI, et al. Distribution of antiretroviral treatment through self-forming groups of patients in Tete Province, Mozambique. Journal of acquired immune deficiency syndromes (1999). 2011;56(2):e39-44.
165. Rasschaert F, Telfer B, Lessitala F, Decroo T, Remartinez D, Biot M, et al. A qualitative assessment of a community antiretroviral therapy group model in Tete, Mozambique. PloS one. 2014;9(3):e91544.

166. AIDS & TB Programme - Ministry of Health and Child Care Zimbabwe. Operational and service delivery manual for prevention catoHiZH, Zimbabwe: AIDS & TB Programme; 2017.
167. Vandendyck M, Motsamai M, Mubanga M, Makhakhe S, Tunggal S, Jonckheree S, et al. Community-Based ART Resulted in Excellent Retention and Can Leverage Community Empowerment in Rural Lesotho, A Mixed Method Study. HIV/AIDS Research and Treatment - Open Journal. 2015;2:44-50.
168. IAS. Summary of Published Evidence. [Accessed May 2021]. Available at https://differentiatedservicedelivery.org/Resources/Summary-of-published-evidence/Client-managed-groups.
169. Pasipamire L, Nesbitt RC, Ndlovu S, Sibanda G, Mamba S, Lukhele N, et al. Retention on ART and predictors of disengagement from care in several alternative community-centred ART refill models in rural Swaziland. Journal of the International AIDS Society. 2018;21(9):e25183-e.
170. Naslund JA, Dionne-Odom J, Junior Destine C, Jogerst KM, Renold Senecharles R, Jean Louis M, et al. Adapting and Implementing a Community Program to Improve Retention in Care among Patients with HIV in Southern Haiti: "Group of 6". AIDS research and treatment. 2014;2014:137545.
171. Nkwemu S. et al. Challenges in providing patients centred care through community adherence groups in three provinces of Zambia. 2018. AIDS 2018 Conference Abstract.
172. Wilkinson LS. ART adherence clubs: A long-term retention strategy for clinically stable patients receiving antiretroviral therapy2013.
173. Luque-Fernandez MA, Van Cutsem G, Goemaere E, Hilderbrand K, Schomaker M, Mantangana N, et al. Effectiveness of patient adherence groups as a model of care for stable patients on antiretroviral therapy in Khayelitsha, Cape Town, South Africa. PloS one. 2013;8(2):e56088.
174. Hanrahan CF, Schwartz SR, Mudavanhu M, West NS, Mutunga L, Keyser V, et al. The impact of community- versus clinic-based adherence clubs on loss from care and viral suppression for antiretroviral therapy patients: Findings from a pragmatic randomized controlled trial in South Africa. PLoS medicine. 2019;16(5):e1002808.
175. Grimsrud A, Sharp J, Kalombo C, Bekker LG, Myer L. Implementation of community-based adherence clubs for stable antiretroviral therapy patients in Cape Town, South Africa. Journal of the International AIDS Society. 2015;18:19984.
176. Tshuma N, Mosikare O, Yun JA, et al. Acceptability of community-based adherence clubs among health facility staff in South Africa: a qualitative study. Patient Preference and Adherence. 2017 ;11:1523-1531. DOI: 10.2147/ppa.s116826.
177. Amanyire G, Wanyenze R, Alamo S, Kwarisiima D, Sunday P, Sebikaari G, et al. Client and provider perspectives of the efficiency and quality of care in the context of rapid scale-up of antiretroviral therapy. AIDS patient care and STDs. 2010;24(11):719-27.
178. Decroo T, Rasschaert F, Telfer B, Remartinez D, Laga M, Ford N. Community-based antiretroviral therapy programs can overcome barriers to retention of patients and decongest health services in sub-Saharan Africa: a systematic review. International health. 2013;5(3):169-79.
179. Selke HM, Kimaiyo S, Sidle JE, Vedanthan R, Tierney WM, Shen C, et al. Task-shifting of antiretroviral delivery from health care workers to persons living with HIV/AIDS: clinical outcomes of a community-based program in Kenya. Journal of acquired immune deficiency syndromes (1999). 2010;55(4):483-90.
180. Davis N, Kanagat N, Sharer M, Eagan S, Pearson J, Amanyeiwe UU. Review of differentiated approaches to antiretroviral therapy distribution. AIDS Care. 2018;30(8):1010-6.
181. UNAIDS. UNAIDS AND MEDECINS SANS FRONTIERES 2015/REFERENCE: COMMUNITY-BASED ANTIRETROVIRAL THERAPY DELIVERY/EXPERIENCES OF MSF. GENEVA, SWITZERLAND: 2015.
182. Okoboi S, Ding E, Persuad S, Wangisi J, Birungi J, Shurgold S, et al. Community-based ART distribution system can effectively facilitate long-term program retention and low-rates of death and virologic failure in rural Uganda. AIDS Res Ther. 2015;12:37.

183. Marseille E, Kahn JG, Pitter C, Bunnell R, Epalatai W, Jawe E, et al. The cost effectiveness of home-based provision of antiretroviral therapy in rural Uganda. Appl Health Econ Health Policy. 2009;7(4):229-43.
184. Zambia Population. https://www.worldometers.info/world-population/zambia-population/.
185. Zambia's Young People and the Road to 2030. UNFPA Zambia. 2016. [cited 2020Jun30]. Available from: https://zambia.unfpa.org/en/news/zambia%E2%80%99s-young-people-and-road-2030.
186. National AIDS Strategic Framework, 2017-2021. Unicef.org. 2019.[cited 29 September 2019]. Available from: https://www.unicef.org/zambia/reports/national-aids-strategic-framework-2017-2021.
187. Fettig J, Swaminathan M, Murrill CS, Kaplan JE. Global epidemiology of HIV. Infect Dis Clin North Am. 2014;28(3):323-37.
188. UNAIDS. Country Factsheets-Zambia. 2019 [Accessed 29 Sep 2019]. Available from:https://www.unaids.org/en/regionscountries/countries/zambia.
189. Differentiated Service Delivery Operational Framework. Zambia. 2018. Ministry of Health.
190. Tun W, Apicella L, Casalini C, Bikaru D, Mbita G, Jeremiah K, et al. Community-Based Antiretroviral Therapy (ART) Delivery for Female Sex Workers in Tanzania: 6-Month ART Initiation and Adherence. AIDS and Behavior. 2019;23(2):142-52.
191. Myer L, Iyun V, Zerbe A, Phillips TK, Brittain K, Mukonda E, et al. Differentiated models of care for postpartum women on antiretroviral therapy in Cape Town, South Africa: a cohort study. Journal of the International AIDS Society. 2017;20(Suppl 4):21636-.
192. Vogt F, Kalenga L, Lukela J, Salumu F, Diallo I, Nico E, et al. Brief Report: Decentralizing ART Supply for Stable HIV Patients to Community-Based Distribution Centers: Program Outcomes From an Urban Context in Kinshasa, DRC. Journal of acquired immune deficiency syndromes (1999). 2017;74(3):326-31.
193. Decroo T, Telfer B, Dores CD, White RA, Santos ND, Mkwamba A, et al. Effect of Community ART Groups on retention-in-care among patients on ART in Tete Province, Mozambique: a cohort study. BMJ Open. 2017;7(8):e016800.
194. Auld AF, Shiraishi RW, Couto A, Mbofana F, Colborn K, Alfredo C, et al. A Decade of Antiretroviral Therapy Scale-up in Mozambique: Evaluation of Outcome Trends and New Models of Service Delivery Among More Than 300,000 Patients Enrolled During 2004-2013. Journal of acquired immune deficiency syndromes (1999). 2016;73(2):e11-22.
195. Okoboi S, Ssali L, Yansaneh AI, Bakanda C, Birungi J, Nantume S, et al. Factors associated with long-term antiretroviral therapy attrition among adolescents in rural Uganda: a retrospective study. Journal of the International AIDS Society. 2016;19(5 Suppl 4):20841.
196. Okoboi S, Ding E, Persuad S, Wangisi J, Birungi J, Shurgold S, et al. Community-based ART distribution system can effectively facilitate long-term program retention and low-rates of death and virologic failure in rural Uganda. AIDS Res Ther. 2015;12(1):1-9.
197. Kipp W, Konde-Lule J, Saunders LD, Alibhai A, Houston S, Rubaale T, et al. Antiretroviral treatment for HIV in rural Uganda: two-year treatment outcomes of a prospective health centre/community-based and hospital-based cohort. PloS one. 2012;7(7):e40902.
198. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook. [
199. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [
200. Woodd S, Grosskurth H, Levin J, Amuron B, Namara G, Birunghi J, et al. Home-based versus clinic-based care for patients starting antiretroviral therapy with low CD4+ cell counts: findings from a cluster-randomized trial. 2014;28(4):569-76.
201. Shanaube K, Schaap A, Hoddinott G, Mubekapi-Musadaidzwa C, Floyd S, Bock P, et al. Impact of a community-wide combination HIV prevention intervention on knowledge of HIV status among adolescents. AIDS. 2021;35(2):275-85.

202. Bwalya C. Acceptability of a Home-Based Antiretroviral Therapy Delivery Model among HIV patients in Lusaka District: University of the Western Cape; 2018.
203. Bond V, Bwalya C, Hoddinott G, Reynolds L, Schaap A, Simuyaba M, et al. "The difference that makes a difference": highlighting the role of variable contexts within an HIV Prevention Community Randomised Trial (HPTN 071/PopART) in 21 study communities in Zambia and South Africa. AIDS Care. 2016;28:99-107.
204. Ministry of Health. Human Resources for Health Planning & Development Strategy Framework 2017 [cited 15 Jun 2020]. Available at: https://www.moh.gov.zm/docs/NationalHRHPlanningAndDevelopmentStrategyFramework.pdf.
205. Geldsetzer P, Francis JM, Ulenga N, Sando D, Lema IA, Mboggo E, et al. The impact of community health worker-led home delivery of antiretroviral therapy on virological suppression: a non-inferiority cluster-randomized health systems trial in Dar es Salaam, Tanzania. BMC health services research. 2017;17(1):160.
206. Topp SM, Chipukuma J, Hanefeld J. Understanding the dynamic interactions driving Zambian health centre performance: A case-based health systems analysis. Health policy and planning. 2014;30.
207. Kombe MM, Zulu JM, Michelo C, Sandøy IF. Community perspectives on randomisation and fairness in a cluster randomised controlled trial in Zambia. BMC Medical Ethics. 2019;20(1):99.
208. Zambia Consolidated Guidelines for Treatment and Prevention of HIV Infection. 2014.
209. National HIV/AIDS/STD/TB Council of Zambia: AIDS Response Fast Track Strategy 2015-2020.
210. Zambia Consolidated Guidelines for Treatment and Prevention of HIV Infection. 2016.
211. El-Sadr WM, Rabkin M, Nkengasong J, Birx DL. Realizing the potential of routine viral load testing in sub-Saharan Africa. Journal of the International AIDS Society. 2017;20 Suppl 7(Suppl 7):e25010.
212. Pellecchia U, Baert S, Nundwe S, Bwanali A, Zamadenga B, Metcalf CA, et al. "We are part of a family". Benefits and limitations of community ART groups (CAGs) in Thyolo, Malawi: a qualitative study. Journal of the International AIDS Society. 2017;20(1):21374.
213. Bemelmans M, Baert S, Negussie E, Bygrave H, Biot M, Jamet C, et al. Sustaining the future of HIV counselling to reach 90-90-90: a regional country analysis. Journal of the International AIDS Society. 2016;19(1):20751-.
214. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7.
215. Flämig K, Decroo T, van den Borne B, van de Pas R. ART adherence clubs in the Western Cape of South Africa: what does the sustainability framework tell us? A scoping literature review. Journal of the International AIDS Society. 2019;22(3):e25235-e.
216. Reidy W, Rabkin M, Syowai M, Schaaf A, El-Sadr W. Patient- and program-level monitoring of differentiated service delivery for HIV: a pragmatic and parsimonious approach is needed. AIDS. 2017;32:1.
217. UNAIDS. Global Aids Monitoring 2017: indicators for monitoring the 2016 United Nations Political Declaration on HIV and AIDS. Geneva: UNAIDS; 2017.
218. PEPFAR. Monitoring, evaluation, and indicator reference guide. October v.2.1. 2017.
219. Meyer AJ, Armstrong-Hough M, Babirye D, Mark D, Turimumahoro P, Ayakaka I, et al. Implementing mHealth Interventions in a Resource-Constrained Setting: Case Study From Uganda. JMIR Mhealth Uhealth. 2020;8(7):e19552.
220. Dharmayat KI, Tran T, Hardy V, Chirambo BG, Thompson MJ, Ide N, et al. Sustainability of 'mHealth' interventions in sub- Saharan Africa: a stakeholder analysis of an electronic community case management project in Malawi. Malawi Med J 2019 Sep;31(3):177-183.
221. Sharer M, Davis N, Makina N, Duffy M, Eagan S. Differentiated Antiretroviral Therapy Delivery: Implementation Barriers and Enablers in South Africa. J Assoc Nurses AIDS Care. 2019;30(5):511-20.
222. Kwarisiima D, Kamya MR, Owaraganise A, Mwangwa F, Byonanebye DM, Ayieko J, et al. High rates of viral suppression in adults and children with high CD4+ counts using a streamlined ART

delivery model in the SEARCH trial in rural Uganda and Kenya. Journal of the International AIDS Society. 2017;20(Suppl 4):21673-.
223. Macdonald V, Verster A, Baggaley R. A call for differentiated approaches to delivering HIV services to key populations. Journal of the International AIDS Society. 2017;20(Suppl 4):21658.
224. Kagee A, Nothling J, Coetzee B. The perspectives of users of antiretroviral therapy on structural barriers to adherence in South Africa. South African Family Practice. 2012;54:540-4.
225. Adjetey V, Obiri-Yeboah D, Dornoo B. Differentiated service delivery: a qualitative study of people living with HIV and accessing care in a tertiary facility in Ghana. BMC health services research. 2019;19(1):95-.
226. Shanaube K, Schaap A, Chaila MJ, Floyd S, Mackworth-Young C, Hoddinott G, et al. Community intervention improves knowledge of HIV status of adolescents in Zambia: findings from HPTN 071-PopART for youth study. AIDS. 2017;31:S221-S32.
227. Eaton JW, Johnson LF, Salomon JA, Barnighausen T, Bendavid E, Bershteyn A, et al. HIV treatment as prevention: systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa. PLoS medicine. 2012;9.
228. Zakumumpa H, Rujumba J, Kwiringira J, Katureebe C, Spicer N. Understanding implementation barriers in the national scale-up of differentiated ART delivery in Uganda. BMC health services research. 2020;20(1):222.
229. MacGregor H, McKenzie A, Jacobs T, Ullauri A. Scaling up ART adherence clubs in the public sector health system in the Western Cape, South Africa: a study of the institutionalisation of a pilot innovation. Globalization and health. 2018;14(1):40.
230. Limbada M, Zijlstra G, Macleod D, Ayles H, Fidler S. A systematic review of the effectiveness of non- health facility based care delivery of antiretroviral therapy for people living with HIV in sub-Saharan Africa measured by viral suppression, mortality and retention on ART. BMC public health. 2021;21(1):1110.
231. Limbada M, Bwalya C, Macleod D, Shibwela O, Floyd S, Nzara D, et al. Acceptability and Preferences of Two Different Community Models of ART Delivery in a High Prevalence Urban Setting in Zambia: Cluster-Randomized Trial, Nested in the HPTN 071 (PopART) Study. AIDS and Behavior. 2021.
232. Jaffar S, Amuron B, Foster S. Rates of virological failure in patients treated in a home-based versus a facility-based HIV-care model in Jinja, southeast Uganda: a cluster-randomized equivalence trial. Lancet (London, England). 2009;374(9707):2080 - 89.
233. Mukumbang FC, Orth Z, van Wyk B. What do the implementation outcome variables tell us about the scaling-up of the antiretroviral treatment adherence clubs in South Africa? A document review. Health Research Policy and Systems. 2019;17(1):28.
234. Roy M, Bolton-Moore C, Sikazwe I, Mukumbwa-Mwenechanya M, Efronson E, Mwamba C, et al. Participation in adherence clubs and on-time drug pickup among HIV-infected adults in Zambia: A matched-pair cluster randomized trial. PLoS medicine. 2020;17(7):e1003116.
235. Bezabhe WM, Chalmers L, Bereznicki LR, Peterson GM, Bimirew MA, Kassie DM. Barriers and facilitators of adherence to antiretroviral drug therapy and retention in care among adult HIV-positive patients: a qualitative study from Ethiopia. PloS one. 2014;9(5):e97353.
236. Rabkin M, Strauss M, Mantell JE, Mapingure M, Masvawure TB, Lamb MR, et al. Optimizing differentiated treatment models for people living with HIV in urban Zimbabwe: Findings from a mixed methods study. PloS one. 2020;15(1):e0228148-e.
237. Eshun-Wilson I, Mukumbwa-Mwenechanya M, Kim H-Y, Zannolini A, Mwamba CP, Dowdy D, et al. Differentiated Care Preferences of Stable Patients on Antiretroviral Therapy in Zambia: A Discrete Choice Experiment. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2019;81(5):540-6.
238. Humphrey JM, Naanyu V, MacDonald KR, Wools-Kaloustian K, Zimet GD. Stated-preference research in HIV: A scoping review. PloS one. 2019;14(10):e0224566.

239. Maranga A, Dias. Feasibility of Improving Access to Antiretroviral Therapy through Community Pharmacies in Mozambique [Internet]. 2018. Available from: www.aids2018.org.
240. Mwamba D, Thulani R, Herce M. Community adherence group (CAG) for HIV viremic patients: early lessons learnt from Lusaka, Zambia. Abstract 184, 12th INTEREST Conference, Kigali, 2018.
241. International AIDS Society, Nov 2020, "Differentiated service delivery for HIV treatment: Summary of published evidence". www.differentiatedservicedelivery.org.
242. Strachan DL KK, Nakirunda M, Ndima S, Muiambo A, Hill Z. Using theory and formative research to design interventions to improve community health worker motivation, retention and performance in Mozambique and Uganda. Human resources for health. 2015 Dec;13(1):1-3.
243. Matovu JK NA, Nakabirye S, Wanyenze RK, Serwadda D. Formative research to inform the development of a peer-led HIV self-testing intervention to improve HIV testing uptake and linkage to HIV care among adolescents, young people and adult men in Kasensero fishing community, Rakai, Uganda: a qualitative study. BMC public health. 2020 Dec;20(1):1-6.
244. Killingo BM, Taro TB, Mosime WN. Community-driven demand creation for the use of routine viral load testing: a model to scale up routine viral load testing. Journal of the International AIDS Society. 2017;20 Suppl 7(Suppl 7):e25009.
245. Roberts T, Cohn J, Bonner K, Hargreaves S. Scale-up of Routine Viral Load Testing in Resource-Poor Settings: Current and Future Implementation Challenges. Clinical Infectious Diseases. 2016;Epub.
246. Sax PE. Editorial Commentary: Can We Break the Habit of Routine CD4 Monitoring in HIV Care? Clinical Infectious Diseases. 2013;56(9):1344-6.
247. Frontières. MS. Making Viral Load Routine. Successes and challenges in the implementation of routine HIV viral load monitoring.
248. Ford N, Meintjes G, Pozniak A, Bygrave H, Hill A, Peter T, et al. The future role of CD4 cell count for monitoring antiretroviral therapy. The Lancet Infectious diseases. 2015;15(2):241-7.
249. Ehrenkranz PD, Baptiste SL, Bygrave H, Ellman T, Doi N, Grimsrud A, et al. The missed potential of CD4 and viral load testing to improve clinical outcomes for people living with HIV in lower-resource settings. PLoS medicine. 2019;16(5):e1002820.
250. World Health Organization [WHO] (2011). Retention in HIV Programs. Defining the challenges and identifying solutions. Meeting Report 13–15 September 2011, Geneva.
251. Ebuy H, Yebyo H, Alemayehu M. Level of adherence and predictors of adherence to the Option B+ PMTCT programme in Tigray, northern Ethiopia. Int J Infect Dis. 2015 Apr;33:123-9. doi: 10.1016/j.ijid.2014.12.026. Epub 2014 Dec 18. PMID: 25529555.
252. Grimsrud AT, Cornell M, Egger M, Boulle A, Myer L. Impact of definitions of loss to follow-up (LTFU) in antiretroviral therapy program evaluation: variation in the definition can have an appreciable impact on estimated proportions of LTFU. J Clin Epidemiol. 2013;66(9):1006-13.
253. Tweya H, Gugsa S, Hosseinipour M, Speight C, Ng'ambi W, Bokosi M, Chikonda J, Chauma A, Khomani P, Phoso M, Mtande T, Phiri S. Understanding factors, outcomes and reasons for loss to follow-up among women in Option B+ PMTCT programme in Lilongwe, Malawi. Trop Med Int Health. 2014 Nov;19(11):1360-6. doi: 10.1111/tmi.12369. Epub 2014 Aug 4. PMID: 25087778.
254. McMahon JH EJ, Hong SY, Bertagnolio S, Jordan MR. . Effects of physical tracing on estimates of loss to follow-up, mortality and retention in low and middle income country antiretroviral therapy programs: a systematic review. PLoS One. 2013;8(2):e56047.
255. Chammartin F, Zürcher K, Keiser O, Weigel R, Chu K, Kiragga AN, et al. Outcomes of Patients Lost to Follow-up in African Antiretroviral Therapy Programs: Individual Patient Data Meta-analysis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2018;67(11):1643-52.
256. Holmes CB, Sikazwe I, Sikombe K, Eshun-Wilson I, Czaicki N, Beres LK, et al. Estimated mortality on HIV treatment among active patients and patients lost to follow-up in 4 provinces of Zambia: Findings from a multistage sampling-based survey. PLoS medicine. 2018;15(1):e1002489.

257. Gumede-Moyo S, Todd J, Bond V, Mee P, Filteau S. A qualitative inquiry into implementing an electronic health record system (SmartCare) for prevention of mother-to-child transmission data in Zambia: a retrospective study. BMJ Open. 2019;9(9):e030428.
258. Moomba K, Williams A, Savory T, Lumpa M, Chilembo P, Tweya H, et al. Effects of real-time electronic data entry on HIV programme data quality in Lusaka, Zambia. Public Health Action. 2020;10(1):47-52.
259. Williams F, Boren S. The role of the electronic medical record (EMR) in care delivery development in developing countries: A systematic review. Informatics in primary care. 2008;16:139-45.
260. Manyazewal T, Oosthuizen MJ, Matlakala MC. Proposing evidence-based strategies to strengthen implementation of healthcare reform in resource-limited settings: a summative analysis. BMJ Open. 2016;6(9):e012582.
261. Greenhalgh T, Robert G, Macfarlane F, Bate P, Kyriakidou O. Diffusion Of Innovations In Service Organizations: Systematic Review And Recommendations. The Milbank quarterly. 2004;82:581-629.
262. Jacobs C, Michelo C, Moshabela M. Implementation of a community-based intervention in the most rural and remote districts of Zambia: a process evaluation of safe motherhood action groups. Implementation Science. 2018;13(1):74.
263. Wilkinson L, Harley B, Sharp J, Solomon S, Jacobs S, Cragg C, et al. Expansion of the Adherence Club model for stable antiretroviral therapy patients in the Cape Metro, South Africa 2011-2015. Tropical medicine & international health : TM & IH. 2016;21(6):743-9.
264. Jones D, Weiss SM, Arheart K, Cook R, Chitalu N. Implementation of HIV prevention interventions in resource limited settings: the partner project. Journal of community health. 2014;39(1):151-8.
265. Dziva Chikwari C, Simms V, Busza J, Dauya E, Bandason T, Chonzi P, et al. Community health worker support to improve HIV treatment outcomes for older children and adolescents in Zimbabwe: a process evaluation of the ZENITH trial. Implementation science : IS. 2018;13(1):70-.
266. Westgard C, Fleming WO. The Use of Implementation Science Tools to Design, Implement, and Monitor a Community-Based mHealth Intervention for Child Health in the Amazon. Frontiers in Public Health. 2020;8(411).
267. French C, Pinnock H, Forbes G, Skene I, Taylor SJC. Process evaluation within pragmatic randomised controlled trials: what is it, why is it done, and can we find it?—a systematic review. Trials. 2020;21(1):916.
268. Moore G AS, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: UK Medical Research Council (MRC) guidance. London: MRC Population Health Science Network; 2014.
269. [Available from: https://www.nihr.ac.uk/news/nihr-publishes-new-framework-on-complex-interventions-to-improve-health/28803.
270. Skivington K, Matthews L, Simpson SA, Craig P, Baird J, Blazeby JM, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. BMJ. 2021;374:n2061.
271. Cassidy S, Okwose N, Scragg J, Houghton D, Ashley K, Trenell MI, et al. Assessing the feasibility and acceptability of Changing Health for the management of prediabetes: protocol for a pilot study of a digital behavioural intervention. Pilot and Feasibility Studies. 2019;5(1):139.
272. Breitenstein SM, Gross D, Garvey CA, Hill C, Fogg L, Resnick B. Implementation fidelity in community-based interventions. Res Nurs Health. 2010;33(2):164-73.
273. Wilkinson LS. ART adherence clubs: A long-term retention strategy for clinically stable patients receiving antiretroviral therapy. 2013. 2013;14(2):3.
274. Kuchukhidze S, Long LC, Pascoe S, Huber AN, Nichols BE, Fox MP, Rosen S.Differentiated models of service delivery (DSD) for antiretroviral treatment of HIV in sub-Saharan Africa: A review

of the gray literature as of June 2019. AMBIT Project Report Number 03. Boston: Boston University and HE2RO, 2019.
275. Paina L, Peters DH. Understanding pathways for scaling up health services through the lens of complex adaptive systems. Health Policy and Planning. 2011;27(5):365-73.
276. Organization WH. Updated recommendations on service delivery for the treatment and care of people living with HIV. Geneva: World Health Organization; 2021.
277. L.Wilkinson. Learning from and beyond COVID-19 for DSD. 23rd International AIDS Conference, 2020.
278. Obunga J. Experiences and lessons learned in implementing the differentiated care model in HIV clinics in Nyamira County. Abstract 184, 12th INTEREST Conference, Kigali, 2018.
279. Semitala FC, Atuhumuza E, Muyindike W, Sabiti L, Karirirwe G, Walusimbi S, et al. Patient's preferences for Differentiated HIV service delivery in a routine program setting in Uganda-A cross sectional survey Background. Abstract 2122, AIDS 2018.
280. Barnabas RV, Szpiro AA, van Rooyen H, Asiimwe S, Pillay D, Ware NC, et al. Community-based antiretroviral therapy versus standard clinic-based services for HIV in South Africa and Uganda (DO ART): a randomised trial. The Lancet Global Health. 2020;8(10):e1305-e15.
281. Mavhu W, Willis N, Mufuka J, Bernays S, Tshuma M, Mangenah C, et al. Effect of a differentiated service delivery model on virological failure in adolescents with HIV in Zimbabwe (Zvandiri): a cluster-randomised controlled trial. The Lancet Global Health. 2020;8(2):e264-e75.