Economic Evaluation Methods for HIV Testing of Children and Adolescents in Zimbabwe

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DECLARATION BY CANDIDATE

I, Arthi Vasantharoopan, 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.

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ABSTRACT

Background

Despite the advances and expansion of HIV testing and treatment programs, children and adolescents in sub-Saharan Africa (SSA) are being left behind. In 2021, more than 46% of children living with HIV were not receiving treatment; among SSA adolescents (aged 10-19) AIDS is a leading cause of death. HIV testing is the first and crucial step necessary in accessing HIV treatment and reducing HIV related mortality, yet current testing strategies have not been sufficient enough to address and overcome the gaps in HIV testing and diagnosis of children and adolescents. Compounded by the fact that HIV case identification will only become more difficult and costly with time, as the remaining undiagnosed population of children and adolescents will require more concerted efforts compared to standard of care, alternative HIV testing strategies are needed. Index-linked HIV testing (ILHIVT) – offering HIV testing to children and adolescents living with an HIV positive parent or guardian – might be an effective method to test and identify HIV positive children and adolescents. As such, the aim of this PhD was to evaluate and generate methods around the economic evaluation (EE) of HIV testing strategies in children and adolescents in Zimbabwe.

Methods

This thesis integrates methods from health economics and mathematical modelling of infectious diseases to both determine and strengthen the ways in which cost-effectiveness analyses of HIV testing strategies focused on the adolescent sub-population in SSA can be conducted. Firstly, a systematic review to identify the modelling methods of EEs of HIV testing strategies in SSA over the past decade was conducted. To assess the quality of model reporting, a multi-component, novel tool based on a gold standard checklist and recommendations was developed. Then, using the findings of the systematic review as a starting point, a narrative review synthesizing, comparing and investigating child and adolescent HIV transmission dynamics representation in popular dynamic mathematical models applicable to the SSA context was conducted. Next, a mixed-methods – both bottom-up and top-down – provider based cost analysis of cost per test and per HIV diagnosis for 2- 18 year olds, through standard of care, along with the incremental cost of ILHIVT via three modalities (facility, home-based and caregiver assisted), in both urban and rural settings was conducted. Finally, using the costs generated via the costing analysis, a proposal for an EE of ILHIVT for children and adolescents in Zimbabwe, through a microsimulation model, (with static, stochastic and individual properties), was generated.

Results

The results generated can be classified according to this PhD's objectives. Objective 1 sought to determine how EEs of HIV testing strategies in SSA were modelled: the majority of model based EEs exhibited dynamic, stochastic and individual properties. Transparency around model-based decisions made were severely lacking, with model reporting across criteria generated via the novel tool, highly mixed. No EE focusing on HIV testing strategies in the sub-population of children and adolescents had been conducted. Objective 2 sought to narratively describe child and adolescent inclusion and representation among high-reviewed and frequently utilized dynamic mathematical model of HIV transmission, pertinent to the Zimbabwean context and SSA as a whole. Half of models meeting the inclusion criteria incorporated child HIV transmission dynamics to some degree within their frameworks, while all models incorporated adolescent HIV transmission dynamics. Each model had room for improvement with regards to child and adolescent integration into the framework. The largest limitations involved omission of children entirely, to poor sexual mixing structuring and partnership formation description amongst adolescents. Objective 3 sought to measure the cost of delivering ILHIVT to children and adolescents in Zimbabwe. In the urban setting, home-based ILHIVT for 2-18 year olds had the lowest incremental cost (US$6.69), while facility-based ILHIVT (US$5.36) was the lowest option in the rural setting. Irrespective of setting, caregiver-assisted testing was always the most expensive option (urban U$17.49, rural US$62.49). Unit costs of ILHIVT was driven by uptake which varied according to both setting and modality. Objective 4 sought to explore practical applications of thesis findings. As this version of ILHIVT had low yield and high incremental cost-per diagnosis, it was unlikely to be a cost-effective option for identifying HIV positive children and adolescents. An EE proposal for ILHIVT, demonstrating the level of transparency needed around 13 modelling features and criteria, was put forth as an example of 'good modelling practice' for future researchers.

Conclusions

The strength and reliability of EE findings are dependent on the validity of the underlying model used to answer a specific decision problem. Moving forward, transparency around all model-based decisions is needed to facilitate understanding, generalizability, reusability and reproducibility of models and results. Existing well-described dynamic mathematical models of HIV, used frequently in the context of strategic population-level decision-making, require improvement and expansion within their existing framework to accurately evaluate the impact and cost-effectiveness of interventions targeting this sub-group. Familiarity and acceptability drove uptake and choice of ILHIVT testing modality, highlighting that current messaging and knowledge around pediatric HIV, even amongst HIV positive indexes is insufficient. As a result, the current iteration of ILHIVT is low yielding and has high cost per diagnosis, translating to low

cost-effectiveness. Alternative solutions which increase efficiency and reduce unit costs, such as testing the entire household of an index, thereby diffusing personnel costs, identified as the largest driver of unit costs, need to be explored. The findings of this PhD contribute to advancing the field of economic evaluation methods for HIV testing strategies in children and adolescents by addressing: 1.) the lack of practical representation of children and adolescents in decision analytic modelling of HIV testing strategies through a behaviorally driven analysis of model structures both within EEs of HIV testing strategies, and highly regarded and frequently used dynamic mathematical models of HIV; 2.) the lack of EE literature focused on HIV testing strategies targeting children and adolescents through a partial EE of ILHIVT.

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ABM	Agent-Based Models
ANC	Antenatal Clinic
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
B-GAP	Bridging the GAP in HIV Testing and Care for Children in Zimbabwe
CBA	Cost Benefit Analysis
CCA	Cost-Consequence Analysis
CEA	Cost-Effectiveness Analysis
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CMA	Cost Minimization Analysis
CUA	Cost Utility Analysis
DALY	Disability-adjusted life years
DES	Discrete Event Simulations
DHS	Demographic and Health Surveys
EE	Economic Evaluation
EMOD	Epidemiological MODeling Software
ESA	East and Southern Africa
GDP	Gross Domestic Product
GHCC	Global Health Cost Consortium
HIV	Human Immunodeficiency Virus
HIVST	HIV Self-testing
HTA	Health Technology Assessment
HTC	HIV Testing and Counselling
HTS	HIV Testing Service
IBM	Individual-Based Model
ICER	Incremental Cost-Effectiveness Ratio
ILHIVT	Index-Linked HIV Testing
ISPOR	The Professional Society for Health Economics and Outcomes Research
LMIC	Low and Middle Income Countries

MoHCC	Ministry of Health and Child Care (Zimbabwe)
MTCT	Mother-to-Child Transmission
NGO	Non-Governmental Organization
OMT	Oral Mucosal Transudate
PLHIV	People Living with HIV
PMTCT	Prevention of Mother-to-Child Transmission
PrEP	Pre-exposure prophylaxis
PRESS	Peer-Review of Systematic Review Search Strategies
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PROSPERO	International Prospective Register of Systematic Reviews
QALY	Quality-Adjusted Life Years
RTGS	Real-Time Gross Settlement (Zimbabwe)
SANRA	Scale for the Assessment of Narrative Review Articles
SD	System Dynamics
SES	Socioeconomic Status
SoC	Standard of Care
SSA	sub-Saharan Africa
STI	Sexually-Transmitted Infection
TB	Tuberculosis
UK	United Kingdom
UNAIDS	Joint United Nations Programme on HIV/AIDS
USD	United States Dollars
WCA	West and Central Africa
WHO	World Health Organization
ZIMPHIA	Zimbabwe Population-Based HIV Impact Assessment
ZIMSTAT	Zimbabwe National Statistics Agency

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CHAPTER 1 – INTRODUCTION

1.1 Overview: HIV, the corresponding economic burden and the role of HTAs

HIV remains one of the world's most serious public health challenges despite the significant progress made in prevention and treatment efforts over the past four decades. Since the beginning of the global epidemic, 84.2 million people have been infected, approximately half (40.1 million) of whom have died from HIV, with southern Africa the area most severely affected [1]. The damage caused by HIV in this part of the world goes beyond its terrible burden of mortality and morbidity. Though the impact of HIV/AIDS on economies will never truly be known, its adverse effects are undisputable. Microeconomic impacts of the disease at the individual, household and community levels are important to understand and mitigate, as these economic states have direct bearings on our wealth, income, health and psychosocial well-being [2]. Macroeconomic impacts of HIV/AIDS, the increased morbidity and mortality caused by the disease, negatively affects and strains labor supply [3]. Modelled for the time period of 1990-2025, the resulting growth trajectories for 30 sub-Saharan countries affected by HIV found that economic growth rates would decline between 0.56-1.47% [2]. Retrospectively, gross domestic product (GDP) per capita was found to decline 0.7% per year [2].

Economic research used to categorize HIV/AIDS as a sharp exogenous shock to the economy [4]. However, given the long standing nature of the global epidemic, HIV/AIDS is now viewed as a disease which affects long term structural changes [4]. Without the appropriate level of response, development and growth are jeopardized. Compounding to other events such as endemic poverty and poor governance, HIV/AIDS has the ability to incapacitate countries [4]. This is understandable given that an appropriate response to the disease does not end with testing and counselling (HTC) alone; antiretroviral therapy (ART) is lifelong, implying a long term commitment from not just governments, but NGOs, as well as donors from both private and intergovernmental organizations [5].

In the context of low and middle-income countries (LMIC) especially, where an infectious disease requiring chronic management such as HIV places a heavy burden on finite resources, health technology assessment (HTA), a multidisciplinary process bridging research and decision making, can be a powerful and valuable policy tool in providing direction and information for budgetary allocation of constrained resources [6, 7]. A robust, evidence based process in aiding systematic priority setting, HTA components encompass medical (i.e. clinical effectiveness), economic (i.e. cost-effectiveness), ethical, legal and social considerations [8]. In order to determine the most efficient and equitable distribution of available (often

limited) resources, capable of maximizing impact to the overall health of a population, HTAs include the entire spectrum of 'technologies' whose purpose is to improve health; pharmaceutical interventions such as medical devices and procedures, medicines and vaccines, as well as non-pharmaceutical interventions such as social, behavioral and structural interventions [6, 7]. The utilization of HTAs to inform legislation is standard practice in many high income settings with universal health-care systems, and has been endorsed by the WHO since 2014 to inform priority decision-making in the context of universal health coverage (UHC) [9, 10]. The pathway towards UHC – defined as a range of sufficiently efficacious, equitable, quality health services that do not expose the user to financial hardship – usually arises through the institutionalization of decision-making for health, and specifically, through the formalization of the HTA processes [11, 12]. Countries such as the United Kingdom (National Institute for Health and Clinical excellence – NICE) and Canada (Canadian Agency for Drugs and Technologies in Health – CADTH) have established organizations whose sole purpose is to execute HTAs, with the aim of determining the optimal mix of publicly funded resources and service allocation for the population at large [9]. Conversely however, in LMIC, where this tool would be most beneficial in supporting the evidence-based decision-making process for priority-setting, the capacity to conduct HTAs and translate findings into routine policy is lacking [6]. Local research infrastructure in these settings is not equipped to provide the evidence necessary for HTAs, while implementation science of research into policy is hindered by both human and health system technical capacity [13]. Coupled with challenges around transparency in decision making, resource-poor settings with constrained health sector budgets which would benefit the most from the systematic evaluation of the best 'value for money' investments in health care, are often those incapable of implementing HTAs [14]. This trend is changing however, as a review published a decade ago (2014) detailing collaborations between health economists in sub-Saharan Africa (SSA) found that more than 50% of articles published since 1994 relating to HTAs in LMIC were published within a 5-year time frame: 2008-2013 [13]. Since 2013, the International Decision Support Initiative, "a global network of health, policy and economic expertise which seeks to support countries make better decisions about efficient spending on healthcare"[10], has been capacity building with local partners in SSA to "help implement robust HTA processes" [10]. Yet despite the support of a global collective of experts, and subsequent interest in HTAs increasing as a result, a systematic review found that many challenges to establishing HTA institutionalization in SSA remain [10]. The largest of these challenges being a lack of infrastructure along with streamlined tools and mechanisms to translate and disseminate research based evidence among the historical/traditional hierarchies of power and policy making [10].

In 2015, the WHO conducted a global survey of member states to ascertain in country HTA processes, and updated the survey again in 2020/2021 [15, 16]. Only 17 countries in SSA responded to the initial survey in 2015, but the number almost doubled to 32 countries, in the most recent round of the survey [15, 16]. Countries such as Ethiopia, Ghana, South Africa and Tanzania, all of whom have initiated some form of in-country HTA processes, consistently responded to the surveys, while countries such as Angola, Botswana, Uganda and Zimbabwe consistently did not [15-17]. Examples of priority setting via HTA usage in the former grouping of countries has ranged from: identification of 'best-value-for-money' health interventions; establishment of treatment guidelines; formulation and revision of the national essential medicines lists [17]. In these LMICs, where resources are constricted, HTA processes integrated into health systems (as opposed to establishment of separate agencies), while acknowledging the need for both public and private sector engagement (including donor support), might help optimize evidence-based decision-making [17, 18]. With regards to HIV management in SSA, where case identification will only become more difficult and costly, evaluating the value of HIV related health interventions, from both a costs and benefits perspective, is crucial to ensuring that no-one is left behind, especially those amongst the most vulnerable sub-populations.

1.2 Theoretical Underpinnings of Thesis

Welfarism and extra-welfarism are two of the most important paradigms of decision-making in the health care sector [19]. Rooted in the theory of welfare economics – optimal resource allocation capable of maximizing overall sum of individual utilities (i.e. satisfaction) and well-being in society – these two models view health, health care, and the resulting health care services through differing lenses [19]. Welfarists approach and weigh health care services as equivalent to all other goods produced within the economy; the consumption of which denotes its utility [19]. The utility of the subsequent health related service is therefore not the direct benefit to health itself, but the individual attributable value to the health care service at large [20]. Extra-welfarists meanwhile, assign value to health services based on their capability of maximizing health itself [20]. By shifting focus from utility maximization to include broader measures of well-being (such as improvement to health related quality of life), Extra-Welfarism extends beyond Welfarist concepts. Economic Evaluations (EE), a component of HTAs, mostly fall within the Extra-Welfarist categorization [19-21] (**C1, Figure 1**).

Most EEs of healthcare interventions, [Cost-Effectiveness Analysis (CEA), Cost-Utility Analysis (CUA), Cost-Minimization Analysis (CMA) and Cost-Consequence Analysis (CCA)], with the exception of Cost-Benefit Analysis (CBA), are extra-welfarist in nature as their primary outcome of interest is concerned

with the improvement of health-related outcomes and quality of life [20]. By contrast however, CBA methodology, focused on utility maximization in monetary terms, is rooted in welfarism [20]. Both theories (and subsequent methodologies) feed in to the concept of Allocative Efficiency: the optimization of resource distribution – programs, services and technologies – for maximum societal benefit and welfare (via improvement in health outcomes or increasing utility) [20, 22]. The concept of allocative efficiency can thus be stated as the theoretical underpinnings of economic evaluation as a whole, and CEA, CUA and CBA (along with CMA and CCA) methodologies specifically [20, 23] (**C1, Figure 1**).

Irrespective of setting and wealth, policymakers in low, middle and high-income countries are all tasked with the same challenging decision; scarce resource allocation in health [24]. In resource constrained setting such as SSA, only a handful of programmatic interventions per disease can be supported and invested in at the ministry/national level. Thus, it is imperative to select strategies which generate the highest benefits with the lowest associated costs, thereby focusing "on the right population, in the right place, at the right time" [25]. Economic evaluation provides a framework to support this decision making by systematically quantifying and comparing the costs and outcomes of a program to decide whether it represents value for money [25, 26]. Generated evidence regarding the potential benefits (i.e. health gained) and associated costs of a new health related investment can then be compared against others to determine which services provide the greatest benefit per unit of cost [26].

Economic evaluation methodologies such as CEA and CUA play a critical role in informing resource allocation. Both approaches aim to assess the efficiency of healthcare interventions by comparing the costs incurred to the health outcomes achieved. While these methods share common goals, they differ in the way outcomes are measured and reported. CEA evaluates the costs of healthcare interventions relative to their outcomes, which are typically expressed in natural units such as life-years gained, cases of disease prevented, or disability averted. The primary objective of CEA is to determine which intervention provides the greatest health benefit for a given level of expenditure [20, 26-28]. This is achieved through the calculation of cost-effectiveness ratios which express the cost per unit of health outcome (e.g., cost per life-year gained). A further refinement of this approach is the Incremental Cost-Effectiveness Ratio (ICER), which compares the additional cost of one intervention over another in relation to the additional health benefit it provides [26, 27, 29]. As such, CEA is widely used to compare interventions aimed at improving health outcomes across a population and to guide decisions about how to allocate scarce healthcare resources most efficiently.

Cost-Utility Analysis (CUA) represents a specific form of CEA in which health outcomes are measured not only in terms of the quantity of life gained but also in terms of the quality of those life years. CUA incorporates metrics such as Quality-Adjusted Life Years (QALYs) and Disability-Adjusted Life Years (DALYs), which combine both the length and the quality of life in a single measure [20, 26, 27]. By accounting for the quality of life, CUA offers a more comprehensive evaluation of interventions that may improve both survival and the overall well-being of individuals [20, 26, 27]. For example, one QALY represents one year of life lived in perfect health, while 0.5 QALYs might represent a year lived at half the full quality of life. This allows for comparisons across diverse health interventions that affect both morbidity and mortality. Like CEA, CUA also employs an Incremental Cost-Utility Ratio (ICUR) to compare the additional cost per QALY gained between different interventions [29, 30].

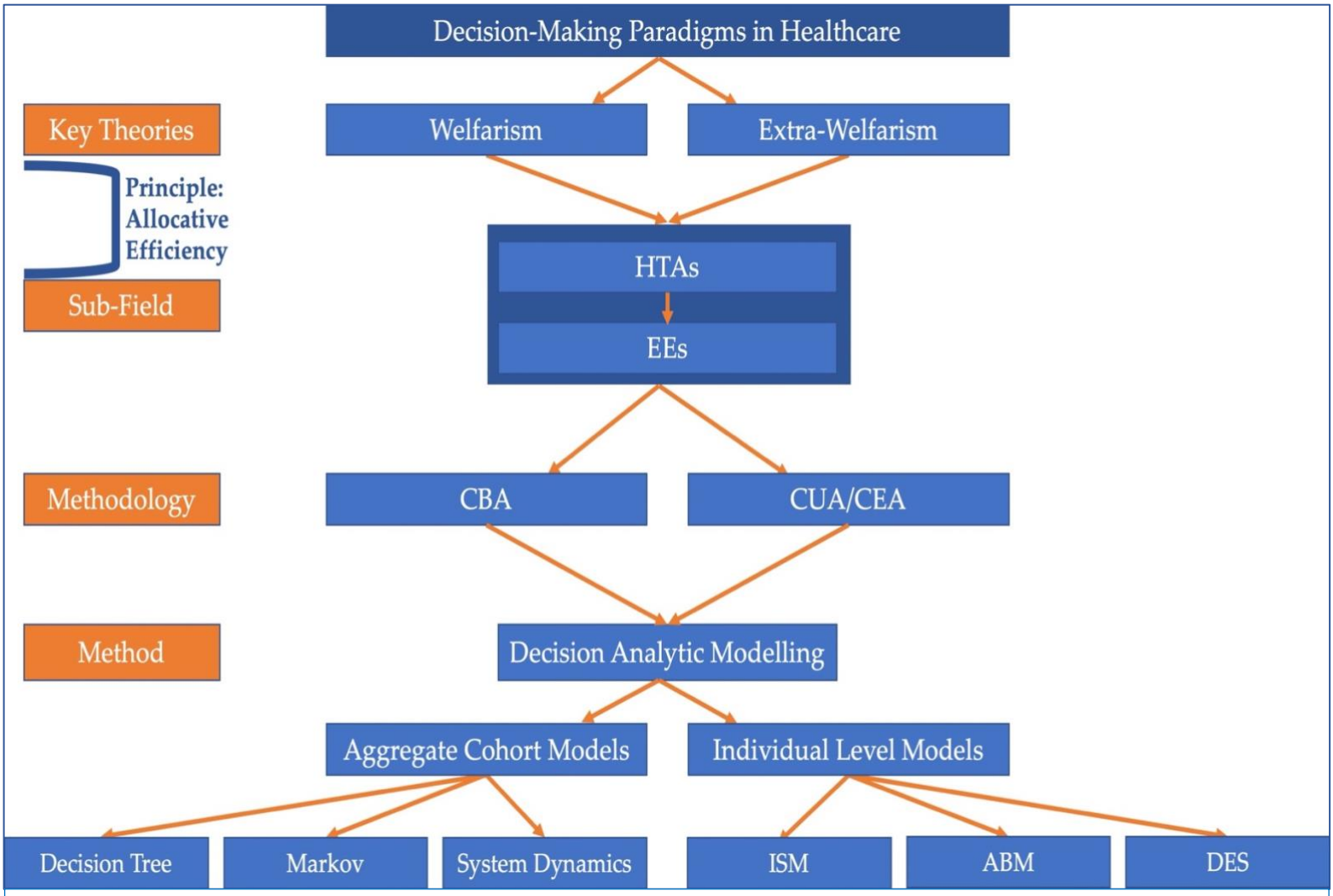
The primary difference between CEA and CUA lies in the measurement of health outcomes. Whereas CEA focuses solely on the length of life or other direct health measures, CUA provides a more nuanced approach by incorporating the quality of life, making it particularly useful for comparing interventions that have complex effects on patients' overall health and well-being [26, 27]. Both methods, however, are essential for assessing the value for money of healthcare interventions, particularly in environments where decision-makers must prioritize between multiple competing interventions within limited budgets [26, 27]. It is becoming increasingly common to rely on CEA/CUA to help inform and guide decisions around resource allocation in healthcare, with the aim of maximizing healthcare spending by funding interventions offering the greatest health benefits at the lowest costs. The use of CEA facilitates transparency in decision making, as the rationale for funding one intervention over another lies in the ‘value for money’ proposition [26, 27].

Decision analytic modeling is a mathematical framework used to extrapolate costs and effects of an intervention beyond observable conditions [31]. The purpose of decision analytic modelling in the context of economic evaluation is to provide decision makers with a rigorous and systematic approach to combining all the available information to help inform a decision whilst also incorporating the uncertainty within that decision [26, 31-33]. By synthesizing evidence from primary and secondary sources ranging from studies such as cohort and randomized controlled trials, to survey, clinical and outcomes data, the resulting costs and benefits of the various healthcare interventions under consideration are produced, to better inform a decision [26, 31-33]. Decision analytic modelling can be dichotomized in the following way [31, 34-36] (**C1, Figure 1**):

1.) Aggregate/cohort models – decision trees, Markov models and system dynamics (SD), (commonly referred to as compartmental or dynamic transmission models);

2.) Individual level models – individual sampling model (ISM), (commonly referred to as microsimulations), agent-based model (ABM), (also referred to as individual-based models (IBM)), and Discrete Event Simulation (DES).

Both the aforementioned categories can be further dichotomized by whether interaction between the population must be factored in, (SD, ABM/IBM or DES), or not, (decision tree, Markov, ISM) [31, 34-36]. This is of particular importance in infectious diseases modelling [34]. Aggregate models focus on the respective proportions of populations which undergo certain events, while individual models follow particular attributes of an individual, over a defined time horizon [34]. The classification of model structures tends to be differentiated by factors involving both time and interaction between individuals [34]. Ultimately, the type of model employed is dependent contextually on the decision problem [34].



C1, Figure 1. Theoretical Underpinnings of Thesis: Concept Flowchart

1.2.1 The Intersection of CEA and HIV Underfunding

A lack of investment, (30% less than estimated need), led to failure in achieving global HIV targets for 2020; the funding gap resulted in 3.5 million more infections and 800,000 deaths than would have occurred if targets had been met [37]. To circumvent the same outcome for 2025 global HIV targets, (thereby missing the mark to end the HIV/AIDS epidemic by 2030), considerable investment and a substantial push by individual nations, bi-and-multilateral donors alike is required [38]. Funding for the global HIV response stalled in 2017, decreased 7% by 2019, and faced further difficulties in 2020 onwards due to COVID-19 pandemic related disruptions and resource diversion [37, 39]. By 2022, global HIV funding was 3% lower than the year prior [40]. Omitting the United States, (the largest individual contributor to the global HIV response remaining stable), funding from bilateral donors has decreased by 57% since 2012-2013 [38]. With domestic funding accounting for only 60% of LMIC expenditure for HIV in 2021, and despite renewed commitments to funding the HIV response made by UN member states in the same year; the funding gap has left the HIV response in LMICs US$ 8 billion short of the necessary resource investment to meet targets for 2025 [38]. Children and adolescents within the HIV response have inequitably been addressed, (so much so that a new global alliance was formed in 2022 to ensure action and address the needs of this sub-population) [38, 41]:

- only 52% of children and 59% of adolescents living with HIV are accessing ART (compared to 75% of adults) [38, 42];
- only 40% of children aged 0-14 are virally suppressed (compared to 67% of adults) [39];
- adolescent girls bear a disproportionate burden of new HIV infection and risk [37-39];
- AIDS related mortality has declined by only 10% in adolescents (compared to 76% in children and 64% in all age groups), ranking AIDS as a leading cause of death globally in this demographic [43].

Funding patterns have contributed to these HIV-related inequalities: in LMICS 48% of adult HIV treatment programs are funded domestically, while only 4% of HIV treatment for children is allocated through domestic sources [41]. Similarly, underinvestment at the country level into early-infant diagnosis has necessitated 24%, 96% and 99% of resource needs to be driven by international donors in low-income, lower-middle income, and upper-middle income countries respectively [41]. Funding earmarked for programs benefitting adolescent girls totals 5% of the HIV response in 78 countries; half of these countries rely on international donors for more than 50% of necessary investment [41]. Thus, the child and adolescent HIV response is predominantly funded through external sources, and with official development assistance for HIV having tumbled by 57% the last decade, children and adolescents (along with other key populations) bear the burden of the HIV/AIDS funding gap [41].

HIV testing is the gateway to treatment and care, and an intersection of the HIV prevention and care cascade. Per UNAIDS:

> " Nearly two thirds of children not on treatment are aged 5 to 14 years – children who cannot be found through HIV testing during post-natal care visits. A priority for the next five years is to expand rights-based index, family and household (HIV) testing and to optimize pediatric treatment in order to diagnose children, link them to treatment and retain them in life-long care" [39]

Index-linked HIV testing, (ILHIVT), a focused HIV testing strategy whereby household contacts, family members including children, and partners (sexual and needle sharing) of people diagnosed with HIV are offered HIV testing, has been recommended by the WHO since 2016 [44, 45]. As 95% of HIV infection in children 0 –14 years of age is transmitted vertically (from mother to child), ILHIVT of children living with an HIV positive parent has the ability to identify children who were missed by infant diagnosis programs [45, 46]. UNICEF implementation of this targeted HIV testing services (HTS) strategy in SSA found undiagnosed HIV prevalence in children to range from 3% in Zimbabwe, to as high as 30% in the Democratic Republic of Congo [46].

Underfunding of the global HIV response significantly affects HIV programming for children and adolescents, requiring country level decision making to revolve around the optimization of scare resources in order to maximize health gains. A framework to aid priority setting is economic evaluation, which in turn, is dependent on the underlying methodological and modelling approach. This dissertation exists in the intersection of these concepts as it seeks to explore and enhance the representation of children and adolescents within the scope of EE frameworks for HTS strategies, with the underlying policy question being whether ILHIVT of children and adolescents can have a role in increasing the efficiency of HTS.

CEA is essential to identify the most impactful interventions in HIV programs, as funding is insufficient. High income countries have reduced their funding due to competing priorities such as the COVID-19 pandemic diverting resources from long-standing issues like HIV [41]. LMICs will bear the brunt of the HIV epidemic and struggle with funding their national HIV programs. CEA will help prioritize high-impact interventions. HIV programs have historically struggled to determine how to allocate funds between prevention/testing and treatment programs. CEA is a powerful tool for maximizing the impact of HIV funding but there are challenges due to data gaps (equity concerns) and threshold affordability [47]. CEA can also be a tool to advocate for more funding and investment into HIV programs, highlighting that the failure to act now will lead to higher costs in the future.

1.3 Scope of Thesis

This thesis contributes to the methodological considerations of future HTAs of HIV testing strategies in Zimbabwe. By focusing on children and adolescents, this thesis enhances knowledge around both economic evaluation methods and index-linked HIV testing through a health economics and infectious disease modelling lens. The underfunding of HIV programs addressing children and adolescent needs has led not only to a gap in overall outcomes progress, but of particular relevance to this thesis; underrepresentation in economic evaluations of HIV testing strategies in SSA. Timely diagnosis of HIV infection along with ART initiation has been shown to significantly reduce morbidity and mortality outcomes in children. Index-linked HIV testing (ILHIVT), whereby household and sexual contacts of an HIV positive individual are offered HIV testing, is a targeted strategy which may allow for the potential of economies of scope by increasing the efficiency of HTS, if offered as an additional strategy within the current HTS infrastructure. Children/adolescents living in households with HIV-positive caregivers are at a higher risk of being HIV positive themselves. By focusing on children of indexes, ILHIVT has the potential to increase identification and resulting yield compared to blanket (voluntary or provider initiated) HIV testing, due to low overall HIV prevalence of children in the general population. By exploring the effectiveness and cost of ILHIVT in Zimbabwean children and adolescents, a key piece of evidence, the financial considerations of implementing and expanding this strategy, may fuel the Ministry of Health to inform and alter HTS policy at a critical time. Thereby enabling this difficult to reach population to access care sooner, as opposed to only presenting with advanced HIV infection, potentially preventing growth failure (stunting and wasting) and respiratory disease, (accounting for more than 50% of HIV associated mortality) [48].

1.4 Rationale, Research Aims and Objectives

1.4.1. Research Rationale

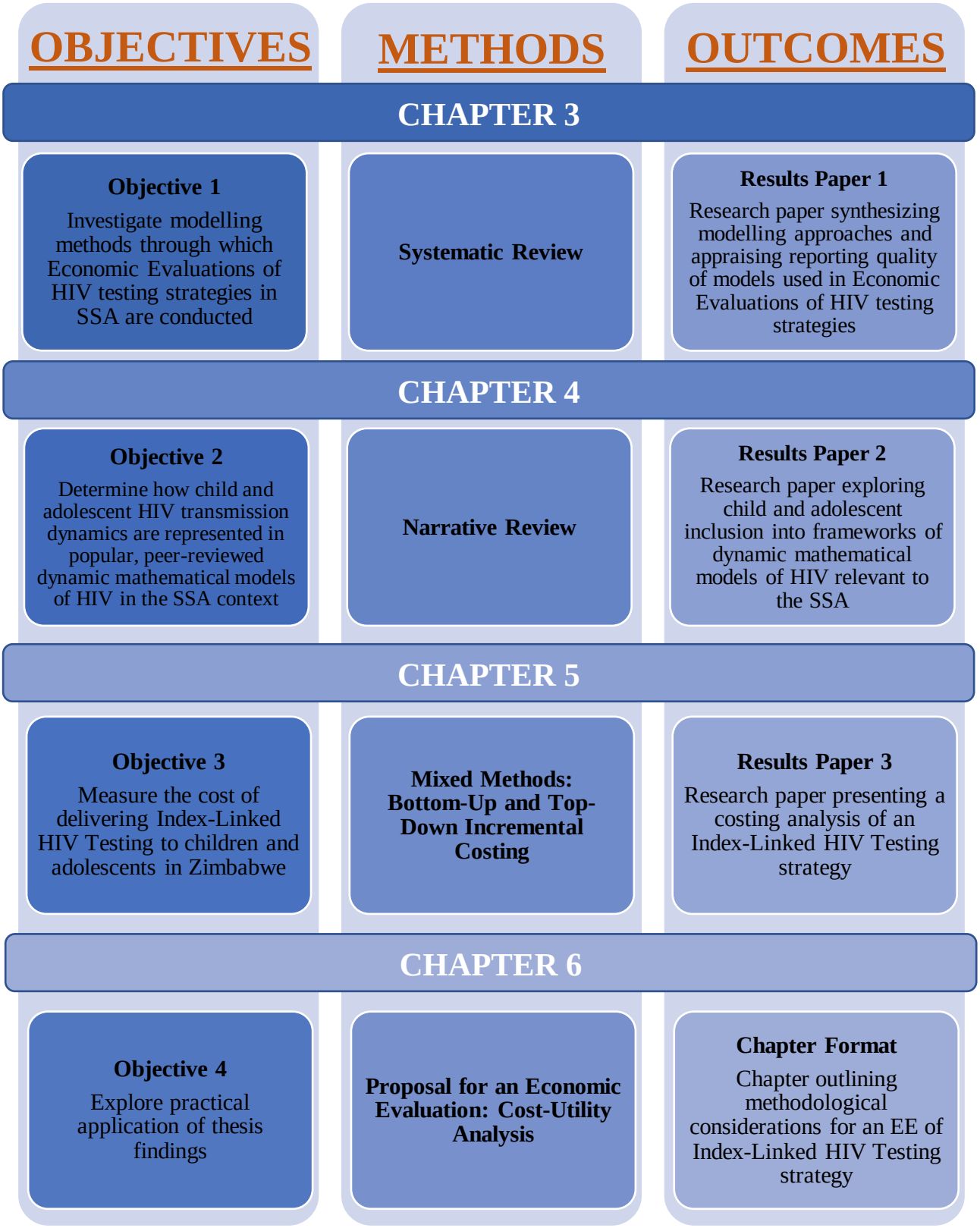
Disparity in the global HIV response targeting children and adolescents, compared to adults, resulting in gaps in HIV diagnosis, delayed treatment initiation and poorer outcomes, compared to adults, is widely recognized and cited by researchers and multilateral organizations alike. Funding, and thus, resource prioritization (and resulting policy and practice) are a root cause. HIV prevalence among children (compared to adults), is low and targeted strategies for testing may provide more value for money. ILHIVT has been shown to be a high yielding strategy for HIV testing in adults (i.e. partner notification) [49-51], but has not yet been thoroughly evaluated in children and adolescents; a search found only five other published studies investigating this strategy in children and adolescents [52]. Children and adolescents with a HIV positive parent or guardian are at higher risk of being positive themselves [51, 53,

54]. Thus, ILHIVT has the potential to identify high risk children and adolescents who might otherwise only be identified when presenting at clinic with advanced disease. This research will augment and endorse existing public health recommendations by the WHO to integrate ILHIVT into HIV program service delivery, and in doing so, contribute towards answering the question of whether ILHIVT of children and adolescents can help increase the efficiency of HTS in Zimbabwe.

1.4.2 Overall Aim and Specific Objectives

The overall aim of this thesis is to investigate, through generation and evaluation via 4 objectives (**C1, Figure 1**), methods around economic evaluation of HIV testing in children and adolescents within a Zimbabwean context.

- **Objective 1**: Investigate modelling methods through which Economic Evaluations of HIV testing strategies in SSA are conducted
    - Method: Systematic Review
    - Outcome: Research paper (**Results P1**) synthesizing modelling approaches and appraising reporting quality of models used in Economic Evaluations of HIV testing strategies which helps inform modelling approach for a future objective
- **Objective 2**: Determine how child and adolescent HIV transmission dynamics are represented in popular, peer-reviewed dynamic mathematical models of HIV in the SSA context
    - Method: Narrative Review
    - Outcome: Research paper (**Results P2**) detailing children and adolescents inclusion into frameworks of dynamic mathematical models of HIV relevant to the SSA are presented.
- **Objective 3**: Measure the cost of delivering Index-Linked HIV Testing to children and adolescents in Zimbabwe
    - Method: Bottom-Up and Top-Down Incremental Costing
    - Outcome: Research paper (**Results P3**) presenting the results of an incremental costing analysis of an Index-Linked HIV Testing strategy
- **Objective 4**: Integrate thesis findings into an actionable format
    - Method: Proposal for an Economic Evaluation of index-linked HIV testing in children and adolescents in Zimbabwe
    - Outcome: Thesis chapter presenting a proposal for an economic evaluation of an Index-Linked HIV testing strategy, using the findings of Results P1, P2 and P3



C1, Figure 2. Thesis Roadmap Outlining Objectives, Methods and Outcomes

1.5 Thesis Outline

This mixed paper-style thesis details the journey of navigating modelling methods of HIV testing strategies in sub-Saharan Africa (SSA), exploration of child and adolescent representation within mathematical models of HIV, costing an HIV testing intervention aimed at improving HIV uptake among children and adolescents, exploration of thesis application, and a discussion of future implications and next steps from the insights gleaned through this PhD. This thesis presents 3 results papers, bridged by an introduction, background, practical applications and discussion chapters.

Chapter 1, the introduction chapter, provides an overview of the economic burden of HIV and the corresponding role of HTAs. The conceptual framework highlights the major concepts relevant to this thesis, while carving out the space it operates in (scope of thesis). Then, research rationale, aims and objectives, along with the outline of the thesis and intellectual contributions are presented.

Chapter 2, the background chapter, provides a review of the literature on HIV relevant to this thesis. A global, epidemiological overview of HIV is presented along with trends and targets. HIV in focus – children and adolescents in SSA – along with HIV testing strategies and HIV within the Zimbabwean context are also highlighted.

Chapter 3, **Results P1**, is a systematic review paper accepted for publication detailing the modelling methods of economic evaluations of HIV testing strategies in SSA, currently in press at *Applied Health Economics and Health Policy*. The introduction of the chapter provides background information on economic evaluations, followed by the paper, and then a chapter discussion and conclusion. Chapter 3 addresses **Objective 1**.

Chapter 4, **Results P2**, presents the results of a narrative review of child and adolescent integration within well described, frequently used and cited dynamic mathematical models of HIV in the SSA context. This chapter will be reformatted for publication. Chapter 4 addresses **Objective 2**.

Chapter 5, **Results P3**, is a published paper describing the costing analysis of an index-linked HIV testing strategy delivered to children and adolescents in Zimbabwe. This paper has been published in *BMC Health Services Research* [55]. The introduction of the chapter provides background information on cost analysis, followed by the paper, and then a chapter discussion and conclusion. Chapter 5 addresses **Objective 3**.

Chapter 6 explores the practical application of thesis findings by presenting a proposal for an economic evaluation of index-linked HIV testing of children and adolescents in Zimbabwe. Chapter 6 addresses **Objective 4**.

Chapter 7 presents an overview of major findings and contributions to knowledge according to two categories: empirical evidence and methods. Thesis strengths and limitations, future considerations and policy implications are also discussed

1.6 Intellectual Contribution

This research was undertaken as part of Professor Ferrand's '*Bridging the Gap in HIV Testing and Care for Children in Zimbabwe'* (B-Gap) project, funded by the UK Medical Research Council, for which I led the costing related project deliverables. With the guidance and input of my supervisors Drs. Simms, Guinness and Maheswaran, **Results P1** and **Results P3** were conceptualized. I led the study design, data collection tools design, data collection, analysis and synthesis for both the systematic review (**Results P1)** and the costing analysis (**Results P3**). I conceptualized **Results P2** originally as a mathematical modelling framework all relevant corresponding components such as structure, ODEs and mixing matrices under the supervision of my primary supervisor (Dr. Simms), along with subject matter expert Dr. Foss. This eventually evolved into an investigation on how children and adolescents were included into modelling structural frameworks of some of the most popular, peer-reviewed mathematical models of HIV relevant to the SSA context, presented here as a narrative review.

I recruited my secondary reviewer and established operating procedures (**Results P1**), and recruited, trained and provided logistical support for my field work assistant (**Results P3**). I wrote the first and final drafts of all research papers (along with the proposal), included in this thesis and was responsible for journal submissions and addressing reviewer comments.

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CHAPTER 2 – BACKGROUND ON HIV IN CHILDREN AND ADOLESCENTS WITHIN SUB-SAHARAN AFRICA: LITERATURE REVIEW

2.1 INTRODUCTION

This chapter presents a brief overview of the epidemiology of HIV and background information related to the work conducted and presented in this thesis. The chapter begins with an accounting of the global burden of HIV, followed by global HIV targets and trends, an overview of HIV burden in children and adolescents, along with study specifics. The ways in which children and adolescents are defined vary throughout the literature and much overlap between categories exist. Both UNAIDS and WHO typically define adolescents as those aged 10-19, but also have other, non-mutually exclusive categorizations which encompass part or all of their definition of adolescents (ex. 'young people' or 'young adults' categorized as 10-24 years and 'youth' as 15-24) [1, 2]. In defining children however, there is notable discrepancy between UNAIDS and WHO, as the former defines children as individuals from birth to age 14 [3], while the later defines children as individuals from 0-9 years, 0-14 years, or 0-18 years [4]. (UNICEF defines children as any person under the age of 18 [5].) For the purpose of this thesis, children are generally defined as aged 0-14, with adolescents being defined as 10-19 year olds, in line with the way UNAIDS defines both of these sub-populations, mainly because UNAIDS will have the most specific and up to date estimates with regards to HIV, (while being mindful of the fact that the UNAIDS definition of children, overlaps with their definition of adolescents). Where deviation from these definitions is present, an explicit age range and definition will accompany the corresponding data.

2.2 GLOBAL BURDEN OF HIV: EPIDEMIC OVERVIEW

In 1981, due to an increasing number of young gay men in the United States dying from atypical opportunistic infections (Pneumocystis pneumonia) and rare malignancies (Kaposi's Sarcoma), Acquired Immune Deficiency Syndrome (AIDS) was officially recognized as a new and devastating infectious disease [6-10]. The causative agent, a lentivirus (a genus of retroviruses), human immunodeficiency virus type 1 (HIV-1), was identified and isolated shortly after (1983/1984) [8-12]. HIV-2, distantly related to HIV-1, (structurally similar but triggering a different antibody/immune response), was discovered to cause AIDS in West African patients in 1986 [9, 13]. Both strains have been traced to non-human primates [9]. Of the two HIV viruses, HIV-1 is responsible for propagating the ongoing HIV pandemic, accounting for more than 95% of infections worldwide, while HIV-2 is typically restricted to West Africa and relatively less pathogenic [9, 14, 15].

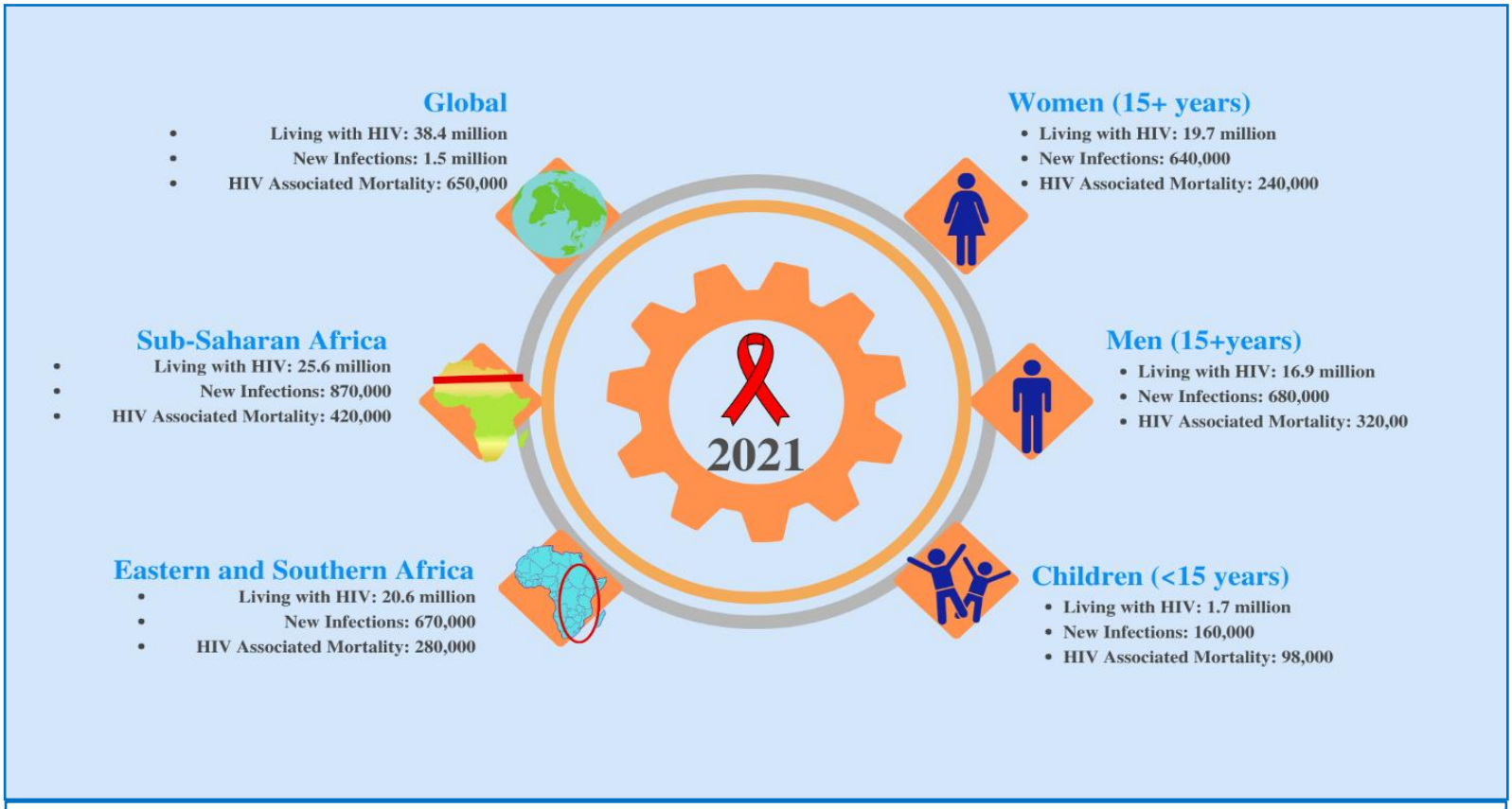
HIV is transmitted through viral permeation across mucosal surfaces through certain bodily fluid, (sexual contact, mother-to child), or via percutaneous inoculation (where needles puncture skin such as blood transfusions or injecting drug use), and is characterized by the progressive loss of immune function through the systemic targeting, attack and depletion of CD4 cells; the white blood cells responsible for fighting infection [9, 10, 16, 17]. If left untreated, the weakened immune system, unable to battle infections, becomes susceptible to a host of serious opportunistic infections and malignancies, progressing to AIDS and ultimately resulting in death [9, 10, 18, 19]. Forty years into the epidemic, 84.2 million people have acquired HIV, with approximately half (40.1 million) having died due to HIV infection [20]. At the end of 2021, 38.4 million including 1.7 million children (<15 years) were living with HIV worldwide, with 1.5 million newly infected and 650,000 having died from AIDS that year [20, 21] (**C2, Figure 1**).

The decline in new HIV infections, (down 54% since the peak in 1996), and AIDS-related deaths, (down 66% since the peak in 2004), is largely attributable to the strides made by global alliances and individual governments alike to increase public education and awareness, as well as systemically scale-up access to, and availability of, antiretroviral therapy (ART) [20, 22]. By curbing viral replication, ART has multifactorial effects on HIV, namely: 1.) onward transmission prevention; 2.) immune function restoration and retention; 3.) prevention of disease progression and thereby HIV-related morbidity and mortality [23]. If people living with HIV (PLHIV) are indefinitely and optimally adherent (defined as taking ≥95% of prescribed dose on schedule adherent) to ART [24-27], the added benefit of viral

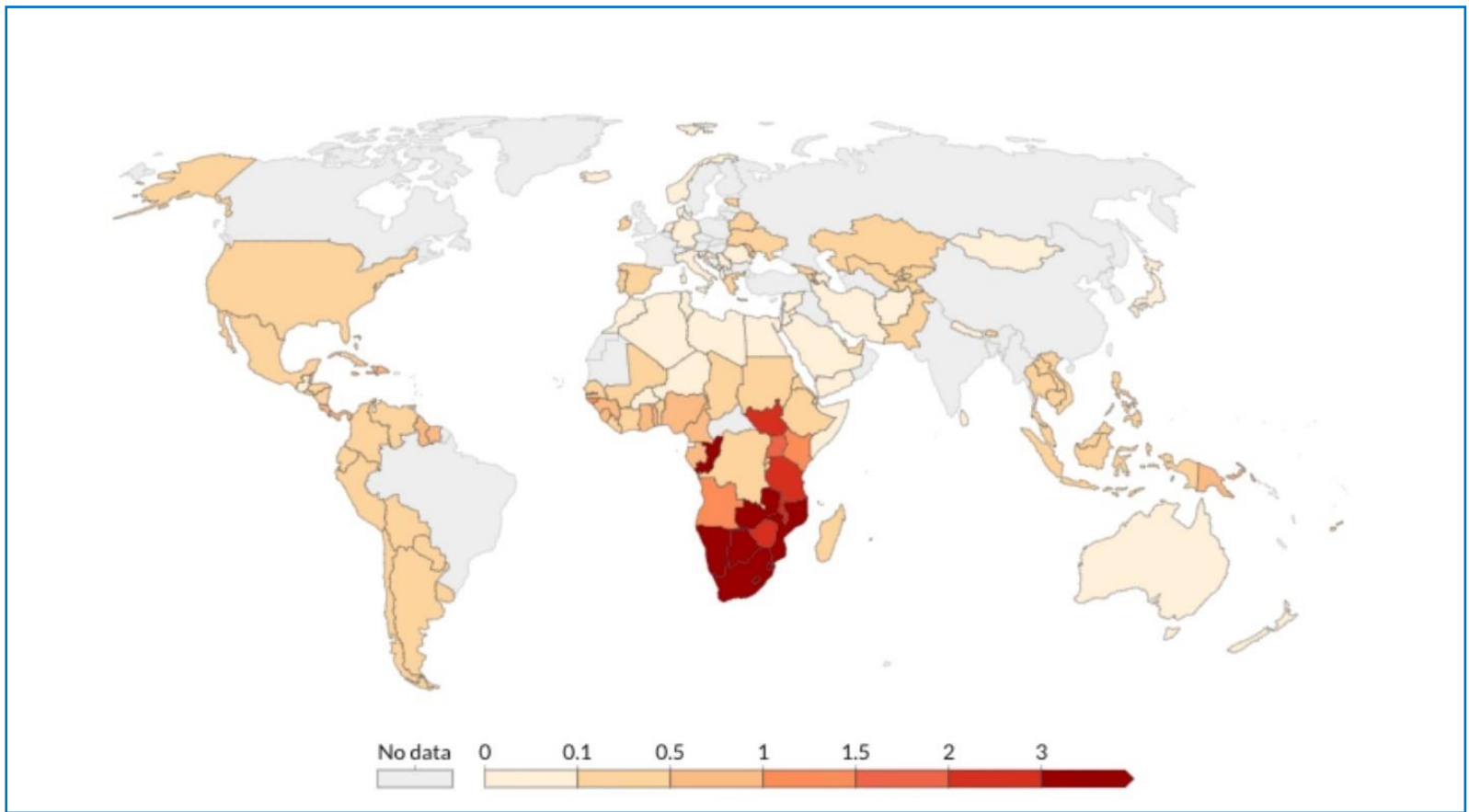
suppression ensures healthy longevity comparable to a HIV-negative individual [28-31]. In 2021, 75% of all PLHIV were accessing ART; 76% of adults (aged 15+) and 52% of children (aged 0-14) [20].
The size and shape of the HIV pandemic is heterogenous and varies across geographical settings both within and across countries. HIV epidemics are typically defined as either *concentrated* (>5% prevalence in at least one sub-or-key population, but below 1% in urban dwelling pregnant women), or *generalized* (firmly established via sustained transmission in the general population where HIV prevalence is consistently >1% in all pregnant women) [32, 33].

SSA, home to only 14.6% of the global population [34], is the epicenter of the HIV/AIDS pandemic and the region most heavily affected by HIV, accounting for two-thirds (67%) of the global burden of people living with HIV, and 60% of new HIV infections worldwide [21] (**C2, Figure 1&2**). SSA is on average, the poorest region in the world [35] and it was theorised that poverty has been the underlying driver of HIV infection in SSA, in line with the global norm where HIV is a disease of inequality and disproportionately affects the poor. However, in SSA the inverse appears to be true; both wealthier countries and wealthier individuals within SSA are at higher risk of HIV infection [36-40]. The strength of this association has attenuated over time, perhaps indicating an appending to the overall global HIV understanding [39, 40].

The SSA epidemic is largely driven through horizontal, heterosexual transmission along with a concomitant vertically transmitted epidemic in children, illustrated by the fact that 4 in 5 pediatric HIV infections in 2021 occurred in SSA [41, 42]. The distribution of new HIV infection acquisition in SSA, while less skewed towards key populations than the rest of the world (70% globally, 94% excluding SSA), is trending in that direction as 51% of new infections in SSA occurred in key populations in 2021: sex workers (15%); people who inject drugs (3%); gay men and other men who have sex with men (6%); transgender women (1%); clients of sex workers and sex partners of key populations (26%) [22]. Additionally, female adolescents and young people (AYP, aged 15-24) are disproportionately affected by HIV in SSA; in this region, female AYP are *3*-times more likely to acquire HIV, and twice as likely to be living with HIV, compared to their male counterparts [22].



C2, Figure 1. 2021 HIV Statistics Synopsis
(Data Source: UNAIDS 2022 Global HIV & AIDS Statistics – Fact Sheet; WHO 2022 – Key Facts HIV)



C2, Figure 2. 2020 HIV Incidence Among Uninfected Adult Population (15 – 49 years), per 1,000 uninfected persons
(Image Retrieved from: https://ourworldindata.org/hiv-aids)

2.3 Global HIV Trends and Targets

Fuelled by achieving the 2015 Millennium Development Goal to reverse the spread of HIV/AIDS (new infections fell by 40% between 2000 and 2013) [43, 44], and increasing access to HIV treatment for those in need (having reached 13.6 million people, an increase from 800,000 in 2003) [43], UN member states committed to ending the AIDS epidemic by 2030 [45, 46]. The accompanying fast-track strategies target rapid and sustained scale-up of HIV services resulting in tandem progress on both the HIV testing and treatment fronts [45, 46]. The global 2020 fast track strategies aimed at diagnosing 90% of all people living with HIV, providing ART for 90% of all those diagnosed, and achieving viral suppression in 90% of those on treatment (all increased to 95% by 2025). While remarkable gains in HIV testing and treatment were made, the 90-90-90 targets were not met, largely due to underinvestment in low-and middle-income countries' (LMIC) HIV response [44, 47]. As of December 2021, 85% of people living with HIV were aware of their status, 88% of those aware of their status were on ART, and 92% of those on ART were virally suppressed [20]. Per UNAIDS, the global community is not on track to reach the majority of the 2025 targets, particularly any of the targets related to HIV prevention [22, 44].

In the face of the COVID-19 pandemic, the global HIV response suffered as a result of constrained resources due to resource relocation, as well as disruption to established services, all while the gap in inequalities and vulnerabilities expanded [22]. Testing and treatment services stalled and 2021 saw the smallest increase of people on treatment since 2009 [22]. HIV infections have fallen by 32% since 2010, however the current trajectory is nowhere near substantial enough to achieve 2025 targets (of 370,000 new infections) [22]. While infections continued to fall worldwide during the pandemic, the decline witnessed in 2021 (only a 3.6% drop since 2020) was the smallest reduction since 2016; at the current rate of infection, [4000 people daily], three times more people than initially targeted for 2025, will be infected [22]. In some regions, the continuing rise in new HIV infections could off-set or even reverse progress made against AIDS-related deaths [22]. Over the last decade, investment into HIV responses of LMICs have been primarily funded by both public and private domestic funding [47]. In 2020, collective resource availability was 29% lower than necessary and targeted for that year [47]. Coupled with donors decreasing international assistance for HIV/AIDS, LMICs, already taxed and struggling due to the economic burden triggered by the COVID-19 pandemic, unlike previous years, were unable to counterbalance the loss of international funding [22]. The resulting threats to financing have left LMICs and their subsequent HIV responses short of 8 billion USD needed to achieve global targets by 2025 [20].

The expansion of universal HIV testing followed by immediate ART – (HIV universal test and treat policy) – to localized clinics in SSA reshaped and accelerated the transition of the HIV/AIDS epidemic

curve from a declining epidemic phase, towards endemicity (in marginalized key populations) and elimination [31, 48]. In SSA, as HIV services expanded over the last decade, subsequent and substantial progress was made towards achieving global targets for ending the AIDS epidemic [22, 31, 47]. Within SSA, ESA and WCA sub-regions have met these targets at variable rates however. ESA is home to 54% of all people living with HIV (i.e. 20.6 million people), and two-thirds of all children living with HIV [22, 47]. ESA accounts for 29% of resource needs among all LMICs in achieving 2025 targets [47]. The strategic investment of bilateral domestic and international funding resulted in "the strongest progress against the HIV epidemic since 2010" of any region [22, 47]. The complete '90-90-90 by 2020' targets were achieved by 6 countries in the region (Botswana, Eswatini, Malawi, Rwanda, Zambia and Zimbabwe) [22]. However, given that fewer HIV tests were conducted in the region in 2020 and 2021, compared to 2019, the ability to achieve the first-95 is in question, jeopardizing the ability to end AIDS by 2030 [22].

While the net increase of people on treatment worldwide in 2021 was the smallest since 2009, WCA comprised the largest increase in treatment coverage globally for the year thereby equalizing rates between ESA and WSA; 78% of all people living with HIV are on treatment in both sub-regions[22]. Resource shortfalls supplemented by reliance on out-of-pocket user fees (for health services) may be the cause of slower overall progress in curtailing HIV incidence and AIDS-related mortality in WCA[47], as there are no reports of any countries in the region having achieved the '90-90-90' targets. Despite progress being made – (80% awareness of HIV status, 98% of those with knowledge of their status accessing treatment, 69% of who are virally supressed) – children in this region especially are being left behind; as of 2021, only 35% had access to ART [22].

The inequalities brought about due to HIV related stigma and discrimination are at the root of the gaps and disparities in HIV testing and treatment; bridging these gaps is the only way to achieve the 95-95-95 targets and end AIDS by 2030 [22, 47, 49]. A pathway to doing so requires efforts to be specifically targeted towards men and youth via unique and innovative methods to increase accessibility and engagement with testing while facilitating linkage to and retention in HIV care [22, 44, 47, 50, 51].

2.4. HIV in Focus

Despite substantial efforts resulting in life-saving interventions, per UNAIDS, "progress against HIV remains acutely inadequate among priority populations such as children, adolescent girls and young women in SSA" [44]. The success of prevention of mother to child transmission of HIV (PMTCT)

programs, and resulting gaps, along with the capacity of individual health systems to find and link children to HIV care – i.e. HIV testing and treatment coverage – is the pathway through which child and (pre-sexual debut attributed) adolescent infections are either acquired or prevented.

Mother-to-child transmission of HIV (MTCT) accounts for over 90% of pediatric HIV infections [52, 53]. Without ART, 15-35% of vertically infected infants die within the first year of life, 50% by age two, and 80% by the age of 5 [42, 54, 55]. While the scale-up of PMTCT programs has contributed to a substantial decline in MTCT globally, it has not been enough to meet the threshold of 2% – 5% (in non-breastfeeding and breastfeeding countries respectively), needed for the pathway towards eliminating MTCT [42]. Halting transmission of new pediatric HIV infections, (by eliminating MTCT), is entirely possible and crucial to improving child health and survival.

In the absence of intervention, the probability of vertical transmission – HIV spread from a HIV positive mother to her child in-utero, intrapartum (labour and delivery) or postpartum (breastfeeding) – is 15 – 45% [42, 56-58]. With the discovery of a 67.5% reduction in MTCT through antiretroviral (ARV) administration (of Zidovudine) antepartum/intrapartum to the mother, and for a period of 6 weeks to the infant after birth [59], recommendations for the use of ARVs to prevent mother-to-child transmission of HIV were first issued by the WHO in 2000 [60]. Spanning a little over a decade, PMTCT strategies have undergone substantial transformation (Option A, Option B, Option B+, universal test and treat), ensuring the provision of lifelong triple ART to all pregnant and breast-feeding mothers, irrespective of CD4 count, along with ARV prophylaxis in infants for 4-6 weeks from birth [60-63]. The impact of PMTCT programs has been lauded as “one of the greatest public health achievements of recent times”[61], as 2.9 million HIV infections and 1.5 million deaths have been averted among pregnant women and children since their commencement (in 2000) [42].

A multi-partnered global campaign launched in 2011 prioritized the elimination of MTCT of HIV (i.e. a 90% reduction in new HIV infections in children), with a specific spotlight on 21 SSA countries (and India), who together, accounted for 90% of pregnant HIV positive women globally in need of PMTCT services [64]. A decade since the start of the campaign ART coverage in this population increased from 46% to 81% globally, (29% to 60% in WCA, and 51% to 89% in ESA), while MTCT transmission rates have fallen to 12% (from 24%) worldwide and new HIV infections in children under 5 declined by 50% globally [42, 53, 65]. As of the 2023 global UNAIDS AIDS update, ART coverage amongst pregnant women living with HIV in ESA has further increased to 93% [8], while MTCT rates in SSA are as low as 10%, 7% in ESA, and 8% in Zimbabwe [42].

Despite these successes, in 2023, approximately 190,000 pregnant women living with HIV were not receiving treatment, (58% of whom were in WCA and 23% of whom were in ESA) [66]. While substantial progress in mitigating new HIV infections in children has been made, gaps in PMTCT programs and ART coverage among pregnant women in ESA and WCA especially, mean that preventable vertical transmission is not being halted, resulting in 120,000 new child acquired HIV infections in 2023 [66]. Compounding the issue, the HIV response is plagued by persistent disparities between children and adults [66]. Testing and treatment coverage among children is markedly lower compared to their adult counterparts [66]. In 2023, approximately 86% of people living with HIV worldwide knew their HIV status, compared to only 66% of children aged 0-14 [66]. Of the 1.4 million children (0-14 years) living with HIV, 43% were not receiving treatment (compared to 23% of adults); the disparity in viral suppression rates among children, 48%, compared to 73% in adults, was even greater [66]. Additionally, 1 in 8 individuals who died due to AIDS in 2023 was a child aged 0-14 years [66]. The largest barrier children face in receiving antiretroviral therapy is timely identification and diagnosis [66].

Similar to children aged 0-14, adolescents aged 15-19 are constantly falling behind their adult counterparts with regards to achieving the 95-95-95 targets. While intensified efforts to reduce HIV among adolescents has been successful, in 2023, 36% of 15-19 year olds living with HIV were still not receiving ART [66]. Worryingly, adolescent girls and young women (aged 15-24) are disproportionately affected by HIV, experiencing a 3-times higher HIV incidence rate compared to their male counterparts [66]. Unsurprising then, the 2025 target of reducing new HIV infections among adolescent girls and young women (aged 15-24), is wildly off track [66]. Capitalizing on multipurpose prevention efforts such as a combination contraception with PrEP, along with prioritizing HIV risk reduction education and services which improves condom usage, reduction in number of sexual partner/concurrent partnerships, and increases knowledge to consistently seek out HIV testing services, may help address the disproportionate HIV risk female adolescents and young women in SSA, are subject to [66].

2.5 The B-Gap Study

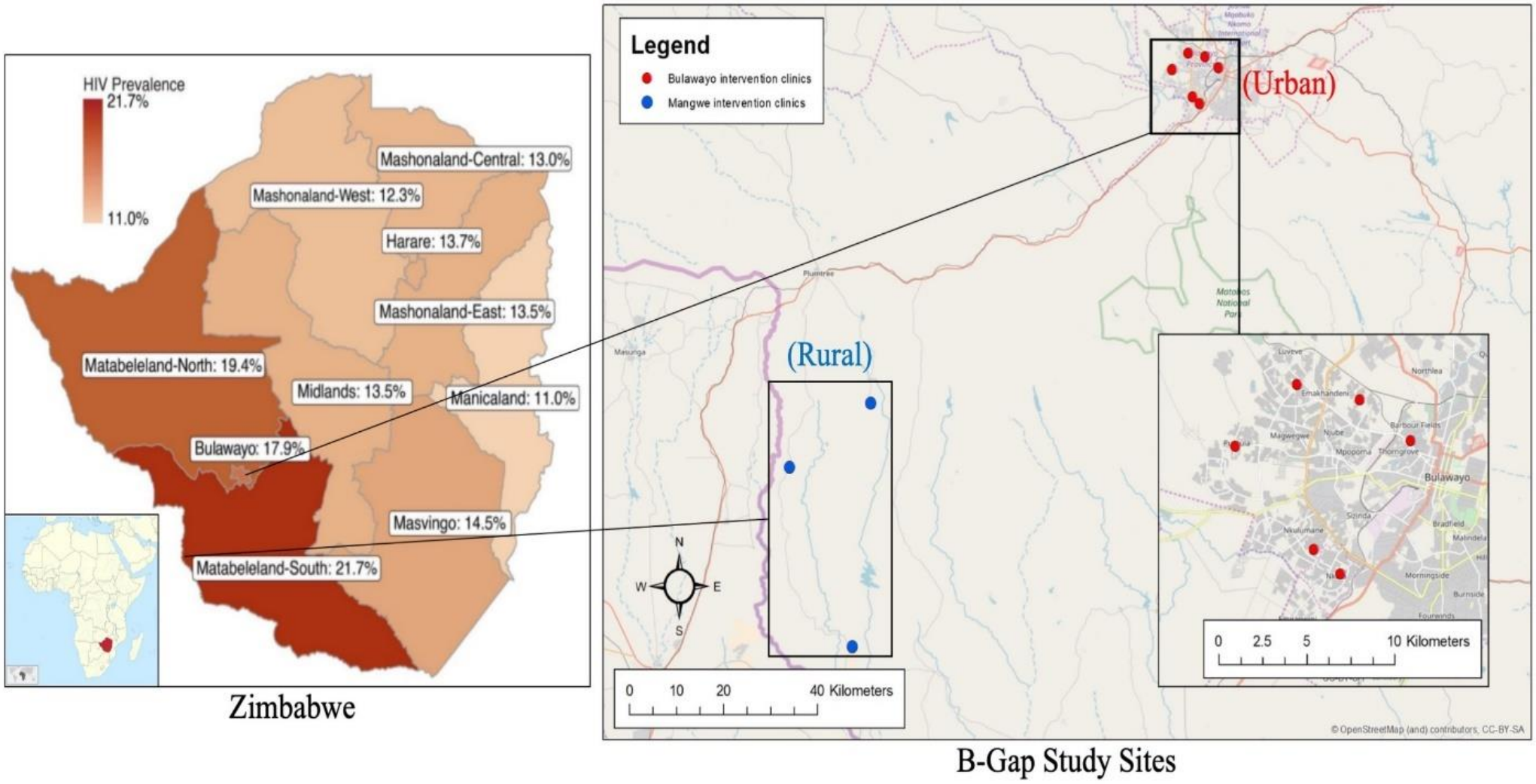
A potential solution to addressing the disparity in child and adolescent engagement with HIV testing and care, and thus, a method to identify and diagnose children and adolescents living with HIV, is index-linked testing. The *Bridging the Gap in HIV Testing and Care for Children and Adolescents in Zimbabwe* **(**B-Gap) study offered index-linked HIV testing (ILHIVT) and serves as the practical underpinnings of this thesis. A community-based, multi-component intervention aimed at improving uptake of HIV testing and engagement with HIV care services among individuals aged 2-18, B-Gap sought to provide and

strengthen support to children and adolescents along various points of the HIV care continuum, with the goal of improving HIV related outcomes, ultimately, leading to viral suppression [66, 67]. The study setting was Bulawayo, (highest adult HIV prevalence in an urban setting in Zimbabwe), and Mangwe (rural setting in Matabeleland South Province with the highest national HIV prevalence in the country). Nine of the 37 possible primary health care facilities in Bulawayo (6 study sites) and Matabeleland South provinces (3 study sites) were chosen which did not employ an index-linked HIV testing strategy, had a sizable (more than 900 adults) index population receiving HIV care, and in rural settings, and could be reasonably accessed by research assistants (RA) [66] (**C2, Figure 3**).

Every HIV positive adult in care at these clinics was offered 3 options for testing any children and adolescents of unknown HIV status in their household: 1.) in clinic (facility-based); 2.) at home by research assistant (community-based); 3.) at home by caregiver using an oral mucosal transudate test (assisted self-testing). Any children who were diagnosed with HIV were linked to a community health worker who delivered 5 core support sessions at the household, the first of which was initiated within a month of diagnosis, and the remaining at 6 weeks, 3, 6 and then 12 months. (If optional support sessions were necessary, an additional 2 sessions were included within the 12 month span). Children diagnosed with HIV were also initiated onto care at their nearest healthcare facility as part of standard of care. Finally, 12 months post diagnosis, a blood sample was collected to determine whether viral suppression has been achieved. The study utilized principles of effective alternative identification and management of HIV recommended by the WHO; namely to offer ILHIVT to household members including children of a known HIV-positive individual to address gaps in testing, and to utilize lay workers to scale uptake and offset costs of HIV testing [68, 69].

A total of 9927 individuals in care were screened at the 9 study sites in 2018, where 2870 eligible index cases were identified, as they had at least one child eligible for HIV testing within the household[67]. A 60% uptake of HIV testing among all eligible children resulted in 3638 children/adolescents – (2322 in urban and 1316 in rural settings) – being tested through the index-linked modality [67]. Reasons for not testing were unsuccessful tracing (i.e. unable to find and contact child/adolescent), and age-related consent barriers when the index was not the child's legal guardian. Among 3638 children/adolescents tested, 39 tested HIV positive resulting in a yield of 1.1%, much lower than anticipated, and indicated in other studies both within Zimbabwe and SSA[67, 70-75]. Facility-based ILHIVT was the preferred modality of testing among indexes, yet there was a higher probability of the child/adolescent being tested if community-based testing (in the home) was chosen [67]. Possible reasons for low HIV positivity rate ascertained in this study include saturation of testing within the study catchment due to a sustained testing

initiative by Population Services International in the area, increased coverage of PMTCT programs in Zimbabwe, or that ILHIVT alone is not enough to identify ‘hard-to-reach’ children/adolescents [67, 76].



C2, Figure 3. B-Gap Study Sites, utilizing 9 of 37 primary health care facilities in Bulawayo and Matabeleland South Province. Study sites spread across Bulawayo (6, urban setting) and Mangwe (3, rural setting).

(Image 1 – Map of Zimbabwe according to Regional HIV Prevalence – Retrieved from: https://phia.icap.columbia.edu/wp-content/uploads/2019/08/ZIMPHIA-Final-Report_integrated_Web-1.pdf)

(Image 2 – B-Gap Study Sites – Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6615786/#R12)

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CHAPTER 3 – RESULTS PAPER 1 (P1) – SYSTEMATIC REVIEW OF MODELLING APPROACHES IN ECONOMIC EVALUATIONS (EES) OF HIV TESTING STRATEGIES

Overview of Chapter 3 (Results P1)

This chapter is the first of the three results chapters of this thesis and presents the findings of a systematic review conducted to understand modelling approaches in EEs of HIV testing strategies conducted in SSA.

Evidence Before this Study

There is a growing body of EE literature concerned with assessing existing and emerging HIV testing strategies. There have also been attempts to systematically identify and categorize the cost-effectiveness of other HIV prevention strategies. No systematic review thus far has consolidated HIV testing strategies in sub-Saharan Africa.

Added Value of this Study

The information presented in this chapter is of value to researchers as it will help strengthen the confidence and generalizability of future EE findings concerning emerging HIV testing strategies, urgently needed to achieve the first 95 HIV target by 2030.

Contribution to the Larger Body of Evidence

This review is the first to consolidate and synthesize economic evaluations (EEs) of HIV testing strategies in sub-Saharan Africa. This paper has been accepted for publication in *Applied Health Economics and Health Policy*.

3.1 INTRODUCTION

This chapter presents background information on Economic Evaluation relevant to this thesis. In particular, this chapter seeks to understand how EEs of HIV testing strategies in SSA are typically modelled. The chapter begins by providing a brief overview of EEs in the context of public health decision making, followed by a summary of the various EE methodologies. The systematic review of modelling approaches in EEs of HIV testing strategies in SSA and accompanying appendices (Results P1), as accepted for publication in *Applied Health Economics and Health Policy* are then presented, followed by a brief discussion and summation of the chapter as it pertains to implications for this thesis.

3.2 BACKGROUND

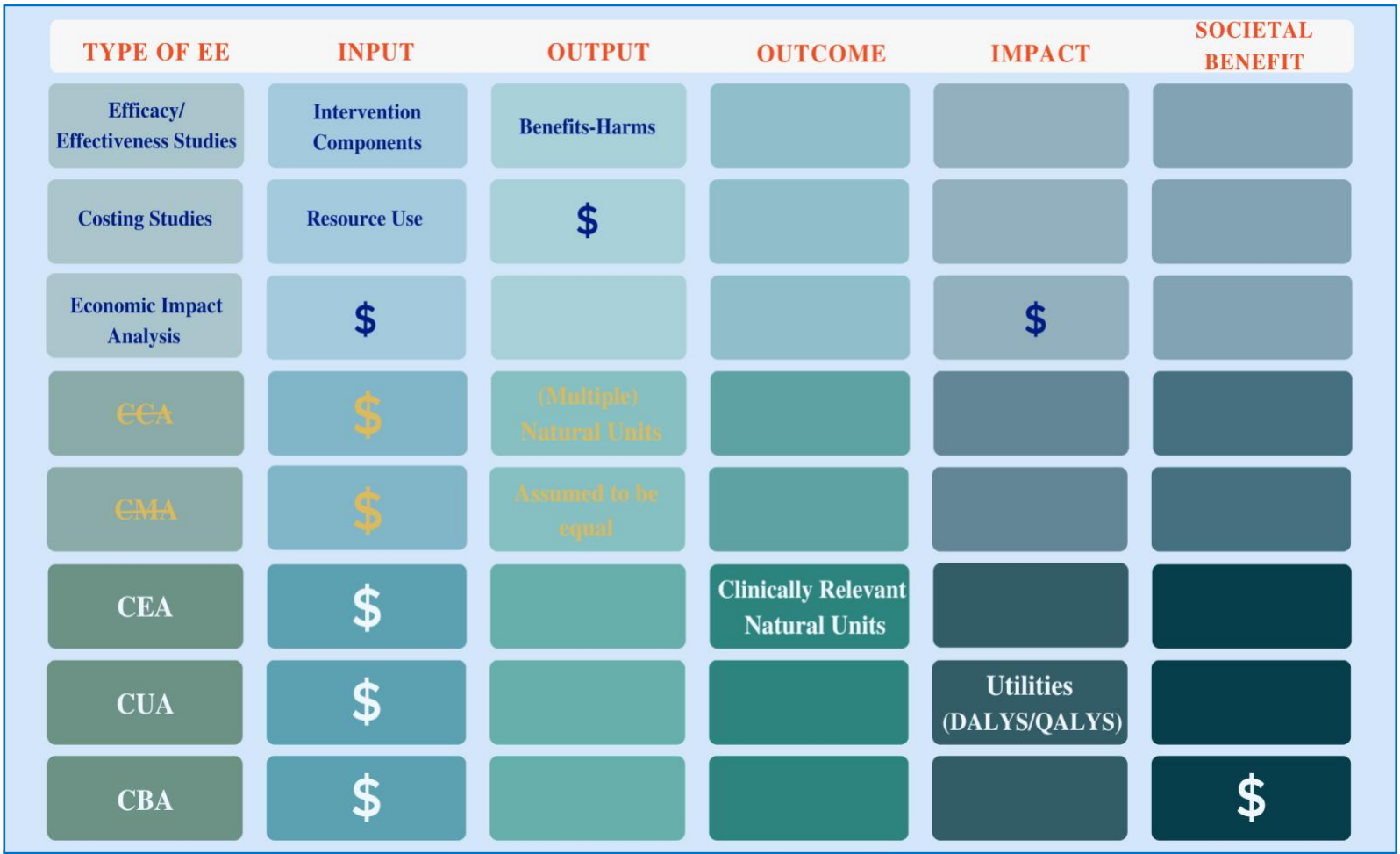
Public health decision making and priority setting involves understanding the costs and subsequent consequences, (i.e. health effects), of current and emerging technologies, interventions, treatments and programs, and allocating health care resources accordingly [1]. Policymakers are inclined to fund and implement specific health intervention, over others where the greatest benefit, at the lowest costs are demonstrated.

Economic evaluation (EE) provides a systematic and structured framework in which the efficiency of alternative courses of action can be measured and compared over time and across populations, leading to a better understanding of how health care resource expenditure should be prioritized [1-3]. While not the only input of health technology assessment, Budget Impact Analysis which assesses the expected change in a designated budget due to adoption or implementation of a particular intervention, programmatic feasibility and sustainability, impact on health status equity are among others; EE can be a useful and comprehensive starting point, and tool for policy implementation[4-6]. When deciding how to allocate finite resources, interventions maximizing health impact while representing the best value for money are chosen [1-3]. For this reason, incremental cost-effectiveness ratio (ICER), the output of EEs which quantifies additional health gained, resulting from expenditure of an additional unit of resource, is a core consideration in health care related decision-making [1-3].

Economic evaluation methodology varies according to the question being posed, the audience it seeks to inform, the outputs of interest, and data availability. There are five types of full economic evaluations, considered as such because they value both costs and outputs of a specific program, service or intervention compared to an alternative [2]. The common denominator between these types of evaluations is the format in which they approach costs, with differences lying in the way they assess and value benefits[2]:

- Cost Minimization Analysis (CMA): Cost per course of treatment where alternatives produce equivalent clinical effectiveness.
- Cost-Consequence Analysis (CCA): Cost per associated, disaggregated, consequences of an intervention, compared to its alternatives.
- Cost Effectiveness Analysis (CEA): Cost per resulting intended effect of an intervention, compared to its alternatives.
- Cost Utility Analysis (CUA): Cost per quality of life measure gained, resulting from an intervention, compared to its alternatives.
- Cost Benefit Analysis (CBA): Cost per policy decision compared to the opportunity costs.

In recent years, CMA is rarely used because of its restrictive criteria and limited applicability. Similarly, CCA while useful for facilitating transparent decision-making, does not produce an output which is succinctly summarized into one comparable measure. CBA, CEA and its subset, CUA, are therefore the most commonly executed forms of full economic evaluations. Economic impact analyses (cost-of illness analysis/burden of illness), which estimates the total costs incurred by a disease to a public health model, costing studies, which only examine the associated costs of an intervention or program compared to another, and both efficacy and effectiveness studies, which only examine the outcomes of an intervention or program, are all considered partial economic evaluations [1]. A comparison of EE methodology according to inputs and outputs is illustrated below (**C3, Figure 1)**.



C3, Figure 1. Economic Evaluation Methodology – Type and Associated Outputs

Partial EE methodology denoted by first three semi-transparent rows:

- Efficacy/Effectiveness studies which evaluate consequences of alternatives, but not costs;
- Costing studies which evaluate costs of alternatives, but not consequences;
- Economic Impact Analysis which evaluates total economic burden of a specific disease to society, but not compared to an alternative.

Full EE methodology delineated by:

- Demoted approaches – CCA and CMA – in yellow font;
- Commonly used approaches – CEA, CUA and CBA – in white font.

As outlined in the previous chapter, HIV testing is a necessary and crucial first step to accessing treatment. Despite efficiency gains such as increasing access to HIV testing through strategies such as HIVST and community outreach, further innovation and cost-effective strategies are needed to achieve the first UNAIDS target of 95% status awareness of those living with HIV by 2030. Cost-effectiveness data is only as reliable as the model and analysis used to generate these data. Appropriate methodology and modelling approach is therefore of importance to future EEs of HIV testing strategies and speaks to the relevance of the first objective of this thesis; *to investigate modelling methods through which Economic Evaluations of HIV testing strategies in SSA are conducted.*

3.3 RESULTS P1 COVER SHEET

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed <u>for each</u> research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1604189	**Title**	Ms
First Name(s)	Arthi		
Surname/Family Name	Vasantharoopan		
Thesis Title	Economic Evaluation Methods for HIV Testing of Children and Adolescents in Zimbabwe		
Primary Supervisor	Dr. Victoria Simms		

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?			
When was the work published?			
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?*	**No**	Was the work subject to academic peer review?	**Yes**

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Applied Health Economics and Health Policy Accepted for publication: Dec 04, 2022

Please list the paper's authors in the intended authorship order:	Arthi Vasantharoopan, Victoria Simms, Yuyen Chan, Lorna Guinness, Hendramoorthy Maheswaran
Stage of publication	**In press**

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)	I am the first author of this paper and wrote the first and final drafts. With the oversight and input of my PhD supervisors, I conceptualized the study, developed methods and data collection tools, and analyzed data. I also conducted primary data collection. Additionally, I was responsible for manuscript submission and addressing peer-review comments.

SECTION E

Student Signature	Arthi Vasantharoopan
Date	Jan 11, 2023

Supervisor Signature	Victoria Simms
Date	12 Jan 2023

3.4 RESULTS P1

Modelling Methods of Economic Evaluations of HIV Testing Strategies in sub-Saharan Africa: A Systematic Review

Systematic Review of Modelling Approaches in EEs of HIV Testing Strategies in SSA

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ABSTRACT

Background

Economic evaluations (EEs), a decision-support tool for policy makers, will be crucial in planning and tailoring HIV prevention and treatment strategies especially in the wake of stalled and decreasing funding for the global HIV response. As HIV testing and treatment coverage increase, case-identification becomes increasingly difficult and costly. Determining which subset of the population these strategies should be targeted to, becomes of vital importance as well. Generating quality economic evidence begins with the validity of the modelling approach and the model structure employed. This study synthesizes and critiques the reporting around modelling methodology of economic models in the evaluation of HIV testing strategies in sub-Saharan Africa (SSA).

Methods

The following databases were searched from Jan 2000 – Sept 2020: Medline, Embase, Scopus, EconLit and Global Health. Any model-based EE of a unique HIV testing strategy conducted in SSA presenting a cost-effectiveness measure published from 2013 onwards was eligible. Data were extracted around three components: general study characteristics; EE design; and quality of model reporting using a novel tool developed for the purposes of this study.

Results

A total of 21 studies were included; 10 cost-effectiveness analysis, 11 cost-utility analysis. All but one study was conducted in Eastern and Southern Africa. Modelling approaches for HIV testing strategies can be broadly characterized as static aggregate models (3/21); static individual models (6/21); dynamic aggregate models (5/21); dynamic individual models (7/21). Adequate reporting around data handling was the highest of the three categories assessed (74%), and model validation, the lowest (45%). Limitations to model structure, justification of chosen time horizon and cycle length, and description of external model validation process, were all adequately reported in less than 40% of studies. The predominant limitation of this review relates to the potential implications of the narrow inclusion criteria.

Conclusions

This review is the first to synthesize EEs of HIV testing strategies in SSA. The majority of models exhibited dynamic, stochastic and individual properties. Model reporting against the 13 criteria in our novel tool was mixed. Future model-based EEs of HIV testing strategies would benefit from transparency around choice of modelling approach, model structure, data handling procedures and model validation techniques.

Keywords: HIV; HIV testing; HIV modelling; Economic Evaluation; sub-Saharan Africa

Systematic Review Registration: CRD42020199170

Word Count: 355

KEY POINTS FOR DECISION MAKERS

- With the aim of assessing modelling approaches only, (and not the overall quality of the economic evaluation), this review is the first to consolidate and synthesize economic evaluations (EEs) of HIV testing strategies in sub-Saharan Africa.
- Chosen EE methodological approach was essentially evenly split amongst cost-effectiveness analysis and cost-utility analysis; the majority of models exhibited dynamic, stochastic and individual properties.
- Future model-based EEs of HIV testing strategies would benefit from transparency around choice of modelling approach, model structure, data handling procedures and model validation techniques.

BACKGROUND

Globally, 38.4 million people are living with HIV, with the burden of disease concentrated in sub-Saharan Africa (SSA) [1, 2] . The UNAIDS 95-95-95 HIV targets – diagnosing 95% of people living with HIV (PLHIV), providing treatment for 95% of those diagnosed, and achieving viral suppression in 95% of those on treatment by 2030 – have helped galvanize testing and treatment efforts since launched in 2014 [3]. Many countries in Eastern and Southern Africa (ESA) have successfully achieved the second and third 95 treatment targets, (with 98% of the West and Central African (WCA) region having achieved the second 95 target). However no country in SSA has met the first 95 (testing) target of having over 95% of PLHIV knowing their status [4]. (Six countries in ESA had achieved at least 90% awareness of HIV status by 2020, and by 2021 80% of PLHIV in WCA knew their status [4].)

HIV testing is the cornerstone of HIV prevention, the conduit to treatment and control, and a key component to ending the HIV/AIDS pandemic. Yet barriers to uptake of HIV testing exist among key populations and demographics in SSA, preventing not only the success of achieving the first 95 HIV target, but access to the HIV care continuum as well. Low socioeconomic status (SES) related barriers such as poverty and poor educational attainment are associated with a lack of HIV knowledge and awareness [5, 6]. Amplified by structural barriers such as large distances to clinics in rural settings, lack of transportation affordability or financial constraints preventing time-off from work, low SES is associated with poor access to, and uptake of, HIV testing services [6, 7]. HIV testing rates in men compared to women are low in SSA. Low HIV risk perception, or conversely engaging in risky sexual behavior, the subsequent fear of a positive HIV status, the lack of trust in healthcare workers' ability to keep status confidential, and the associated stigma of a positive diagnosis are some of the perceived barriers to increasing engagement with HIV testing services in men, in this region [6, 8]. These same challenges, along with the criminalization of sex work and homosexuality have been cited as impediments to accessing HIV testing services among female sex workers, men who have sex with men and transgendered women in the region as well [9, 10]. Legal barriers, i.e. age of consent to access HIV testing independently, compounds to the social and structural barriers preventing HIV testing among adolescents [11, 12]. With domestic funding and international bilateral donations for the HIV response having declined during the pandemic [4], determining and routinely implementing HIV testing strategies capable of reaching and engaging these holdouts, while achieving the greatest benefits at the lowest cost, is urgently needed [13].

Economic evaluation (EE) provides a framework to support decision making by comparing the costs and consequences of a program or health intervention to decide whether it represents value for money [14], and are either trial- or model-based [15]. Model-based EEs are particularly relevant to infectious diseases

and numerous modelling approaches are used, ranging from decision trees to static state transition models, (i.e. Markov models, microsimulations), to more complex dynamic models, [i.e. compartmental/transmission models, agent-based models, and discrete event simulations (DES)] [16-18]. The quality of evidence generated by EEs is highly dependent on the validity, accuracy and appropriateness of the model and its inputs. While there is guidance in the literature for model selection [16, 17], the lack of transparency involved in the choice of a modelling approach has been noted [19, 20]. Systematic reviews of EEs of prevention of mother-to-child transmission (PMTCT) and pre-exposure prophylaxis (PrEP) highlight the range of modelling approaches used [21, 22]. Regarding EEs of HIV testing strategies however, no review has been carried out on the various modelling approaches applied, and therefore little is known about the strengths and weaknesses of the different methods within this context. As such, the aim of this systematic review was not to evaluate the expected costs and health gains of HIV testing interventions, but instead, assess the state of the science surrounding model-based EEs of HIV testing strategies conducted in SSA in recent years, by synthesizing and critiquing their reporting of modelling methods. To this end, this review summarized EE methodology employed, identified modelling approaches taken and appraised reporting quality of models used for the decision problem.

METHODS

Protocol and Registration

This study was designed in accordance with the *Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols* (PRISMA) checklist [23]. The protocol for this study was registered in advance on PROSPERO (CRD42020199170).

Information Sources

Database selection was informed from previous research around efficient combination of databases for identification of EEs in SSA [24]. Medline, Embase and Scopus were chosen. EconLit (a general economics database), and Global Health (focusing on international public health) were also searched, due to the focus of this systematic review being EEs of HIV testing strategies in SSA.

Search Strategy

The full search strategy is provided in **Appendix** I. The search strategy was derived from the 4 core concepts relevant to this systematic review: HIV; Testing; Modelling; Economic Evaluation. This strategy underwent a peer-review of systematic review search strategies (PRESS) by LSHTM librarians and

information specialists. Results were retrieved by combining search terms for the core concepts, accounting for syntax and MeSH terms in all databases, where applicable.

Eligibility Criteria

Any model-based retrospective or prospective EE of a HIV testing strategy which presented a cost-effectiveness estimate (e.g. cost per DALY/QALY/life year saved/infection averted/positive case identified/HIV death averted), when comparing one *unique* HIV testing modality to any alternative, was eligible. EEs which focused on evaluating the same HIV testing strategy in different contexts, (i.e. frequency for increasing threshold coverage from for example 40% uptake to 80% uptake, or targeted vs universal delivery of the same testing approach), along with EEs focusing on the diagnostic aspects of the same HIV testing strategy (i.e. rapid vs laboratory, confirmatory testing, change in assay types etc.), did not qualify. The search strategy included evaluations of all unique HIV testing modalities, undertaken from all perspectives (e.g. patient, healthcare provider, societal, donor), and all types of economic evaluations (i.e. cost-effectiveness, cost-utility, cost-benefit, cost-minimization, cost-consequence).

All countries and settings were eligible in the initial search to avoid exclusion of potentially relevant articles. Region was screened manually. The search timeframe was from January 1, 2000 to September 16, 2020. After search execution, a systematic review of cost-effectiveness modelling studies of PrEP for HIV prevention published in 2013 [22], was found. As modelling approaches for evaluating PrEP require incorporation of HIV testing somewhere along the programmatic pathway, and would be comparable to those evaluating HIV testing strategies, all retrieved articles published before 2013 were removed.

Study Selection

Search results were imported into Endnote X9 for storage and duplicate removal. Titles and abstracts were screened independently by two reviewers, (AV and YC), with disagreements resolved by discussion and consensus, and excluded based on the following criteria: 1.) Unrelated to HIV Testing; 2.) HIV Testing – Epidemiological studies only; 3.) HIV Testing – Costing studies only; 4.) PMTCT interventions focused exclusively on ART provision – excluded as HIV testing is part of any PMTCT program; 5.) Non-English studies; 6.) Full text unavailable (including conference abstracts). EEs meeting the inclusion criteria were reviewed as full-text. High-income or non- SSA countries (as defined by the World Bank) were excluded [25, 26].

Data Extraction

A multi-component data extraction tool was developed. Firstly, general information including publication date, country of study, population of interest and type of HIV testing strategy assessed was extracted. The

second component was based on the CHEERS (Consolidated Health Economic Evaluation Reporting Standards) checklist [27, 28]. Items relating to type of EE and modelling approach, perspective adopted, time horizon, cycle length and discount rate, and outcome measures presented, were extracted. The third component assessed model reporting quality via a novel tool developed, building on the recommendations from ISPOR's Principles of Good Practice for Decision Analytic Modelling in Health-Care Evaluation [29]. Reporting quality was evaluated against three categories – structure, data handling and validation – each differentiated into attributes. Attributes not limited to a specific model type, and having descriptions enabling nominal assessment (i.e. yes/no), were adapted into criteria, (n=13), to evaluate individual model reporting quality of EEs included in this review. (See **Appendix II** for attributes and scoring strategy). Data extraction was completed by one reviewer (AV), and verified by another (HM).

Data Analysis

Descriptive analysis was conducted to present EE methodological features using the CHEERS checklist and to delineate modelling parameters according to HIV natural history (i.e. transmission, progression, treatment). Model reporting around disease process and decision problem presented (structure), consideration of how parameter inputs impacted model outputs (data handling), and accuracy and generalizability of model results (validation), was differentiated across 13 criteria. Six criteria determined the appropriateness of the model structure for the question modelled, and if structure justifications (cycle length, limitations etc.), were provided. Five criteria determined the method with which parameters were populated, and their appropriateness. The last two criteria determined whether both an internal and external model validation was conducted. Criteria were evaluated as adequately reported, inadequately reported, not reported, or not applicable (N/A), and presented as a compound bar graph. As pooled results were not intended, risk of bias was not evaluated.

RESULTS

Study Selection

From the years 2000 – 2020, the search strategy yielded a total of 10, 988 records. Following removal of duplicate records (3,813) and articles published prior to 2013, 3,704 records remained. After reviewing title and abstracts, 56 records proceeded to full-text review of which 21 qualified for inclusion (**Figure 1**). (It should be noted that of the 602 titles with no full text (all of which were conference abstracts), review of titles showed 582 were unrelated to HIV testing. Abstract review found 2 of the 20 remaining conference abstracts would have qualified for the systematic review if a full text had been available.)

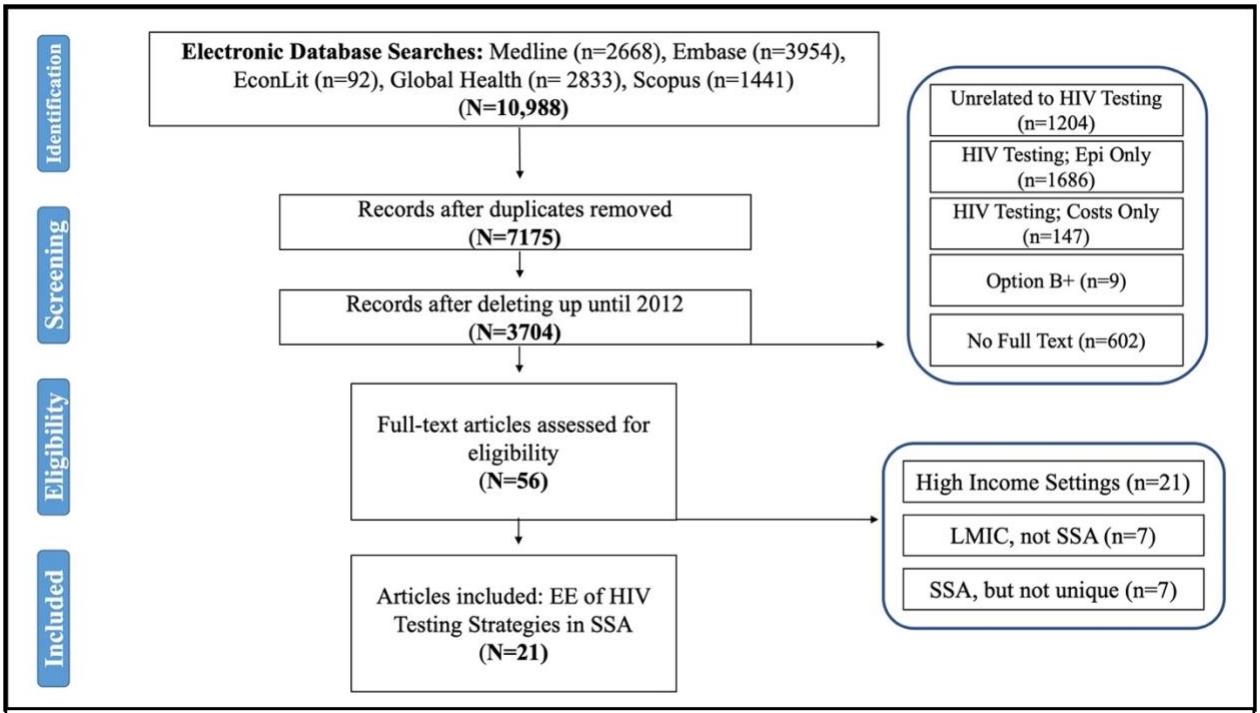

Figure 1. PRISMA flowchart of the inclusion and exclusion process for the systematic review

Option B+ = Initiation of lifelong antiretroviral therapy for all HIV-positive pregnant mothers irrespective of CD4 count
EE = Economic Evaluation
SSA = Sub-Saharan Africa
LMIC = Low and Middle Income Countries

Study Characteristics

Table 1 summarizes features of the 21 EEs of HIV testing strategies in SSA included in this review. Twenty studies were set in Eastern and Southern Africa, with one multi-country study including two West African countries (Ivory Coast and Sierra Leone) [30]. The most common population of interest was the general adult population (12/21), with varying age ranges considered. The remaining nine studies considered targeted populations. The majority of HIV testing, (12/21), was community-based (including home-based and self-testing). Facility-based testing was the focus in 7/21 studies; while two studies conducted testing in both clinics and the community [31, 32]

Table 1. Features of Reviewed Economic Evaluations of HIV Testing Strategies in SSA

	STATIC			DYNAMIC		
	Decision Tree (n=3)	**State-Transition: Markov** (n=0)	**State-Transition: Microsimulation** (n=6)	**Compartmental** (n=5)	**Agent-Based** (n=7)	**DES** (n=0)
Model Properties						
Aggregate vs. Individual Deterministic vs. Stochastic	Aggregate (n=3) Deterministic (n=3)		Individual (n=6) Stochastic (n=6)	Aggregate (n=5) Deterministic (n=5)	Individual (n=7) - Deterministic (n=1) - Stochastic (n=6)	
Year of Pub						
2013-2015	3		1	1	2	
2016-2018	0		4	3	2	
2019-2020	0		1	1	3	
Setting						
Eastern Africa	2		2	1	2	
Southern Africa	1		4	3	5	
Other	0		0	1	0	
Pop of Interest						
General/Adult	1		3	3	3	
Pregnant Women and/or couples	2		0	2	1	
Targeted	0		1	0	2	
HIV Testing						
Facility	2		2	1	2	
Community	1		3	4	4	
Both	0		1	0	1	
EE Methodology						
CEA	3		3	2	2	
CUA	0		3	3	5	
Main Outcome						
DALY	0		2	1	5	
QALY	0		1	2	0	
Other	3		3	2	2	

Economic Evaluation Overview

EEs only took the form of cost-effectiveness analyses (CEAs) (10/21), or cost-utility analyses (CUAs) (11/21). EEs conducted from the healthcare provider perspective (16/21) were the most common. Where reported, time horizons ranged from 1–50 years. Cycle lengths mostly varied from 1–3 months where applicable and reported. The preferred discount rate was 3% (16/21). Major outcomes of interest reported were: cost per DALY averted (8/21); cost per life year saved (7/21); cost per QALY gained (3/21); cost per HIV transmission/infection averted (2/21); cost per positive HIV case identified (1/21). Characteristics of the EE approaches are detailed in **Table S1** (**Supplementary File**).

Modelling Approach

Modelling approaches identified included static aggregate models, i.e. decision trees (3/21); static individual models, i.e. microsimulations (6/21); dynamic aggregate models, i.e. dynamic compartmental models (5/21); and dynamic individual models, i.e. agent-based models (7/21) (**Table 2**). All dynamic aggregate (compartmental) models were deterministic in nature (5/21), while all static individual models (microsimulations) were stochastic in nature (6/21). Six of seven dynamic individual models, (agent-based models) were stochastically configured [33].

HIV Transmission

Dynamic models predominantly modelled heterosexual horizontal transmission only (11/12) [32], with two including vertical transmission also [34, 35] (**Table 2**). Three static models modelled vertical transmission, with two (static, individual) including pregnancy and postpartum periods only [36, 37], while the other, (static, aggregate), also included labor [38].

The most frequently incorporated demographic parameter amongst all models was age. Models either: 1.) did not specify cohort age range (5/21); 2.) used varying definitions of adult populations (7/21); 3.) modelled age group as an ordinal variable (9/21). Age-differentiated modelled cohorts were either inclusive of infants, children, adolescents and adults (5/9), or adolescents and adults only (4/9). Two dynamic individual models also considered migration status [35, 39] (**Table 2**).

Static aggregate models, [i.e. (assumed) decision trees (3/21)], modelled HIV transmission via probabilities along event pathways, while static individual models, [i.e. microsimulations) (6/21)], modelled transmission using incidence/prevalence estimates. The number of variables considered in both the contact rate (Beta) and force of infection (Lambda) calculations between both categories of dynamic models varied substantially (**Table 2**). Among both categories of dynamic models [i.e, aggregate-compartmental and individual-agent-based (12/21)], contact rates were usually characterized by

partnerships (6/12), or sex acts per partnership (5/12); the exception being the compartmental model which focused on TB-HIV co-screening, where HIV transmission probability was proportionate to HIV prevalence in the population [40]. Amongst the 12 dynamic models, additional variables included in force of infection calculations were: ART status (8/12); circumcision status (8/12); condom use (8/12); female sex work (4/12); STI co-infection (4/12); and PrEP (2/12).

Table 2. *HIV Transmission* Variables Among the Models Used in Economic Evaluations of HIV Testing Strategies			
Reference	**Demographic Parameters**	**Horizontal Transmission**	**Vertical Transmission**
Static Models – Aggregate [(Assumed) Decision Trees]			
Kim (2013) [38]	Age: Unspecified	*Not Included*	Mother to child transmission probability: - during pregnancy no ARVs - during pregnancy if HAART - if nevirapine given during labor - during labor if acute HIV - during lactation if acute HV - during lactation at 6 months - during lactation at 6 months if on HAART - during lactation at 18 months
Mulogo (2013) [41] *Decision Model Unspecified*	*Model Structure and Parameters Unspecified*	*Model Structure and Parameters Unspecified*	*Model Structure and Parameters Unspecified*
Rutstein (2014) [42]	Age: 15-49 years - Non-age differentiated	Transmission: Heterosexual <u>Transmission Probability</u> - Acute Infection - Chronic Infection - HIV positive: Not on ART - HIV positive: On ART	*Not Included*
Static Models – Individual [Microsimulation]			
Bassett (2014) [43]	Age: 20-46 (assumed) - Non-age differentiated	Transmission: Heterosexual <u>Transmission Probability</u> *Not reported*	*Not Included*
Francke (2016) [37]	Age: Birth-Death - Non-age differentiated	Transmission: Heterosexual <u>Transmission Probability</u> *Not reported*	Maternal HIV Status: - CD4 ≤350/μL or >350μL; receiving or not receiving ART Intrauterine/Intrapartum (1-time risk): - Receiving ART - Not receiving ART Postpartum (monthly transmission risk until weaning): - On ART - Not on ART
Olney (2016 & 2018) [31, 44]	Age: 0-80+	Transmission: Heterosexual <u>Transmission Probability</u>	*Not Included*

	- Age-differentiated into 5-year age stratum: 0-4, 5-9, …, 70-74, 75-79, >80	HIV Transmission in the model is driven by incidence estimates derived from UNAIDS/Spectrum Software	
Maheswaran (2018) [45]	Age: 16-50+ - Age-differentiated into 5 groups: 16-19; 20-29; 30-39; 40-49; 50+	Transmission: Heterosexual <u>Transmission Probability</u> Dependent on number of individuals who already have the infection, varied by sex and age.	*Not Included*
McCann (2020) [36]	Age: 0-59 - Age-differentiated into 9 groups: 0-2; 3-5; 6-8; 9-11; 12-17; 18-23; 24-35; 36-47; 48-59	Transmission: Heterosexual <u>Transmission Probability</u> *Not reported*	Maternal HIV Status: - CD4 ≤350/μL or >350μL; receiving or not receiving ART Intrauterine/Intrapartum: - Started ART before pregnancy (both chronic and acute maternal HIV) - Started ART during pregnancy (both chronic and acute maternal HIV) - Not on ART (both chronic and acute maternal HIV) Postpartum: - On ART (both chronic and acute maternal HIV) - Not on ART (both chronic and acute maternal HIV)
Dynamic Models – Aggregate [Compartmental]			
Hove-Musekva (2014) [46]	Age: 15-49 - Non-age differentiated	Transmission: Heterosexual <u>Transmission Probability</u> Adjustment factors to contact rate (Beta) that reflect the influence of pre and post-counselling on biological and behavioral processes (that influence risk of transmission) - Behavior change: individual withdrawal from risky sexual activity; i.e. proportion of people using condoms Efficacy of community home based care	*Not Included*
Gilbert (2016) [40]	Age: 15-64 - Non-age differentiated	Transmission: Heterosexual→ (But the aim of the model was to evaluate impact of integrating combined TB/HIV case finding, on HIV/TB Coinfection epidemic) <u>Transmission Probability</u> HIV negative persons: Can acquire HIV at a rate proportional to the HIV prevalence in the population HIV positive: - Not on ART	*Not Included*

		- On ART	
Sharma (2016) [34]	Age: 0-59 - Age-differentiated into 5-year age stratum: 0-4, 5-9,…, 55-59	Transmission: Heterosexual <u>Transmission Probability</u> Estimated by number of sex acts per partnership, per year and the probability of HIV transmission per sex act (and viral load), factoring in the following: Sexual risk group defined by number of (coital acts) partnerships: - Low Risk; Medium Risk; High Risk Circumcision status	<u>Vertical Transmission Probability:</u> HIV Positive women not on ART (have a probability of transmitting to their infants.) - Stratified by CD4 count and viral load If HIV positive, women transition into pregnancy states according to age and CD4 count.
Ying (2016) [47]	Age: 0-59 - Age-differentiated into 5-year age stratum: 0-4, 5-9,…, 55-59	Transmission: Heterosexual Transmission Probability Estimated by number of sex acts per year and the probability of HIV transmission per sex act, factoring in the following: Sexual risk group defined by number of partnerships: - Low Risk; Medium Risk; High Risk Circumcision status PrEP: - No PrEP/on PrEP Condom Use: - Among HIV negative persons - Among PrEP users - Among ART users	*Not Included*
Wall (2020) [30]	Age: 15 – 64 - Non-age differentiated	Transmission: Heterosexual <u>Transmission Probability</u> Discordant couples (among stable couples) Concordant negative couples (among stable couples)	*Not Included*
Dynamic Models – Individual [Agent-Based]			
Cambiano (2015 & 2019); **Phillips (2019)** [48-50]	Age: 15-64 - Age-differentiated into 5-year age stratum: 15-24, 25-34,…, 55-64	Transmission: Heterosexual <u>Transmission Probability</u> Number of condom-less, short term sex partners (in a 3 month period) - Groupings of short term partnerships: none, 1, medium number, high number o Probability of HIV Infection	*Not Included*

		▪ Dependent on HIV prevalence in opposite gender of same age group Long term partnership: - Condom-less sex within 3 duration groups: 1;2;3 (higher class, higher tendency to endure) - HIV positive: Not on ART - HIV positive: On ART Female Sex Worker: >3 sex partners in a 3 month time period Probability of Circumcision	
Smith (2015); Sharma (2018) [35, 39]	Age: ≥ 18 years - Non-age differentiated Migration Status	Transmission: Heterosexual <u>Transmission Probability</u> Sexual Activity: - Coital Frequency Circumcision status Condom use by: - Partnership Type - HIV Status Partnerships: - Long-term/short-term - Concurrent partnerships (up to 2) o (Inc. outside of the community) STI Co-infection (HSV2 and others) CD4 count and ART Status of Partner	*Not Included*
Nguyen (2018) [33]	Patients generated via random draws of characteristics from distributions of *sex* and *age*	Transmission: Heterosexual <u>Transmission Probability</u> Low-Risk Population (88% Proportion): Number of monthly contacts = 4 (via reference) High-Risk Population: Number of monthly contacts=35 (via assumption) Probability of Transmission per Contact: - Acute Infection - Infection, not treated - Treated, Suppressed - Treated, Not Suppressed	*Not Included*

Johnson (2019) [32]	Each simulated individual is randomly assigned an age, sex and race	Transmission: Heterosexual and Homosexual <u>Transmission Probability</u> Probability of Transmission per Sex Act calculated according to relationship, sexual behavior, health and healthcare utilization variables. Relationship variables: - New Partner (sexual mixing pattern – highly assortative) - Marrying Partner - Ending Relationship - Casual Sex - Commercial Sex Sexual behavior variables: - Propensity for Concurrent Partners - Sexual Preference - Number of Current Partners Health variables: - Acquisition of HIV - Acquisition of STI Healthcare variables: - Adoption/Discontinuation of Contraception - Condoms - PrEP - ART - MMC	Mother-to-child transmission simulated; further details not provided

HIV Progression

Static aggregate models (3/21) did not include any progression-related variables. One dynamic aggregate (compartmental) model also did not represent HIV progression [30]. The remaining 17 models accounted for HIV progression by changes in CD4 count, WHO stage, HIV viral load, and considered hospitalization, occurrence of TB or opportunistic infections (OI) and HIV related mortality. Typically, no more than four variables were represented among individual static models and both types of dynamic models; the exception being one individual static model which accounted for HIV progression through all 6 of the above mentioned categories [43]. All 17 models which incorporated HIV progression variables included HIV-related mortality parameters, followed by CD4 count (16/21), WHO staging (10/21), viral load (7/21), hospitalization (6/21), TB event or OI (4/21). **Table S2** (**Supplementary File)** presents an overview of all progression-related variables incorporated into the included models.

ART

ART parameters were abstracted according to five broad categories: 1.) ART Initiation; 2.) Retention in Care; 3.) Viral Suppression; 4.) Loss from Care; 5.) Other. Static aggregate models did not account for ART within branch pathways (3/21). All individual static models (6/6), and all dynamic individual models (7/7) incorporated an ART initiation variable. Amongst dynamic compartmental models, 2/5 did the same, while the other 3/5 dynamic compartmental models did not consider the effects of ART initiation on costs and outcomes. Following ART initiation (15/21), loss from care was the second most commonly included parameter (13/21). No study included ART-related variables from all five categories. **Table S3 (Supplementary File)** presents a summary of all ART-related variables incorporated into the models.

Model Reporting Quality

Figure 2 depicts the reporting quality of the models.

Model Structure

Model outcomes are conditional upon structural limitations; a lack of transparency around these assumptions and limitations exaggerates their accuracy [29]. Only one study adequately reported all six criteria related to model structure [50], while two did not adequately report any. Relevant inputs/outputs for the decision-making perspective (C1), was adequately reported in fourteen of 21 studies, but for seven studies, it was not clear that input parameters and specifically costs reflected the chosen perspective [51]. It was difficult to assess model structure consistency with available evidence and current understanding of the HIV disease (C2), for 2/21 studies or it was not reported (4/21) [52]. Limitation to model structure (C3), were adequately reported only in 8/21 studies. C3 also had the most studies (8/21), which did not

report on it at all; 5/21 studies mentioned limitations but did not discuss the impact of those limitations on reported outcomes. Justification of time horizon and cycle length (C4), was adequately reported criteria in only 2/21 studies, with the majority of studies (14/21) inadequately reporting the rationale behind their choices. Observations on the final two criteria in the model structure category – simple as possible model structure capable of accurately capturing the underlying disease process (C5) and appropriateness for the question modelled (C6) – similar to C2, were dependent on structure elucidation. Both C5 and C6 were adequately reported in 15 studies, but difficult to assess in the remaining 6 studies since structure complexity and appropriateness was not fully described.

Data Handling

Data handling had the highest proportion (74%) of adequately reported criteria; six studies adequately reported all five criteria. Disclosure of input parameter sources is necessary to determine their suitability [53]; conducting a literature review for key model parameters (C7), was adequately reported 90% of the time. Sensitivity analyses quantify the uncertainty of input parameters and their effects on a model's output [54]. Inclusion of upper and lower bound ranges for input parameters (C8) was adequately reported 81% of the time. Within the data handling category, acceptable data modelling methods in line with biostatistics and epidemiology (C9), was the least adequately reported criteria (62%). Transparency around data transformation for relevant inputs and outputs, (e.g. adjusting for inflation or purchasing power across time and countries; discounting, transformation of health values/scales into quality of life weights), is needed for valid and accurate model outcomes [29]. The same is true for disclosure of data modelling assumptions (C10), which was adequately reported among 14 (of 21) studies (67%). Lastly, consistency between measurement units and population characteristics throughout the model (C11), was evaluated as a summary of reporting across C4, C5, C7 and C9. Seventy-one percent of studies adequately reported this criteria.

Model Validation

Model validation had the lowest percent (45%) of adequately reported criteria. Evidence of internal model validation (C12), where applicable, was adequately reported 79% of the time; four studies did not provide evidence of internal testing and debugging. Failure to report if/how models were calibrated challenges the validity of findings, if the model cannot reproduce observed effects [55]. Evidence of external model validation (C13), (along with C4), was the least adequately reported criterion: adequately reported in 2/19 studies only (11%), inadequately in 7/19 (37%), not reported in 10/19 (53%). Only two of 19 studies accurately reported on both internal and external model validation processes [33, 45], while three studies did not report any validation criteria.

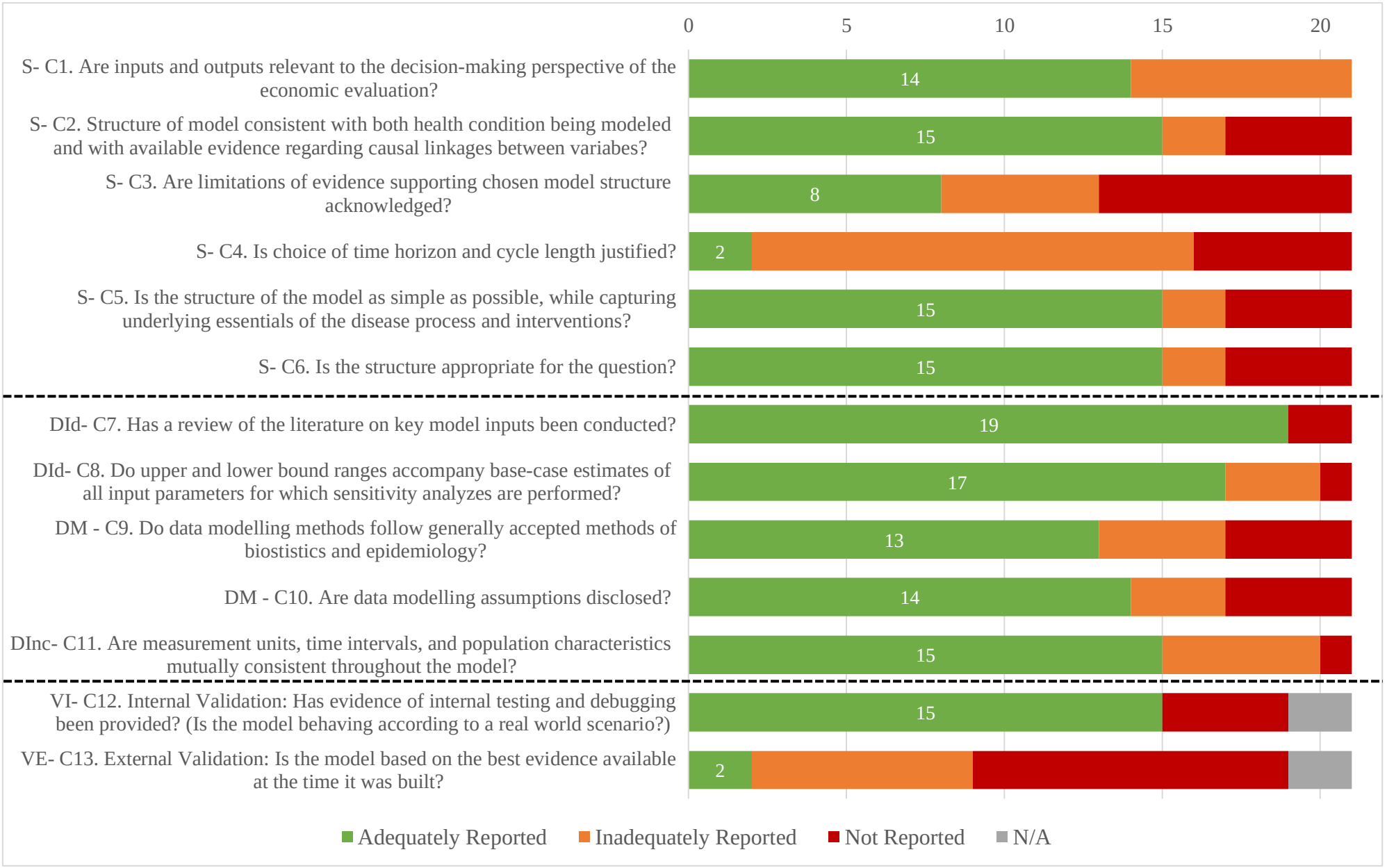

Figure 2. Assessment of Model Reporting Quality

Models were assessed against a total of 13 criteria (developed around ISPOR's Principles of Good Practice for Decision Analytic Modelling in Health-Care Evaluation), and were gauged against a 3 point scale: Adequately reported; Inadequately reported ; Not reported.

- *Model Structure* – 6 criteria (C1 – C6)
- *Data Reporting* – 5 Criteria from 3 sub-categories: Data Identification (C7, C8); Data Modelling (C9, C10); Data Inclusion (C11)
- *Validation* – 2 Criteria from 2 sub-categories: Internal Validation (C12); External Validation (C13)

DISCUSSION

This systematic review sought to determine how EEs of HIV testing strategies in SSA have been conducted, and to namely highlight what modelling approaches have been used to do so. Spanning 2013 to 2020, 21 economic evaluations of HIV testing strategies were included; all were either CUAs (11/21), or CEAs (10/21). EE modelling approaches fell into four categories: 1.) Static aggregate (3/21); 2.) Static individual (6/21); 3.) Dynamic aggregate (5/21); 4.) Dynamic individual (7/21). When graded against model reporting criteria adapted from ISPOR guidelines, 6 of 13 criteria were adequately reported at 70% or above. Except for one model, all economic evaluations were confined to East and Southern Africa, where the largest HIV burden resides. There was no discernable relationship between testing approach, modelling approach and location.

In line with previous reviews [56, 57], the included models were classified according to the following properties: Static vs Dynamic; Deterministic vs Stochastic; Aggregate vs Individual.
The majority of papers represented the disease process dynamically (n=12), favoured stochastic functions (n=12), and individual population representation (n=13). There were no cohort-based Markov models or DES included. This finding was aligned with results from a systematic review of EEs of adult male circumcision which did not have any Markov-modelled evaluations [58], but not with the results of two other systematic reviews of EEs [of PrEP [22] and PMTCT [59]], which did. The 'memoryless' Markovian property, while well suited for chronic diseases [60], may not be appropriate for HIV prevention decision problems where transitioning to the next state is dependent on the previous state, and accounts for this lack of Markov models for HIV testing.

A key challenge was discerning the authors' intention behind the use of modelling terminology; for example, both microsimulations and agent-based models were referred to as 'individual-based' models. Standardization of mathematical model reporting in terms of explicit categorization of the above-mentioned three properties may provide clarity for future researchers seeking to replicate an approach for their decision problem, and consequently a better understanding of its appropriateness and applicability for their specific context.

Six of 21 models in this review were static. Static models have less data and computational requirements than dynamic models, yet a disadvantage is that a constant force of infection disregards real-world contact and mixing patterns, as well as variable risk within partnerships [61]. For HIV, dynamic models are conceptually more desirable than static ones [21]. However, if a static model predicts that an intervention is cost-effective, a dynamic model will as well [56]. A comparison between a dynamic transmission model and a well-known static HIV model - the 'Modes of Transmission'(MOT) model – found that

when the MOT model structure was equivalent to that of the dynamic model, the static model estimates improved [62]. The validation also cited the quality of data as another key to improving the MOT model's outputs [62]. Depending on parameter availability and quality, a static model might be an acceptable alternative if structure (i.e. natural history/health states and parameters), inputs (data sources) and model outputs (i.e. cost-effectiveness measures), are standardized. A first step would be to produce a limited number of cost-effectiveness measures (i.e. cost per DALY or QALY only), to reduce variability within outcomes presented by various modelling approaches, thereby facilitating comparability. A more ambitious next step would entail universal accessibility of datasets (ideally in a repository) to aid in reproducibility of parameter inputs and facilitate a higher research standard.

Viral load is widely considered the most important risk factor in HIV transmission, and a good proxy indicator for ART monitoring, highly sensitive to treatment adherence and failure [63]. However, a review of HIV mathematical models found that only 6% (i.e. 17 of 279) of models incorporated a viral load parameter [63]. This may be in part due to lack of data access, especially in low-income settings where monitoring CD4 count rather than viral load was historically the norm [64]. Only seven of the 21 included studies (33%), incorporated a viral load parameter under the HIV progression category, and three of them were from a single working group using the same model [48-50]. Moving forward, inclusion of a viral load parameter may help homogenize structural/natural history considerations, consequently advancing HIV model standardization.

While recommendations and classifications exist [16, 17, 29, 65], model structure taxonomy and reported rationale for modelling approach in the literature is inconsistent and non-transparent, evidenced by the inadequate reporting around certain model structure criteria observed. No study stated their rationale for choice of model used. Without disclosure of reasons behind model choice, assessing criteria around appropriate model structure for question (C6), was difficult and subjective. Oftentimes, limiting factors to modelling approach and structural considerations are largely contextual, such lack of data, ease of use and technical aptitude hinging on resource availability [66]. Brief explanations accompanying modelling decisions would help modellers determine if a structure is appropriate for replication in future evaluations. The 2022 update to the CHEERS statement encourages researchers to explain their reasoning behind model-based decisions [28]. Future researchers would benefit from closely adhering to the updated CHEERS checklist as it would strengthen the accuracy and validity of both methodology and results generated, and aid the audience (other researchers, policy makers etc.) understand the context of all decisions made. Journals compulsorily requiring a completed 2022 CHEERS checklist alongside EE manuscripts might increase transparency in EE modelling and facilitate the modification, reusability,

reproducibility of existing models, and analyses as a whole, thereby reducing redundancy and limiting resource use.

Reporting around data handling was the highest of the three model appraisal categories. Across the 21 studies, the proportion of adequately reported criteria in this category ranged from 62% (C9) to 90% (C7). However, scarcity of externally validated models, or at the very least, adequate reporting around external validation, (C13, 11%), is a cause for concern. This questions model generalizability and results upon which policy decisions are made, and the likelihood that predicted effects would occur outside of the study [55, 67]. This is particularly problematic in the HIV context, where drivers of epidemics vary substantially according to population and region. ISPOR's good modelling practices cites the need for a formal process evaluating external validity of models [55]. The difficulty of establishing a formalized process may account for the rarity of evaluating external model validation [68]. The structuring of research reporting itself might also contribute to the problem. The focus almost always lies on the results of the modelling study – i.e. how cost-effective the intervention was, how many DALYs were averted etc. – and rarely is space and time given to the model itself. Peer-review processes would benefit from better guidelines for model reviews. ISPOR's modelling practice recommendations are a great starting point, however, evidenced by the difficulty encountered in adapting the guidelines into an actionable format for the purposes of this systematic review, they would benefit from a structural overhaul to become more user-friendly and executable. Altering the format to resemble the resulting tool (**Appendix II**) may be useful for future modellers and reviewers, irrespective of research area, and could facilitate higher quality economic evaluations.

When reviewing the results of this systematic review, the following limitations must be considered. Modelling methods are complex and terminology used vaguely and interchangeably adds to the confusion. There is a possibility of incorrect interpretation of model components due to variation and inconsistent use of terminology. However, explicitly attempting to categorize models according to three fundamental properties – static vs. dynamic; deterministic vs. stochastic; aggregate vs. individual – possibly mitigated some of the misunderstanding. While no study was excluded solely based on the availability of English text, relevant model-based evaluations of HIV testing strategies based in WCA, under-represented in this review and a largely Francophonie area, may have been missed if a translated abstract did not accompany the manuscript, as the search strategy (and accompanying terms) were in English. Though database selection was informed via research findings [24], omitting other relevant databases (e.g. Web of Science, grey literature databases etc.), and excluding studies without full text (as a detailed methods section outlining model structure and parametrizations was necessary to abstract relevant data for this review), may have prevented gaining a holistic and representative view of model-

based economic evaluations of unique HIV testing strategies in SSA. Additionally, the search timeframe did not include studies published in 2021 and 2022, potentially hampering the ability to observe any recent modelling-based trends in EEs of HIV testing strategies (in SSA), that may be forming. Finally, the scope of this review excluded the possibility of exploring the potential policy implications of the studies included; future research may entail assessing the overall quality and conclusions of these EEs and their impact on HIV testing recommendations and policy implementation within SSA.

CONCLUSION

No single modelling approach and structure will ever fully represent HIV disease transmission and the impact of testing. Similarly, while standardization of HIV testing models would facilitate generalizability and reproducibility of results in the region, economic modelling studies are conducted within a specific context or setting to answer a distinct question or policy consideration. Models are further limited by practical and real-world data considerations. Therefore, generating quality evidence via economic evaluations begins with the validity of the modelling approach chosen and the model structure employed. Conducting an economic evaluation of a HIV testing strategy via an agent-based model – a dynamic, stochastic, individual representation capable of calculating nuanced interactions and mixing patterns while accounting for variability and changes over time – would be ideal. However, most settings, especially SSA suffer from constraints related to data and resources, at which point static and compartmental models can be as effective, particularly if future researchers and modelers adhere to several key recommendations. Namely: 1.) rationalization and explanation of model-based decisions surrounding model structure, parametrizations and analytic components in line with the 2022 updated CHEERS statement; 2.) explicitly highlight model structure, data handling procedures and processes for both internal and external validation of models using the tool generated by this systematic review as a frame of reference; 3.) facilitate data sharing; 4.) generate at least one summary measure of population health (cost per DALY or QALY) to facilitate policy implementation comparison and decision making across the spectrum of health technologies.

DECLARATIONS

Ethics Approval and Consent to Participate

Not applicable: data in this review was obtained from previously published studies.

Consent for Publication

Not applicable.

Availability of Data and Materials

The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request. Search strategy available in appendix. Code availability not applicable.

Competing Interests

The authors declare that they have no competing interests.

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Author Contributions

AV, LG, HM and VS conceptualized the study and developed methods. AV and HM developed data collection tools. AV and YC executed data acquisition. AV and HM analyzed data. First draft of the manuscript was written by AV and all authors commented on subsequent versions. All authors have read and approved the final draft and declare no competing interests.

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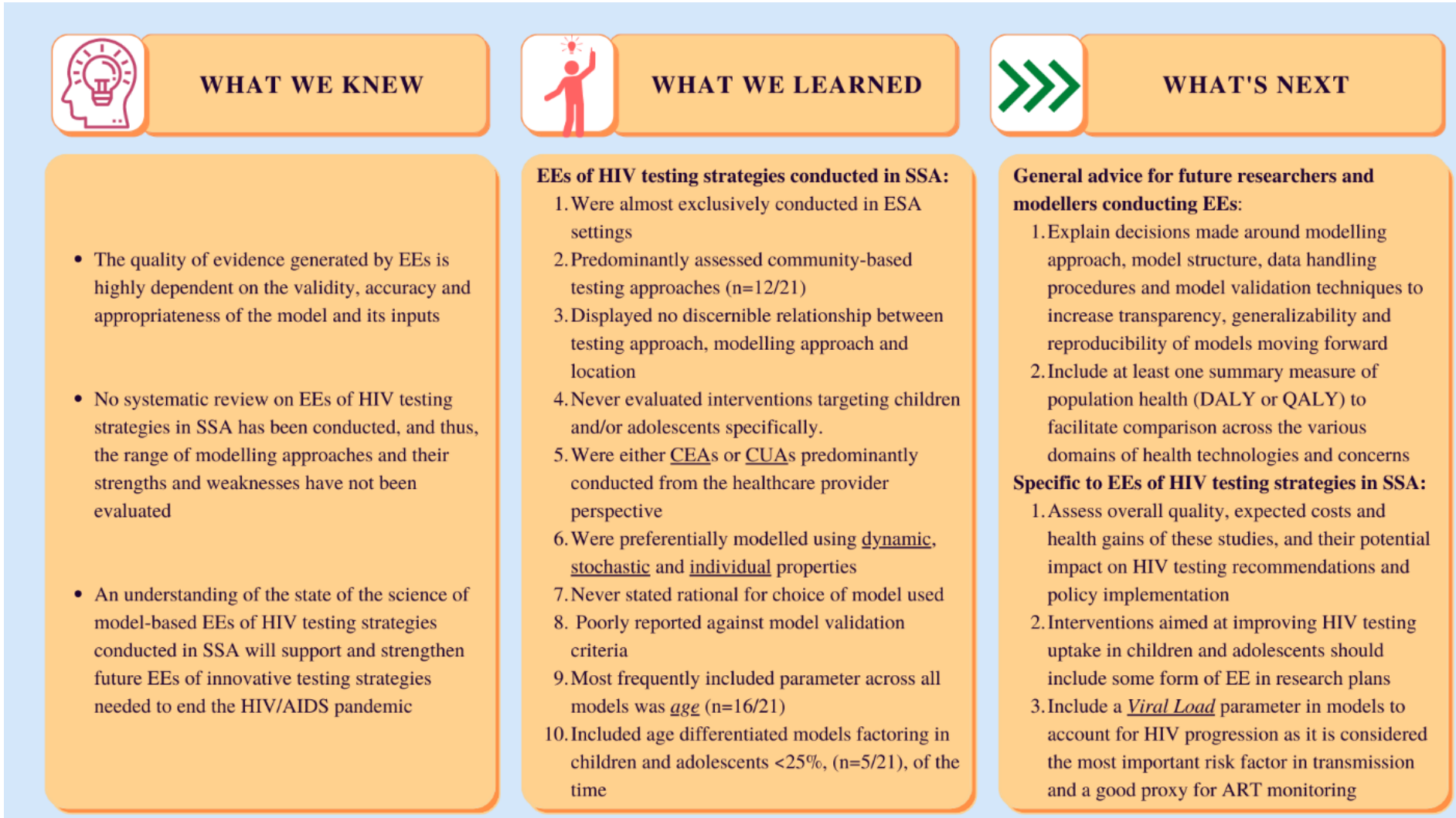
3.5 CHAPTER 3 KEY TAKEAWAYS

This systematic literature review highlighted that despite the quality of evidence generated by EEs being dependent on the validity, accuracy and appropriateness of the model and its inputs, EEs of HIV testing strategies conducted in SSA did not provide rationalization for modelling approach used, lacked transparency around model-based decisions made, and reported poorly against model validation criteria in the checklist developed using best practice recommendations by CHEERS and ISPOR. Additionally these evaluations were almost exclusively conducted in ESA settings and though the most frequently included parameter across all models was age, considered children and adolescents in model structures less than 25% of the time. The under-representation of children and adolescents in EEs of HIV testing strategies, along with a lack of representation of evaluations focused on WCA settings, which in 2020 represented 39% of global HIV-related mortality in children and adolescents aged 0-14 years [7], is not only troubling, but proof that the HIV response is failing children and adolescents, leaving them behind (**C3, Figure 2**).



C3, Figure 2. Results P1 Key Takeaways: What We Knew; What We Learned; What's Next

3.6 IMPLICATIONS FOR THESIS

The overall aim of this thesis is to contribute to the methods of EEs of HIV testing in children and adolescents in a Zimbabwean context. This chapter contributed to achieving this aim by synthesizing the typical modelling methods and approaches researchers conducting EEs of HIV testing strategies in SSA have utilized. In doing so, **Objective 1** of this thesis – to investigate modelling methods through which EEs of HIV testing strategies in SSA are conducted – was fulfilled. In answering **Objective 1**, an important implication for this thesis was uncovered: concrete proof that children and adolescents are not represented in literature focusing on EEs of HIV testing strategies in not only a specified context such as a Zimbabwe, but even in the larger SSA context. A secondary implication of this chapter, for this thesis, is that moving forward, an understanding of how to augment and elevate current practices when conducting and reporting EEs (in domains not only restricted to HIV testing) was generated. This is of relevance to not only this thesis, but future EE research and literature. The practicality of the findings of **Objective 1** will be built on, and demonstrated later on in this thesis.

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CHAPTER 4 – RESULTS PAPER 2: A NARRATIVE REVIEW OF CHILD AND ADOLESCENT INTEGRATION WITHIN WELL – DESCRIBED, FREQUENTLY USED AND CITED DYNAMIC MATHEMATICAL MODELS OF HIV IN THE SSA CONTEXT

Overview of Chapter 4 (Results P2)

Learnings and conclusions drawn from **Results P1** form the basis of, and feed into, the rationale of this chapter. Results P1 demonstrated that the predominant manner in which EEs of HIV testing strategies are conducted, are via dynamic models, with children and adolescents underrepresented amongst these EEs. This chapter presents a deeper dive into well-described, frequently used and cited dynamic models of HIV to investigate whether children and adolescents are under-represented in EEs only, or in mathematical models as well. A narrative review highlighting child and adolescent HIV transmission dynamics and risk representation in highly visible, peer-reviewed dynamic mathematical models, was conceptualized for the purpose of achieving **Objective 2** of this thesis. This chapter will be reformatted and restructured to submit for publication.

Evidence Before this Study

Mathematical models of HIV typically emphasize adult transmission dynamics and oversimplify children and adolescents integration, including them (if at all), in broader categorizations, which omit the nuances of their disease dynamics, barriers, behavioral and clinical characteristics. Several modelling studies to inform HIV programs in SSA include interventions targeting children and adolescents. No study thus far has evaluated whether the frameworks on which these decisions made for children and adolescents, are appropriate.

Added Value of this Study

The information presented in this chapter is of value to decision-makers, modelers and researchers as it provides a comparative evaluation of model structures, uncovers key limitations and offers practical recommendations to enhance child and adolescent specific representation of HIV epidemiology.

Contribution to the Larger Body of Evidence

Several model comparison studies including models reviewed in this chapter have been published; this is the first to investigate how, and the extent to which the unique child and adolescent HIV epidemiology is represented in these model structures. Without representative and precise modelling, critical gaps in prevention and care may not be effectively addressed.

4.1. INTRODUCTION

As previously expounded throughout my thesis, children and adolescents especially in sub-Saharan Africa pose a key challenge for HIV prevention and control measures, as they are a difficult to reach population. In this chapter, through a narrative review, I will explore, evaluate and discuss how well-described mathematical models of HIV categorize HIV risk in children and adolescents living in sub-Saharan Africa. I begin by briefly introducing the need for such an exploration, with a targeted review of existing models. I then elucidate the aims and objectives of this chapter within the larger context of the thesis, and outline the methods used to achieve them. Afterwards, I describe how these mathematical models of HIV incorporate children and adolescents within their frameworks. Finally, I discuss how to integrate the learnings and findings of the review, to generate ideal and best practice recommendations, applicable to modelers in their future work.

4.2 BACKGROUND

4.2.1. The Epidemiology of HIV transmission

Epidemiologically, HIV transmission is classified as either *horizontal* (both sexual and non-sexual) or *vertical* (from mother to child) [1]. Vertical transmission, i.e. mother-to-child transmission (MTCT), occurs at a rate of 15% - 45% (in HIV-1, and less than 5% in HIV-2) without intervention, accounts for approximately 90% of pediatric HIV infections globally, and can occur at three points across the perinatal continuum: prepartum (pregnancy via placental barrier), intrapartum (labor and delivery via exposure to maternal blood and vaginal secretions) and postpartum (breast-feeding via breast milk) [2-6]. Elevated maternal viral load is the main driver of vertical transmission [3-6]. Substantial progress in preventing mother-to-child transmission (PMTCT) of HIV has been made since the introduction of PMTCT programs in 2011.

4.2.2 HIV, Children and Adolescents

Children and adolescents experience higher levels of HIV under-diagnosis and correspondingly lower levels of HIV treatment coverage compared to their adult counterparts [7, 8]. In Zimbabwe for example, the 95-95-95 targets have almost been met in adults: 95% of people living with HIV are aware of their status; 94% of whom are on treatment; 92% of whom are virally suppressed [9]. However in children and young adolescents (0-14 years), only 69% of those infected, are aware of their status; 69% of whom are on treatment; 59% of whom are virally suppressed [9]. Additionally, children and adolescents often present to clinical services with advanced HIV disease and consequently poorer outcomes [10-12]. Adolescents are the only age-group in whom HIV-related mortality has not declined in recent years, with children experiencing high rates of AIDS-related deaths. Amongst older adolescents aged 15-19 in SSA as a whole, 3 out of 5 new infections occur among females, leading UNAIDS to conclude that adolescent girls are disproportionally affected by HIV [13]. While Eastern and Southern Africa (ESA) comprise 6.2% of the global population [14], this region is the epicenter of the HIV epidemic with 54% of the 37.9 million people living with HIV globally [15, 16], living here. In ESA, 50 adolescent (aged 10 – 19) girls die daily due to HIV, while 460 are newly infected [13]. Young females (aged 15-24), despite representing just 10% of the population [16], account for 26% of new HIV infection in this region [17], and are twice as likely to be living with HIV compared to their male peers [17].

Societal norms, gender-based violence and discrimination are factors contributing to the higher risk of HIV within adolescent females [13]. The fear of violence and discrimination lessens agency among younger women, leading to diminished access to overall health services, but especially sexual and reproductive resources, as well as an inability to negotiate safer sex practices [13, 18]. Additionally, age-disparate relationships, defined as partnerships with male partners five or more years older, can be a

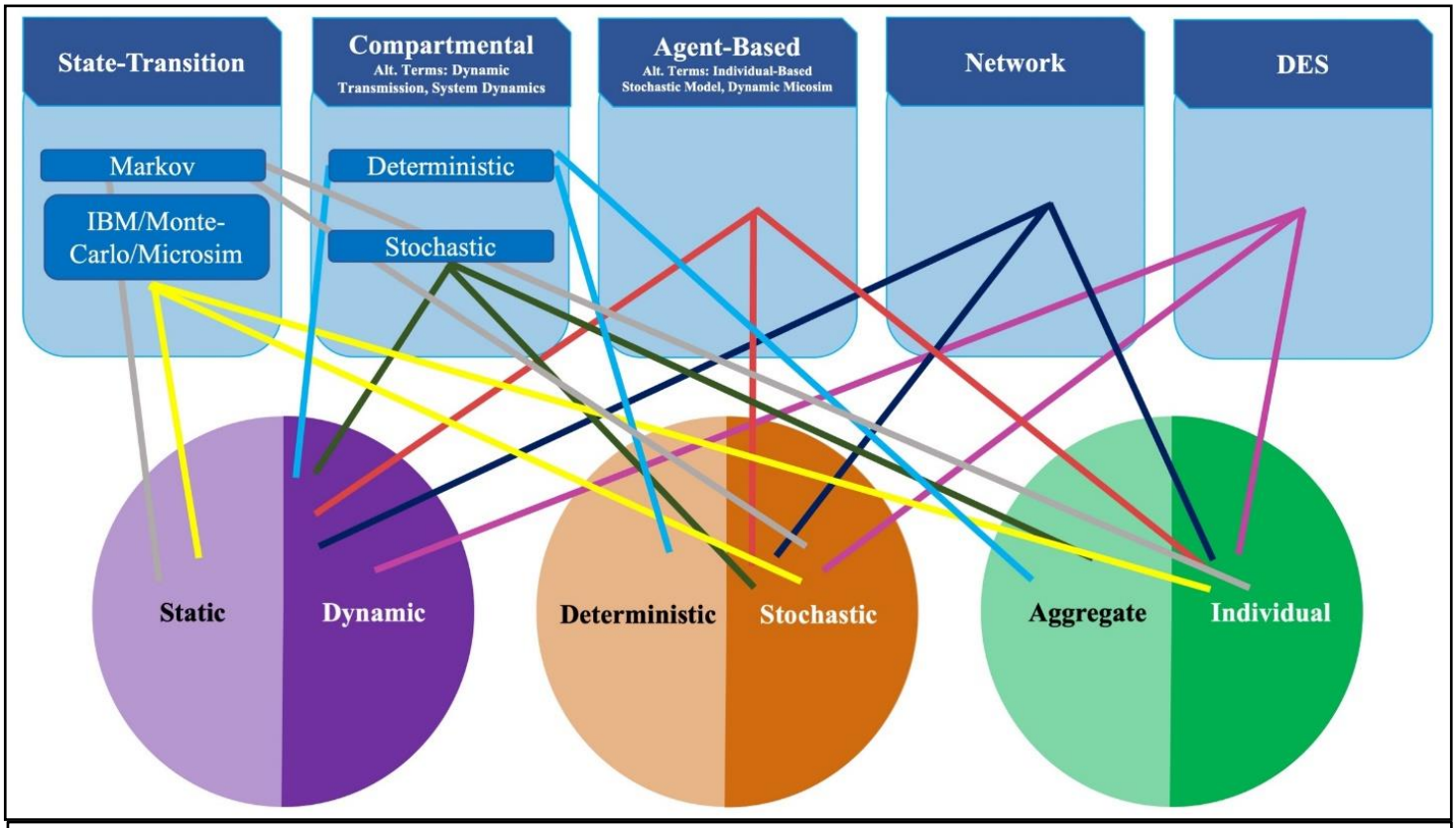
causal contributor to HIV risk among these girls [18-21]. HIV prevalence among men steadily increases with age, peaking around 35-40 years of age [20]. Furthermore, older men in age-disparate relationships are less likely to be virally suppressed due to poor care-seeking and adherence behaviors, again increasing HIV risk to their partners [20, 22]. Socioeconomic asymmetries along with power imbalances present in age-disparate relationships introduce elements of riskier sexual behaviors such as infrequent condom use and higher sexual frequency, coupled with concurrent and multiple partnerships [18-21]. To alleviate economic hardship, transactional sex within age-disparate relationships is often a motivating factor among adolescent females for engaging in relationships with older men [23-25]. All these factors mean that partnerships with older men present a higher risk of HIV infection, compared to partnerships with younger men [18-21].

4.2.4 Mathematical Modelling of Infectious Diseases

Mathematical models are simplified representations of complex phenomena [26]. They provide us with the opportunity to analyze multifaceted and complicated relationships through the simplification of real world interactions, via assumptions made about one or more key behavioral, environmental, epidemiological or etiological features [26]. These models are invaluable tools capable of testing variable hypotheses without large scale data collection [27]. Mathematical models can help inform public health policy and practice by estimating the effectiveness and cost-effectiveness of interventions and control measures on the trajectory of a disease or epidemic [28]. Bernoulli published the first mathematical model of an epidemic in 1766, yet it was the seminal publication by Ross in 1911 (along with two others by Kermack and McKendrick) which gave way to modern mathematical epidemiology and deterministic compartmental models [27]. Infectious diseases, outbreaks, epidemics and pandemics have shaped history. The value of mathematical models in understanding the dynamics of infectious diseases lies in preventing and controlling its spread as evidenced in recent history by the 2003 SARS outbreak, the 2009 Influenza epidemic and the 2014-2015 West African Ebola epidemic [29]. The importance and necessity of mathematical modelling is evident with every news cycle that features the current global COVID-19 pandemic. From predicting weekly case identification and mortality, to estimating the impact of measures such as lockdowns on both hospital capacity and economic repercussions, to the speed at which vaccination may be able to achieve herd immunity; COVID-19 has thrust the role of mathematical modelling in public health, into the spotlight.

Mathematical modelling of HIV is an effective tool for informing public health policy, capable of predicting the trajectory of the HIV epidemic and evaluating the impact and cost-effectiveness of different prevention and control strategies. Published mathematical models of population level HIV transmission

dynamics designed to improve understanding of the course of disease, adhere to standard infectious diseases modelling practices of the mechanistic state-space model classification [27], generated through real life observation and assumptions underlying causal mechanisms [30]. HIV models can be furthered classified according to various properties: static vs. dynamic; deterministic vs. stochastic; aggregate vs individual (**C4**, **Figure 1**).



C4, Figure 1. Standard Classification of Mathematical Models According to 3 Properties: 1.) Static vs. Dynamic; 2.) Deterministic vs. Stochastic; 3.) Aggregate vs. Individual. (These classifications are how models are typically delineated. There are many exceptions to these properties, especially as hybrid-modelling approaches emerge)

4.2.4.1 Static Models

Static models represent a system or process at a specific point in time [26]. As a result, incidence of infection within a static model is independent of the changing prevalence of infection over time [31]. Static models are less complex, and easier to construct, but by affixing a predetermined, constant force of infection, contact or mixing patterns are not explicitly accounted for within the probability of transmission of infection between individuals [26]. For these reasons, static models estimate the direct effects of control strategies but tend to underestimate the indirect impact of interventions (such as vaccines) which reduce the prevalence of the incidence of infectious individuals [26]. One of the most well-known and routinely used static models of HIV is the *Modes of Transmission (MOT)* model, a deterministic, static, compartmental model [32] recommended by UNAIDS to inform country-specific HIV policy, focusing on subpopulations most at risk, and risk behaviors likely to drive HIV transmission [33, 34]. The *MOT* model stratifies mutually exclusive HIV risk groups (FSW, MSM, IDU, casual partnerships etc), indiscriminate of setting (i.e. not region-specific) [33, 34]. However, the most common category of static models are state-transition models, comprised of cohort-based Markov models and Individual-Based Models (IBMs), referred to as 'first-order Monte-Carlo' or microsimulations [35].

4.2.4.2 Dynamic Models

Unlike static models, dynamic models describe varying contact within the population, and can estimate both the direct and indirect effects of interventions on both the individual and population level. Incidence of infection is dependent on prevalence of infection as a function of time [31]. Dynamic models are typically more demanding due to their data needs, as detailed parameter and probability estimates are necessary [26, 36]. Dynamic models can take the form of compartmental models, agent-based models, network-based models and discrete event simulations.

4.2.4.2a Compartmental Models

The concept of a compartmental *SIR* – susceptible to infection (S); actively infected (I); recovered (R) – model was established in 1922 by Kermack and McKendrick, and was co-opted for many infectious diseases such as HIV [27, 37, 38]. Compartmental SIR models specific to HIV epidemiology (describing spread of infection within the population) started to appear in the literature during the mid-to late 1980s following the identification and isolation of the virus [38, 39].

There are two varieties of dynamic models, deterministic and stochastic. The characterization of a dynamic model is often defined by movements between states [26, 40]. Deterministic models are aggregated macrolevel representations, determined by differential equations, initial conditions and average parameters [40]. Stochastic models are more complicated, individual microlevel representations,

based on a range of probability distributions for each parameter, attempting to reflect inherent randomness [40]. Stochastic models are often viewed as a more realistic representation of the disease process, compared to their deterministic counterparts, as the amount of HIV virus entering a susceptible individual and establishing an infection is a chance event based on several factors (elucidated below). Stochastic models are also known to be more complex due to the difficulty involved in computing the inherent randomness of variables (most rigorously via Monte Carlo simulations), probabilities and risk factors populating the model and for moving from one state to the next [40-42]. The complexity and factors involved in computing the force of infection (λ) – the rate at which a susceptible individual becomes infected – is one of the foundational building blocks for variation in dynamic transmission models of HIV found throughout the literature [31]. Simpler interactions tend to model the force of infection (λ) as a function of transmission probability at contact (β) and the contact rate (c), where the proportion of infectious sexual contacts is equivalent to prevalence of HIV in the population [31, 40, 43, 44]. Whether a 'contact' (and associated transmission probability) is modelled as a partnership formed, or sex act,; these are only the basis for decisions around how to compute force of infection (λ) [45]. The complexity of computing force of infection (λ) can increase when attempting to incorporate some of the following factors: categorizing transmission rate (β) via various stages of HIV infection (i.e. infectiousness), rate of acquiring new partners, duration of partnerships, frequency of sex acts per partnership, condom use per sex act, concurrent sexual relationship, circumcision, social mixing patterns, etc[40]. Dynamic models are then further differentiated by their demographic considerations (sexual orientation, age-differentiation, risk group differentiation such as FSW or IDU), handling of treatment (varying according to CD4 count or viral load), incorporation of coinfections (STIs, TB), hospitalization etc [46]. It was the dual implementation (both deterministic and stochastic) of a basic (undifferentiated by age and sex) dynamic model by Granich et al. (2009), which led to the conception of the universal HIV test and treat policy [47].

4.2.4.2b Agent-Based Models

System dynamics (i.e. compartmental) models employ a top-down approach, and analyze systems at the macro or meso-level [48]. Agent based models (ABMs), known alternatively as individual based stochastic models, or dynamic microsimulations are extremely detailed, stochastic representations capturing individual social and sexual behavior within a bottom-up, modelled environment [31] that allows for artificial intelligence / machine learning. Agent-based models expand the realm of possibility by simulating counterfactuals and assessing the outcomes of multiple scenarios, but they are difficult to parameterize, analyze and generalize [49, 50]. ABMs capture interactions among and between different agents (e.g.. people), and their environments [51]. ABMs are built on the premise that simple inputs and

observations of individual behavior, will aggregate to reveal macroscopic, complex phenomena [51]. Network models can be seen as a subset of ABMs as they are also stochastic in nature [52], but focus heavily on partnership dynamics (i.e. networks) [53].

4.2.5 A Brief Overview of Modelling Approaches of HIV Testing Strategies in SSA

To review relevant models for this chapter, mathematical models of HIV testing strategies in SSA were reviewed to determine how they accounted for and incorporated the child (ages 0-9) and adolescent/youth (ages 10-24) demographics into the model (**C4, Table 1**).

The targeted search in Medline incorporating terms around 4 concepts – HIV, Testing, Modelling and SSA – yielded a total of 39 relevant articles where mathematical modelling was used to assess the impact of various HIV testing strategies on population level outcomes. (Complete search strategy can be found in the **Thesis Appendix, Supplementary File 2**.) The most frequent modelling approaches used were compartmental modelling (16/39) and agent-based modelling (14/39). There were 5 state-transition models which all answered a similar question; to (solely) determine the cost-effectiveness of an HIV testing strategy. An additional 2 studies used a network modelling approach, and 1 study evaluated multiple models (ranging from variously structured compartmental models to variously structured microsimulations), to understand the implication of model structures on generated outcomes. The modelling approach was unclear in the remaining study. Eastern and Southern Africa (ESA) were the focus and region for model calibration data in a majority of these studies (32/39). Of the remaining 7 studies, data for model calibration came from:

1.) West Africa (2/39);
2.) both ESA and West Africa (2/39);
3.) 40 SSA countries (1/39);
4.) ESA, South America and Eastern Europe (1/39);
5.) was not reported (1/39).

Incorporating children and adolescents into model structures was heterogenous even within the same category of models. Sixteen of the 39 models reviewed *did not* include both children and adolescents within their modelled cohort, [state-transition (n=1); compartmental (n=7); agent-based (n=7); unknown structure (n=1)] ,while 7 *did* include both these age groups, [state-transition (n=3); compartmental (n=3); network (n=1)]. Ten of the 39 models, [state-transition (n=1); compartmental (n=5); agent-based (n=4)], *did not represent children* within their modelling structures but *did include adolescents* [usually aged

15+, (n=9)] into their age structured cohort. It was not possible to determine age-structuring of cohorts in the remaining 6 studies.

In Zimbabwe, the legal age of consent is 16, (however 13-15 year olds are deemed able to consent) [54], and only 5-6% of those aged 15-24 have reported having sex before age 15 [55]. Model structures are highly contextual [56], and research questions interested in assessing trends and interventions pertaining to sexual/horizontal transmission only, are justified in modelling cohorts from age 15 onwards. However, in doing so, the opportunity to accurately capture the full burden of HIV and corresponding epidemic impact are missed. Despite the progress of PMTCT programs in Zimbabwe, 3600 children under 15 were newly infected with HIV in 2023, and notwithstanding the success of the adult population in reaching the 95-95-95 targets, ART coverage in children under 15 was only 63% [57]. Methodologically rigorous models such as HIV-Synthesis and Goals-ASM that capture the dual burden of horizontal and vertical transmission, but do not allow for structural considerations to propagate those newly infected children forward, miss an opportunity to identify and implement instances for something as simple and effective as early infant diagnosis, to more complex evaluations of tailored interventions that address the unique needs of the child population. Integrating children into HIV model frameworks is integral to ensuring equitable care, not to mention, achieving country and global targets.

The 7 studies identified which explicitly represented both children and adolescents within their cohort for analysis had different research questions, for two of which the rationale behind age-structured cohorts were immediately apparent. One study assessed the costs and outcomes of three HIV testing strategies for early infant diagnosis [58], using a cohort which only included infants (aged up to 12 months) and the ageing of potential HIV infection (children) until sexual debut (adolescence) and subsequent representation of horizontal transmission (adolescents and adults). Another study was a home-based testing and counseling intervention for pregnant woman and their partners [59]. A third study was an age structured model inclusive of children and adolescents, assessing the effects of a combination HIV intervention on the youth population (15-24 years) compared to adults (≥15), and age stratification was necessary for parameterization of mean years of survival with untreated HIV by age of infection [60]. A fourth study was a combination intervention targeting male migrant workers. The need for modelling children and adolescents was not evident, however can potentially be explained by the use of an established (age-structured) individual-based network model (EMOD) [61]. Age-structuring and the rationale behind its use in assessing the cost-effectiveness of various interventions along the programmatic pathway targeting adults was difficult to determine [62], (however, used an established

age-structured modelling framework – Spectrum), but clearer in a study attempting to determine the cost-effectiveness of home-based counselling and testing offered to all ages [62, 63].

An additional ten studies did not model children, but had an age-structured model inclusive of adolescents. Adolescents (and children especially) are only included in cohorts for analysis where interventions specifically address them. Thus, while many HIV testing interventions targeting children and adolescents exist, their specific impact on population levels outcomes have rarely been modelled. Recommendations for future research within this sub-population may benefit from modelling impact of newly emerging interventions, to demonstrate their value to decision makers.

C4, Table 1. A Targeted Review of Mathematical Models of HIV Testing Strategies in sub-Saharan Africa				
Reference	**Question Modelled**	**Country of Calibration**	**Type of Model**	**Handling of Children/Adolescents within Model**
STATIC MODELS				
State-Transition Models				
Maheswaran et al[61] (2018)	To assess the cost-effectiveness of adding HIV self-testing to existing facility-based HIV testing and counseling services	Malawi	Individual-Level Simulation (Monte-Carlo or microsimulation)	- Age differentiated cohort: 16 – 50+ years - 5 age categories: 16-19; 20-29; 30-39; 40-49; 50+ Children not explicitly modelled, Adolescents explicitly modelled
McCann et al[58] (2020)	To examine clinical benefits and costs of 3 EID strategies (including HIV testing) in Zimbabwe for infants 6 weeks of age	Zimbabwe	Monte-Carlo Microsimulation	- Age differentiated cohort: 0 – 59 years - 9 age categories: 0-2; 3-5; 6-8; 9-11; 12-17; 18-23; 24-35; 36-47; 48-59 - Children and Adolescents explicitly modelled
Meisner et al[64] (2021)	To determine the optimal timing and cost-effectiveness of maternal HIV retesting during pregnancy (and breast-feeding)	South Africa, Kenya, Columbia, Ukraine	Deterministic State-Transition Model	- Non-age differentiated cohort - Women of reproductive age only: 15 – 49 years Children and Adolescents not explicitly modelled
Olney et al[65] (2016)	To assess a combination of interventions (including HIV testing) and determine the optimal cost-effective mix of strategies with the largest impact on population health	Kenya	Individual-Based Microsimulation	- Age differentiated cohort: 0 – 80+ years - 5 year age groups: 0-4, 5-9, …, 70-74, 75-79, >80 Children and Adolescents explicitly modelled
Olney et al[62] (2018)	Determine optimal timing of home-based HIV testing and counselling to generate maximum health outcomes at lower costs	Kenya	Individual-Based Microsimulation	- Age differentiated cohort: 0 – 80+ years - 5 year age groups: 0-4, 5-9, …, 70-74, 75-79, >80 - Children and Adolescents explicitly modelled
DYNAMIC MODELS				
Compartmental Models				
Alsallaq et al[66] (2013)	To determine the effect a combination of prevention interventions (including HIV testing) have on HIV incidence in South Africa	South Africa	Deterministic Transmission Model (compartmental mathematical model)	- Non-age differentiated cohort - Adult population: 15 – 49 years - Children and Adolescents not explicitly modelled

Alsallaq et al[60] (2017)	To compare the impact and costs of HIV prevention strategies (including HIV testing) on youth versus adults in a large generalized epidemic	Kenya	Deterministic Compartmental Model	- Age differentiated cohort: 0 – 69+ years - 14, 5-year age groups: <5 - ≥69 - Children and Adolescents explicitly modelled
Blaizot et al[67] (2016)	To determine whether multiple prevention interventions (including HIV testing) may reduce HIV incidence in hyperendemic settings	Kenya	Deterministic Dynamic Transmission Model	- Age differentiated cohort: 15 – 59 years - 3 age categories: 15-24; 25-34; 35-59 Children not explicitly modelled, Adolescents explicitly modelled
Cori et al[68] (2014)	To assess whether a combination prevention package (including HIV testing) can reduce HIV population-level incidence	Multi-country: - Zambia - South Africa	Deterministic Compartmental Model	- Non-age differentiated cohort - Adult Population: 18 – 44 years Children and Adolescents not explicitly modelled
Giguere et al[69] (2021)	To estimate the efficiency of HIV testing services in Africa as they pertain to estimating progress and gaps in achieving the UNAIDS '90% knowledge of status' target	Multi-country: - 40 countries in SSA	Deterministic Compartmental Model	- Age differentiated cohort: 15 – 49 years - 3 age categories: 15-24; 25-34; 35-49 Children not explicitly modelled, Adolescents explicitly modelled
Gilbert et al[61] (2015)	To evaluate the effectiveness of integrating HIV and TB case finding through a novel screening program (including HIV testing), in averting HIV and TB transmission over a 10 year time period in South Africa	South Africa	Deterministic Dynamic Transmission Model	- Non-age differentiated cohort - Adult population: 15 – 64 years Children and Adolescents not explicitly modelled
Hove-Musekva et al[61] (2014)	To evaluate the cost and benefits of home-based care and various other intervention strategies (including HIV testing) in Zimbabwe	Zimbabwe	Deterministic Dynamic Transmission Model	- Non-age differentiated cohort - Adult population: 15 – 49 years - Children and Adolescents not explicitly modelled
Johnson et al[70] (2015)	To estimate the rate of HIV diagnosis (via HIV testing) in South Africa	South Africa	Deterministic Compartmental Model	- Age differentiated cohort: 0 – 90+ years - Age categories not presented Unclear - Assuming both Children and Adolescents explicitly modelled
Maheu-Giroux et al[71] (2019)	To estimate the proportion of people living with HIV who know their status (i.e. through HIV testing)	Multi-country: - Cote D'Ivoire - Malawi - Mozambique	Deterministic Compartmental Model	- Age differentiated cohort: 15 – 50+ years - 4 age categories: 15-24; 25-34; 35-49; 50+ Children not explicitly modelled, Adolescents explicitly modelled

Maheu-Giroux et al[72] (2017)	To estimate the impact of scaling up of interventions (including HIV testing) to meet the UNAIDS 90-90-90 targets, would have on HIV transmission in adults and children	Cote D'Ivoire	Deterministic Compartmental Model	- Age differentiated cohort: 15 – 50+ years - 4 age categories: 15-19; 20-24; 25-49; 50-59 - Children not explicitly modelled, Adolescents explicitly modelled
Omondi et al[73] (2018)	Determining the impact of interventions (including HIV testing) on HIV transmission	Kenya	Deterministic Dynamic Transmission Model	- Non-age differentiated cohort - Adult Population: 15+ years Children and Adolescents not explicitly modelled
Ronoh et al[74] (2020)	Determine how combination control measures (including HIV testing) influences HIV/AIDS rates among Kenyan youth	Kenya	Deterministic Compartmental Model	- Non-age differentiated cohort: - Adolescent/Youth Population: 15 – 24 years Children not explicitly modelled, Adolescents explicitly modelled
Sharma et al[59] (2016)	To determine the health and economic benefits of implementing a home-based partner (education) and HIV testing intervention for pregnant women and their partners	Kenya	Deterministic Dynamic Transmission Model	- Age differentiated cohort: 0 – 59 years - 5 year age groups: 0-4, 5-9, …, 55-59 - Children and Adolescents explicitly modelled
Smith et al[75] (2016)	To determine the ideal mix of interventions (including HIV testing) to achieve the greatest possible prevention impact	South Africa	Deterministic Compartmental Model	- Non-age differentiated cohort - Adult Population: 15 – 49 years - Children and Adolescents not explicitly modelled
Wall et al[76] (2020)	To assess the cost-per-HIV infection averted by voluntary couples' testing in six African countries	Multi-country: - South Africa - Zimbabwe - Kenya - Tanzania - Ivory Coast - Sierra Leone	Deterministic Dynamic Transmission Model	- Non-age differentiated cohort - Adult Population: 15 – 64 years Children and Adolescents not explicitly modelled
Ying et al[63] (2016)	To assess the effect of a periodic home HIV testing program on HIV incidence in South Africa	South Africa	Deterministic Dynamic Transmission Model	- Age differentiated cohort: 0 – 59 years - 5 year age groups: 0-4, 5-9, …, 55-59 Children and Adolescents explicitly modelled
Agent Based Models				
Abuelezam et al[77] (2016)	To assess which combination of efficacious HIV prevention measures (including HIV testing) has the potential for HIV elimination in South Africa	South Africa	Agent-Based Model linked to CEPAC (a monte-carlo simulation)	- Mention of an age-differentiated structure, but categories not explicitly outlined in paper or supplementary materials. Assuming that age differentiating follows CEPAC model: 0 – 59 years - 9 – Age categories: 0-2; 3-5; 6-8; 9-11; 12-17; 18-23; 24-35; 36-47; 48-59

				Assuming Children and Adolescents explicitly modelled
Abuelezam et al[78] (2019)	To assess scenarios of incremental improvements to the testing and ART continuum in South Africa	South Africa	Agent-Based Model linked to CEPAC (a monte-carlo simulation)	- Mention of an age-differentiated structure, but categories not explicitly outlined in paper or supplementary materials. Assuming that age differentiating follows CEPAC model: 0 – 59 years - 9 – Age categories: 0-2; 3-5; 6-8; 9-11; 12-17; 18-23; 24-35; 36-47; 48-59 Assuming Children and Adolescents explicitly modelled
Brookmeyer et al[79] (2014)	To determine what combination of prevention packages (including HIV testing) can prevention significant numbers of infection among MSM in South Africa	South Africa	Agent-Based Model	- Age of cohort unspecified in both paper and supplemental material. - Assuming cohort of analysis is sexually active MSM, undifferentiated by age. Children and Adolescents not explicitly modelled
Cambiano et al[80] (2015)	To determine the cost-effectiveness of self-testing over a 20 year time period in Zimbabwe	Zimbabwe	Individual Based-Stochastic Model	- Age differentiated cohort: 15 – 64 years - 5, 10-year age groups: 15-24, 25-34,…, 55-64 Children not explicitly modelled, Adolescents explicitly modelled
Cambiano et al[81] (2019)	To determine the epidemiological impact and cost-effectiveness of community-based HIV self-testing in various sub-populations with differing HIV prevalence rates	Multi-country: - Zimbabwe - Zambia - Malawi	Individual Based-Stochastic Model	- Age differentiated cohort: 15 – 64 years - 5, 10-year age groups: 15-24, 25-34,…, 55-64 Children not explicitly modelled, Adolescents explicitly modelled
Johnson et al[82] (2019)	To compare the impact and cost-effectiveness of several new HIV testing strategies in South Africa	South Africa	Agent-Based Model	- Age differentiated cohort: 15 – 50+ years - 3 age categories: 15-24; 25-49; 50+ - Children not explicitly modelled, Adolescents explicitly modelled
Lilian et al[83] (2014)	To identify the optimal HIV testing intervals to maximize the number of perinatal HIV infections diagnosed.	South Africa	Individual Based Stochastic Model	- Age differentiated cohort: Infants - 4 age categories: Birth, 6 weeks, 10 weeks, 14 weeks - Children and Adolescents not explicitly modelled
Luong Nguyen et al[84] (2018)	To determine the effectiveness and cost-effectiveness of a voluntary community testing program in Kenya	Kenya	(Dynamic Microsimulation & Agent Based Model) – i.e. Individual Based Stochastic Model	- Cohort for analysis generated via random draws of characteristics from distributions of *sex* and *age* - No further resolution regarding age structure was presented in paper or supplementary material - Unsure if Children and Adolescents are explicitly modelled or not.

McCreesh et al[85] (2017)	To determine the cost and effects of different ART scale-up options (including HIV testing)	Uganda	Individual-Based/ Agent-Based	- Non-age differentiated cohort - Adult population: 15 – 49 years - Children and Adolescents not explicitly modelled
Monteiro et al[86] (2015)	Evaluate the effects of prevention interventions (including HIV testing) on HIV incidence trajectories	Cabo Verde	Individual-Based Model	- Non-age differentiated cohort - Adult Population: 15 – 49 years - Children and Adolescents not explicitly modelled
Phillips et al[87] (2019)	To use 'cost-per-diagnosis' as a surrogate metric to help guide country based HIV testing programs	Malawi	Individual Based-Stochastic Model	- Age differentiated cohort: 15 – 64 years - 5 age categories: 15-24; 25-34; 35-44; 45-54; 55-64 - Children not explicitly modelled, Adolescents explicitly modelled
Sharma et al[88] (2018)	To determine the health impact (incident HIV and mortality) as well as the economic impact of implementing assisted partner services/provider notification (i.e. testing) for sexual partners of newly diagnosed positive individuals	Kenya	Individual Based Stochastic Model	- Non-age differentiated cohort - Adult Population: ≥ 18 years - Children and Adolescents not explicitly modelled
Smith et al[89] (2015)	To assess the cost-effectiveness and population-level impact of a home-based prevention package (including HIV testing)	South Africa	Individual Based Stochastic Model	- Non-age differentiated cohort - Adult Population: ≥ 18 years - Children and Adolescents not explicitly modelled
Thomas et al[90] (2021)	To determine the cost-effectiveness of a combination prevention package (including HIV testing) shown to reduce population level incidence	Multi-country: - Zambia - South Africa	Individual-Based Model	- Non-age differentiated cohort - Adult Population: >14 years - Children and Adolescents not explicitly modelled
Network Models				
Bershteyn et al[91] (2016)	To determine whether age-targeted prevention (including HIV testing) could avert HIV infections in South Africa	South Africa	Individual Based Network Model	- Age differentiated cohort: 0 – 80+ years - Multiple age range classifications: 2, 5, 10 and 20 year age blocks. Depending on classification, children and adolescents explicitly modelled
Klein et al[61] (2015)	To estimate the community-wide impact of targeting treatment and prevention (including HIV testing) to male migrants.	South Africa	Individual Based Network Model	- Age differentiated cohort: 0 – 80+ years - Age differentiated with multiple age range classifications: 2, 5, 10 and 20 year age blocks. - Children and Adolescents explicitly modelled

Other				
Hontelez et al[92] (2013)	The understand the implications of different model structures and their resulting predictions of the impact of the 'Universal Test and Treat' strategy, aimed at HIV elimination in South Africa	South Africa	9 Models: Various Deterministic Compartmental Models (where the structures build on each other) to Stochastic Microsimulations (where the structures build on each other)	- Cohort for analysis: 15+ years - 2 of 9 models are non-age differentiated - 7 of 9 models are age structured - Age classifications/groupings difficult to discern for the 7 age structured models - Children not explicitly modelled, unsure if Adolescents were explicitly modelled
Salvatore et al[93] (2021)	To determine the impact of PoC HIV testing on early infant diagnosis	Calibration details not presented. (Population simulated was representative of a high burden country in SSA)	Unclear: (Model structure not presented in paper/no accompanying technical appendices or supplemental material)	- Age differentiated cohort: Infants - 2 age categories: 6 weeks, 9 months - Children and Adolescents not explicitly modelled

4.3.2 AIMS AND OBJECTIVES

The targeted review above highlights that children and adolescents are not routinely or frequently incorporated into modelling structures, when considering the impact of HIV testing interventions in SSA, problematic, considering the significantly lower HIV testing coverage rate in children and adolescents, compared to adults. The omission of children and adolescents from these models results in underrepresentation and ineffectual response measures to the HIV epidemic in these sub-populations. An understanding of how the most popular, utilized and referenced HIV models in the SSA context address and account for child and adolescent HIV transmission dynamics, is of interest when targeting HIV prevention and treatment strategies for this cohort, currently not keeping pace with the global HIV targets and response. Through a narrative review, I aimed to synthesize, compare and investigate SSA child and adolescent HIV transmission dynamics representation in popular dynamic mathematical models, through the following objectives:

1. To determine how the force of infection equations are calculated in (highly publicized) HIV models and if vertical transmission, and adolescent sexual mixing dynamics is accounted;
2. To identify and describe the interplay of the most relevant variables in adolescent HIV transmission within (highly publicized) HIV models;
3. To compare the appropriateness of adolescent HIV transmission representation among (highly publicized) HIV models, against current epidemiological knowledge;
4. To amalgamate the learnings of model structure and force of infection calculations into best practice recommendations for future work in the field.

4.4 METHODS

4.4.1 Study Design

In order to investigate the variation in ways adolescents are represented and included in dynamic HIV epidemic models developed for the SSA context, a comprehensive narrative review of well-described, frequently used and cited mathematical models was conducted via a snowball literature search. The HIV Modelling Consortium's high visibility publication in the Lancet, (cited 200+ times), which characterized 5 models as 'well-described' was used as the seeding reference for this search [94]. These 5 models earned the distinction of 'well-described' based on 2 main criteria: 1.) discussions within an ad hoc group of experts; 2.) model conception based on 'many data sources' [94]. While current guidelines recommend the use of Google Scholar for snowball searches, Web of Science was chosen for its superior data visualization of both references included in published works, and citations of published works [95]. The references and citations of the 5 models – Epidemiological MODeling software (EMOD) [96], Goals [97],

HIV Synthesis [98], Imperial College London Model [99] and Optima HIV [100] – were the starting point of the snowball literature search.

4.4.2 Search Strategy

The search strategy was derived from a subjective point of origin as the reference and citation profile of each of the 5 models directly cited in the Lancet article [94], were 'referenced tracked' via Web of Science to determine how many times these models were cited in literature, in order to establish a consensus for a definition that encapsulated 'well-described' and 'frequently used/cited' dynamic mathematical models of HIV. To further strength the definition of 'well-described and frequently used/cited' models, the original 5 model names were generically searched in Web of Science to determine how many publications using those 5 specific models, existed. Based on the results and commonalities found between these 2 exploratory search strategies, a definition for 'well-described and frequently used/cited' dynamic models was formed. The citations of the models and publications that met the definition for 'well-described and frequently used/cited' were then title and abstract searched, looking specifically for modelling review studies where 2 or more dynamic mathematical models of HIV were compared, to use as a starting point to identify any other potential dynamic mathematical models of HIV which would meet the definition of 'well-described and frequently used/cited'. Any new models identified, (outside of the original 5 seed models), was subjected to the original process of identifying, (via a search in Web of Science), the number of model citations in the literature along with the number of published analysis using said new model.

4.4.3 Eligibility Criteria

Any dynamic mathematical model of HIV published in the last 10 years, i.e. 2013 onwards, which calibrated data to any country and setting in SSA, irrespective of population of interest, (general or key population), and type of analysis, (retrospective vs prospective, real vs hypothetical cohort, impact/trends vs economic evaluation) was eligible. Any HIV modelling studies evaluating any strategy (e.g. prevention, treatment, adherence, behavioral, technological, diagnostic etc.) was included.

4.4.4 Study Selection

Search results were imported into Endnote X9 for storage and duplicate removal. Titles and abstracts were screened and excluded based on the following criteria: 1.) Was published more than 10 years ago; 2.) Did not meet the definition of a 'well-described and frequently used/cited' model; 3.) Was not calibrated to the SSA context; 4.) Non-English language; 5.) Full text unavailable (including conference

abstracts). Dynamic mathematical models of HIV meeting the inclusion criteria were reviewed as full-text.

4.4.5. Data Extraction

A multi-component data extraction tool was developed. Firstly, general features of the model including publication date, model version, setting/country of study, population of interest, modelling approach, objective/purpose of analysis, comparator strategies and outcomes measured were extracted. The second component was based on the determination of population construction (i.e. age stratification and age-dependent sexual risk behaviors) within the models along with the evaluation of force of infection equations (i.e. transmission probability and contact rates).

4.4.6. Data Analysis

Descriptive analysis was conducted to present the methodological features of models, along with a narrative review of model attributes and dynamics with regards to appropriateness for inclusion (or lack thereof), within an adolescent population. The quality of the narrative review was evaluated against the SANSRA – (scale for the assessment of narrative review articles) – appraisal tool [101].

4.5 RESULTS

4.5.1 Defining ‘Well-Described’ and ‘Frequently Used/Cited' Dynamic Mathematical Models of HIV

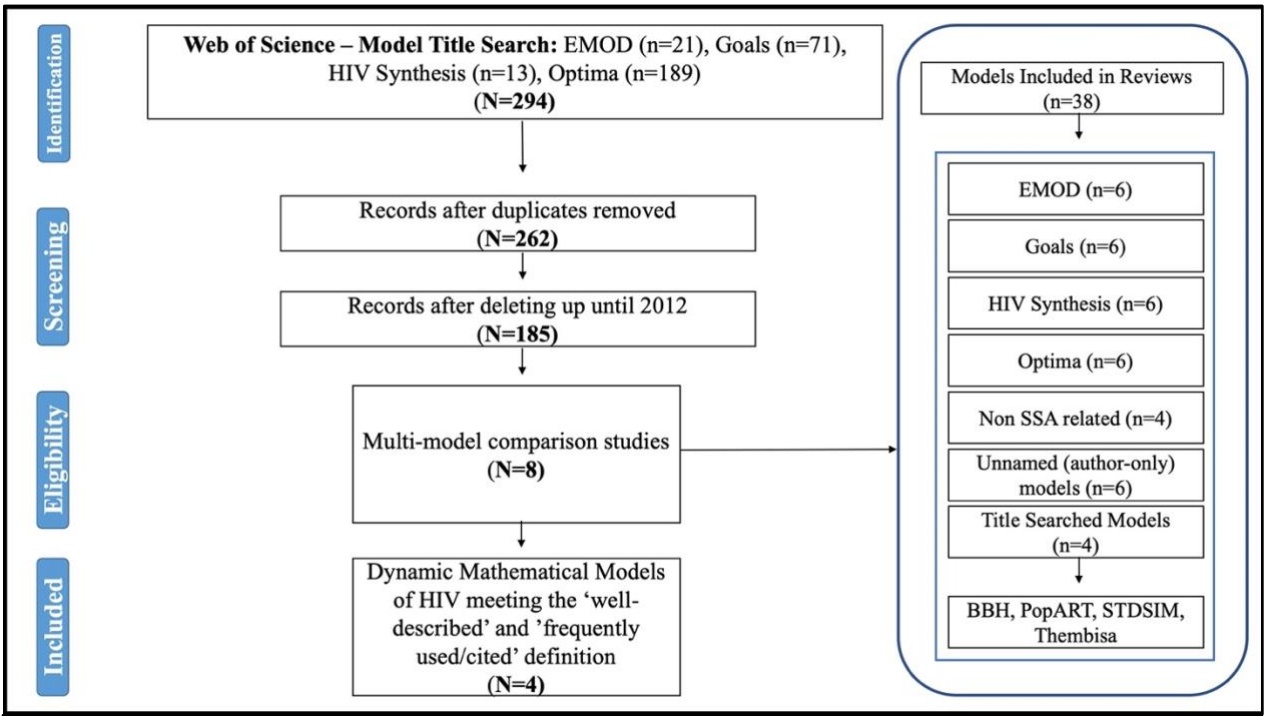
The 5 models in the seed reference were Epidemiological MODeling software (EMOD) [96], Goals [97], HIV Synthesis [98], Imperial College London Model [99] and Optima HIV [100]. Judging against the criteria of ‘well-described’, (i.e. model conception based on ‘many data sources’) and ‘frequently used/cited’ (i.e. large number of citations), the model publications displayed the following number of references and citations respectively: EMOD – 34 and 88; Goals – 22 and 160; HIV Synthesis – 44 and 69; Imperial College London Model – 17 and 6; Optima – 23 and 73 (**C4, Table 2**). The Imperial College London Model was cited 86.4% or 11.5 times less than the next lowest option (Synthesis), and 96.3% or 26.7 times less than the highest option (Goals). Given that the model was cited significantly less than the other 4 models, and a title and abstract search of the model (i.e. Imperial College London (HIV) Model) did not retrieve any relevant results, I made the determination that it was not frequently used/cited, and dropped it from the search. (The remaining 4 models were title searched in Web of Science with no restrictions on date and yielded the following number of publications each: EMOD (HIV Model)– 21; (Avenir/Spectrum) Goals HIV Model– 71; HIV Synthesis (Model)– 13 ; Optima (HIV Model)– 189. Based on these findings, a ‘well-described’ and ‘frequently used/cited’ dynamic mathematical model of

HIV was defined to be a model that had 10 or more publications using the model, along with at least one of the model publications having been cited 65 times or more.

C4, Table 2: Search Results en route to Identifying 'Well-Described' and 'Frequently Used/Cited' Dynamic Mathematical Models of HIV			
Seed Reference Models	**References Used**	**Citations in Literature**	**Title search Results in Web of Science**
EMOD	34	88	21
Goals	22	160	71
HIV Synthesis	44	69	13
ICL	17	6	Dropped
Optima	23	73	189

4.5.2 Study Selection

The results of the title search of the 4 models in Web of Science were exported into Endnote, yielding a total of 294 records. Following removal of duplicate records (32), and articles published prior to 2013 (77), 185 records remained. Titles and abstracts were then reviewed to isolate modelling review studies, where 2 or more dynamic mathematical models of HIV were compared, in order to identify other models which could meet the definition of a 'well-described' and 'frequently used/cited' dynamic mathematical model of HIV. A total of 8 multi-model review studies were identified, covering 38 models between them. EMOD, Goals, HIV Synthesis and Optima, were included 6 times each in various combinations across the multi-model comparison studies. Of the remaining 14 models, 4 were excluded for being non-related to the SSA context, while 6 were excluded for being nameless models, which could not be searched further. The remaining 4 models were title searched through Web of Science, repeating the original process to determine whether they were 'well-described' and 'frequently used/cited'; i.e. ≤10 model related publications, and cited ≤65 times. Of the 4 remaining models, three models – PopART, STDSIM and Thembisa – partially met the definition of 'well-described' and 'frequently used/cited', but were ultimately excluded. (The PopART model met the required citation threshold, but did not have ≤10 model related publications; the STDSIM model met the definition on both the citation and publication front, but the papers that did, were published prior to 2013; the Thembisa model did not meet the required citation threshold, but did have ≤10 model related publications; BBH did not meet the citation or publication threshold.) As a result, the original 4 models (EMOD, Goals, HIV Synthesis and Optima), were the only models included in this narrative review (**C4, Figure 3**).



C4, Figure 2. Flowchart of the Inclusion and Exclusion Process for the Narrative Review

Definition of 'well-described' and 'frequently used/cited' models= ≤10 model related publications, with at least one publication having been cited ≤65 times
SSA = Sub-Saharan Africa

4.5.3 Model Overview and Characteristics

C4, Table 3 provides an overview of the 4 models included in this review. The modelling approach was evenly split amongst the 4 model: 50% of models – (EMOD and HIV-Synthesis) – were individual-based stochastic models; 50% of models – (Goals and Optima) – were compartmental models. There was no overlap in rationale for model conceptualization (i.e. initial objective for building the model), and thus comparator strategies, along with software used between the 4 models.

C4, Table 3: Narrative Review - Model Inclusion – Model Features Overview				
Features	**EMOD-HIV [102]**	**Goals [103]**	**HIV-Synthesis [98]**	**Optima-HIV [100]**
Model Features Overview				
Model Version/ Pub Date	V08, 2014	2021	2014	2015
Setting	South Africa and Zambia	Countries in SSA	Southern Africa	40 countries, including 14 SSA
Pop. Of Interest	Unrestricted (Any age entering treatment cascade through 5 testing pathways)	Individuals 15-80	Individuals 15-64	Distinct population groups living with HIV (Including general population children/youth/adults, FSWs, IDUs, MSM)
Modelling Approach	Individual-Based Stochastic Model	Compartment Model	Individual-Based Stochastic Model	Compartment Model
Objective/Purpose	Identify possible explanations for the HIV epidemic by examining a diverse set of structural and parametric modelling assumptions	Determine resource allocation of services needed to achieve national HIV program goals	Determine the impact (effectiveness and cost-effectiveness) of various HIV interventions on the levels of transmitted drug resistance	Allocative efficient HIV response: Address practical policy and programmatic issues encountered by funders, governments, health planners and program implementers
Comparator Strategies	Various different structural and/or parametric assumptions, and the impact on the HIV epidemic	Epidemic under varied behavioral change program considerations	Standard of Care ART regimen and monitoring, based on current guideline	Current versus optimal allocation of resources for a given objective
Outcomes Measured	HIV prevalence; HIV Incidence; HIV related mortality	New Infections; HIV related mortality	Prevalence; HIV related mortality; % drug resistance; % VL suppression, QALY	Allocative HIV efficiency: Identify priority prevention and treatment programs; coverage levels (needed to achieve targets); Prevalence; Incidence; HIV-related mortality
Software	C++	Spectrum Software Suite	SAS	Matlab and Python

C4, Table 4: Narrative Review - Model Inclusion – Sexual Mixing Considerations				
Features	**EMOD-HIV [104]**	**Goals [103]**	**HIV-Synthesis [98]**	**Optima-HIV [100]**
Sexual Behavior	Type of Relationship: - Transitory; - Informal; - Marital; Concurrent Partnership/Coital Dilution: - With 2 partners; - With 3 partners; - With 4+ partners Condom Use by: - Relationship; - Sex Act	Sexual Partnerships according to: - Age when partner acquisition peaks; - Age by which half of lifetime partners have been acquired Difference between males and their female partners according to: - Mean Age; - Variance in Age Condom Use in partnerships by: - Last Sex	Level of sexual risk activity differentiated by: - Gender (Male/Female); - 5 year age bands depicting the sexually active population aged: - 15-19; - 20-24; - 25-29; - 30-35; - 35-39; - 40-44; - 45-49; - 50-54; - 55-59; - 60-64 <u>Risk Categorization</u> Number of short term condomless sexual partners in the 3 month time period: *Men (n=4)* - - No short term condomless partner - Low number of short term partners - Medium number of short term partners - High number of short term partners *Women (n=2)* - - No short term condomless partner	Type of Partnership/Interaction: - Casual; - Regular; - Commercial homosexual; - Commercial heterosexual; - (Injecting) Number of sexual partners according to: - Type of partnership/interaction Intercourse Type: - Insertive; - Vaginal Receptive; - Anal Receptive Condom use by: - Sex act

			- 1 or more short term condomless partner(s) *Female Sex Worker (n=5)* - - No short term condomless partner - Low number of short term partners - Medium number of short term partners - High number of short term partners - Very high number of short term partners Of note: PrEP is offered to people who have at least one new condomless sex partner in a 3 month period, with 85% uptake willingness (and 95% in FSW). - Modelling assumption related to PrEP: No increase of condomless sex in population due to introduction of PrEP. Current long term condomless sex partner in the 3 month time period within 3 duration groups: - 1;2;3 (higher class, higher tendency to endure/more durable) - Non Gender Specific, but differentiated according to 3 age groups: - 15-44; - 45-54;	

			- 55-64; - Also factoring HIV status: - Infected and undiagnosed (primary infection) - Diagnosed, not on ART - Diagnosed, on ART - Current viral load <2.7 log cps/mL or not	
Sexual Mixing	Pair Formation Algorithm to balance supply and demand of partnerships through: - 3 Matrices of partnership age distributions	Partner change rates balanced to account for partnership supply and demand through: - Mixing Coefficients; - Balancing Terms	Sexual mixing matrices differentiated by: - Gender (Male/Female); - 10 year age bands depicting the sexually active population aged: - 15-24; - 25-34; - 35-44; - 45-54; - 55-64	No explicit sexual mixing considerations was presented in any of the technical documentation accompanying the model publications.
Horizontal Transmission Related Parameters	Calculated per Sex Act, considering the following: 1. Disease stage of partner: - Acute; - Latent; - AIDS-stage 2. ART status of partner: - Not on ART; - On ART;	Calculated per Partnership, considering the following: 1. Infection stage of partner: - CD4>500 cells/μL - 500>CD4>350 cells/μL - 349>CD4>250 cells/μL - 249>CD4>200 cells/μL - 199>CD4>100 cells/μL - 99>CD4>50 cells/μL - CD4<50 cells/μL	Calculated per Sex Act, considering the following: 1. Probability of Circumcision 2. STI Status: - Existing - Risk of new STI 3. PrEP: - Use	Calculated per Sex Act, considering the following: 1. Type of Partnership/Interaction & Intercourse 2. 14-20 population groups, such as: - Low-risk males; - Low-risk females; - Female Sex workers;

	- ART dropout 3. Male Circumcision 4. Presence of STIs 5. Condom Use 6. Anal intercourse: - Infected receptive female partner; - Infected insertive male partner	2. ART status of partner: - No ART; - On ART <6 months; - On ART 6-12 months; - On ART >12 months 3. Presence of STIs 4. Use of PrEP: - Oral; - Injectable; - Vaginal Gel; - Vaginal Ring 5. Male Circumcision 6. Condom Use: - Frequency at last sex (within heterosexual partnerships)	- Adherence Level 4. Male Circumcision 5. Transmission rate according to type of condomless partnership: <u>*a.) Short Term*</u> - - Probability of HIV infection is dependent on HIV prevalence in opposite gender and age group of partner - Viral load groups in HIV infected (and sampled from uniform distribution) <u>*b.) Long Term*</u> - - Total number of HIV subjects (diagnosed and undiagnosed) - Differentiated according to the following categories: - Primary infection; - Diagnosed not on treatment; - Diagnosed on ART; - On ART with a viral load <2.7 log cps/ml;	- Clients of female sex workers; - Females who inject drugs - Males who inject drugs; - Men who have sex with men; - Children (most likely aggregated by gender; - Etc. (Existence of other group types alluded to, but not explicitly stated, such as adolescent males and adolescent females) 2. STI Co-Infection: - Prevalence of HSV-2 and Syphilis 3. Effect of: - PrEP Use; - PEP Use - Circumcision Status (set to zero in women) 4. Condom Use: - Number of unprotected sex act 5. Health State of Partner: - CD4>500 cells/μL - 500>CD4>350 cells/μL - 350>CD4>200 cells/μL - 200>CD4>50 cells/μL - CD4<50 cells/μL 6. Treatment Status of Partner

				7. Male Circumcision (Injecting-related transmission/force of infection variables are also determined per act and include: probability that syringe is cleaned; methadone use; number of receptively shared injections.)

Vertical Transmission Related Parameters	Mother to Child transmission:
	- No intervention (1 in 3 births);
	- Not on ART but receive single-dose Nevirapine prophylaxis (1 in 10 births);
	- On ART (1 in 100 births)
		Mother to Child Transmission [105]:
		- Peripartum (in utero, intrapartum, 4-6 weeks postnatal) Transmission according to ART started:
		  - before pregnancy
		  - during pregnancy
		  - just before delivery
		- Postpartum (via breastfeeding) Transmission according to ART started:
		  - before pregnancy
		  - during pregnancy
			Mother to Child Transmission (risk per mother's viral load):
			- >100,000 copies/ml: 40%;
			- 10,000-100,000 copies/ml: 20%;
			- 1000-10,000 copies/ml: 10%;
			- <1000 copies/ml: 0.02%
				Mother to Child Transmission determined by:
				- Birth rate among HIV positive women;
				- Proportion of HIV positive women who breastfeed;
				- Proportion of women receiving PMTCT

EMOD [104]:

EMOD-HIV, an open-source, agent based model (i.e. individual-based stochastic simulation), having undergone over a decade's long development by a diverse group of professionals, is considered one of the most feasible and reliable representations of the dynamics of HIV transmission modelling [96]. Coded in C++, the modelling framework integrates both (heterosexual) horizontal and vertical HIV transmission through a series of discrete events and time steps. The model explores an evolving network of relationships through sexual behavior, mixing patterns and partner concurrency. Initially parameterized for South Africa, parametric considerations were extended to Zambia as well in version 08 (**C4, Table 3**). (**C4, Table 3**). [96].

The model treats individuals as agents characterized by demographic attributes (such as age, gender, birth and death), with varied sexual behavior traits around type of partnership (transitory, informal, and martial) and concurrent partners. Each partnership type varies in duration and likelihood of concurrency, with higher concurrency rates seen in shorter partnerships, such as transitory and informal relationships, while martial partnerships allow for fewer concurrent partners. Parametrized using partnership age data collected in KawZulu-Natal, sexual mixing is modeled through three distinct Matrix of Partnership Age Distributions (MOPAD) to reflect age distribution of partners and adjusted by relationship duration to capture new partnerships. With equal numbers of male and female agents entering, the Pair Formation Algorithm (PFA) matches individuals into relationships, ensuring target age patterns are reflected via the distribution of partnerships (**C4, Table 4**). The base relationship formation and dissolution rates differ according to type of partnership: transitory partnerships are marked by quick formation and brief duration, while marital partnerships are more stable. Young individuals tend to enter short-term transitory partnerships, while older individuals engage in longer marital relationships.

Horizontal transmission probability is calculated per sex act and determined according to disease stage (acute, latent, AIDS) and ART status (not on ART, on ART, ART drop out) of partner, according to age dependent mixing patterns of an individual and the age of their partner. The effect of behavioral modifiers such as condom use (varied across relationship type), presence of STIs, concurrent partnerships (2,3,4+) affect transmission risk rates. Vertical transmission is modelled according to ART status – no ART, single-dose Nevirapine prophylaxis, on ART – of the mother (**C4, Table 4**). The most recent version of the model (version 08), expands representation of the HIV treatment cascade, testing modalities and management of ART within the model's structural considerations [102].

Goals (ASM) [103]:

The Goals model, a deterministic compartmental model, is a part of the Spectrum software suite developed by Avenir Health (**C4, Table 3**) [97]. Spectrum is a system of policy models developed to support "analysis, planning and advocacy for health programs in public health and accompanying research" [106]. The Goals model is one of nine impact models in the Spectrum suite [106]. Two different versions of the Goals model exist: 1.) Goals-ASM, the age-structured version developed for settings with generalized epidemics where HIV transmission is driven by age and sexual contact patterns; 2) Goals-RSM, the risk-structured version developed for settings with concentrated epidemics where HIV transmission is driven by key populations and their partners [103]. (This review will focus only on describing the Goals-ASM model due to relevance related to this chapter and the overall thesis.)

Goals-ASM, developed for the SSA context to support national and international planning for HIV programs by projecting the expected impact and cost of combinations of prevention and treatment interventions on the reduction in HIV-related mortality, uses the Spectrum suite's AIDS Impact Module (AIM) as the basis of its model structure and compartments [103]. The way in which Goals-ASM models disease progression, [denoted by 7 stages of infection (CD4 cell count >500, 350-500, 250-349, 200-249, 100-199, 50-99, <50 cells/μL)], ART status (naïve, <6 months, 6-12 months, on ART >12 months) and AIDS related mortality (disaggregated by age, sex and CD4 count), is the same as the AIM model [103]. (Incidentally, AIM is used by national programs and international organizations such as UNAIDS to produce estimates and projections of HIV indicators [105].) The novelty of Goals-ASM lies in its extension of the AIM model's mechanistic (i.e. the system of non-linear ordinary differential equations) representation of horizontal transmission, by improving and refining the sexual mixing considerations by age, in those 15 years and older [103, 107]. Goals-ASM does not extend AIM's vertical transmission force of infection considerations [103]. (In AIM, and thus Goals-ASM, mother-to-child peripartum and postpartum transmission rates are determined by timing of initiation of ART – prior to pregnancy, during pregnancy, or just before delivery (**C4, Table 3**) [105].)

Sexual behavior in the model is denoted by partner change rates, which are adjusted to ensure balance between the supply and demand for partnerships across sexes. This adjustment takes into account the following factors: population size; nominal partner change rates; mixing coefficients; balancing terms. Nominal partner change rates in the model are specified by a logistic curve depicting age-specific, average number of lifetime partners. The mixing coefficients specify the extent to which people of *age a,* engage in partnerships with opposite-sex partners *aged b*. Mixing coefficients for females are determined by the sexual mixing age difference between partners via a normal distribution, accounting for mean and

variance in partner age differences. The balancing terms are calculated dynamically to ensure that the number of partnerships between males and females between the age range of 15 – 80, remains balanced (**C4, Table 4**).

Horizontal transmission in the model is determined per partnership and dependent on HIV prevalence based on sex and age of partner, stratified according to stage of infection and ART status, along with partner change rates. The presence of STIs (based on age and sex specific prevalence) increases the risk of HIV acquisition three-fold, while male circumcision is assumed to decrease risk of HIV acquisition by 60%. The use of PrEP is represented in the model through 4 modalities: oral; injectable; vaginal gel; vaginal ring. Based on sex, age and PrEP method, varying coverage levels and static effectiveness toward HIV acquisition reduction is assumed. Condom use is assumed to reduce HIV acquisition by 80% and is specified by the frequency of condom use at last sex. Condom use frequency is based on male partner's age. Goals-ASM then simulates behavior change programs and measures their impact across 5 outcomes age of sexual debut; age-disparate mixing, number of partners; condom use; partner or sexual violence – which in turn affects parameters used in the force of infection equations to calculate.

HIV-Synthesis [98]:

HIV-Synthesis, an individual-based stochastic HIV model simulates HIV transmission, including sexual behavior considerations, HIV progression and treatment, within a southern African context. Initially calibrated to data from studies and surveys conducted in KwaZulu-Natal, it simulates individuals aged 15 (age of sexual debut), to 64 (assumed cessation of sex), from 1989 (assumed starting point of HIV epidemic in South Africa) to 2069, with variables updated in 3 month periods (**C4, Table 3**). Coded in SAS, the modelling framework considers horizontal transmission in detail, along with vertical transmission predominantly differentiated according to the viral load of pregnant mothers.

A very detailed and involved model, each model run simulates the lifetime adult experience of 100,000 people specific to a SSA setting, by sampling a range of parameter values inclusive to the SSA setting, while also incorporating uncertainty around the parameter values and assumptions made. The model structure can largely be categorized according to parameters relating to: 1.) Population Demographics (age and gender specific growth and death rates); 2.) HIV Acquisition (factoring in sexual behavior, male circumcision, female sex work, PrEP, transmission related factors); 3.) HIV diagnosis and pre-ART care (HIV testing, linkage, lost after diagnosis, CD4 count, development of TB and WHO stage 4 diseases); 4.)

HIV treatment (ART adherence, ART regimen, resistance/mutation, ART interruption, toxicity, viral load.) **(C4, Table 4**).

Sexual behavior is determined by the type of condomless partnership (short or long term), and the number of short term partnerships in a 3 month period, per risk category: no condomless short term partner; low number of condomless short term partners; medium number of condomless short term partners; high number of condomless short term partners; very high number of condomless short term partners. The threshold number for low, medium, high/very high numbers of condomless short term partners differs by gender and whether sex work has been initiated **(C4, Table 4**). HIV status, indicative of infection, diagnosis, treatment status (on ART) and viral load suppression of long term comdomless partners are tracked over time and contribute to the probability of HIV infection, linearly. HIV status of short term partnerships are not tracked, are generated randomly, and independent of status in the previous cycle; ie. having an HIV infected short term partner in the current cycle (*time t*), is independent of the probability of having any HIV infected short term partner in the following cycle (*time t+1*).

Of note, gender specific sexual risk activity is presented in 5 year specific age bands (i.e. age 15-19; 20-24 etc.), along with 15 transition matrices per gender, denoting the probability of an individual transitioning from partnerships of various risk categories. These matrices account for substantial intra-personal sexual behavior variability over time, and illustrate, for example, a man at *time t-1* having zero short term condomless partners, transitioning to the 'low' risk categorization at *time t*, to the 'medium' risk categorization at *time t+1*. With regards to sexual mixing, gender specific matrices representing the proportion of short term partnerships formed between men and women of different ages are presented in 10 year age bands (i.e. age 15-24; 25-34 etc.), according to 6 matrices per gender. These sexual mixing matrices account for various probabilities, that for example, a woman falling between the ages of 15-24 is likely to choose a male partner in the same of age strata, or a partner from an older age strata. Each model run samples transition and sexual mixing matrices independently, and randomly, by gender. Transmission risk is then calculated according to sex act and is based on the HIV prevalence of the opposite gender, after accounting for sexual mixing by age, sampling viral load from a uniform distribution, considering STI status, circumcision status of male partner (determined by age specific VMMC rates), whether the subject is on PrEP and PrEP adherence levels **(C4, Table 4**).

Long term condomless partnerships are non-gender specific and categorized by 3 age strata (i.e. 15-44; 45-54; 55-64), along 3 partnership categories denoting a different tendency to endure, with a higher class equaling more durability (i.e. class 1; class 2; class 3). HIV infectivity amongst long term partnerships is

determined by the total number of individuals with HIV (both diagnosed and not), and the proportion of those who at *time t-1* are classified according to the following: primary infection; HIV diagnosed without treatment; HIV diagnosed on treatment; on ART with a viral load <2.7 log cps/mL. Transmission risk is calculated factoring normal sampling of the aforementioned partnership parameters (3 age strata, 3 partnership categories and 4 infectivity categorizations), along with the same parameters as short terms partnerships, namely: STI and PrEP status of the subject, along with circumcision status of the male partner **(C4, Table 4**).

Age dependent pregnancy probability is represented in 10 year age bands (15-24; 24-34; 35-44, 45-54 and 55+), (reflecting the declining fertility rate in ageing women, with a zero probability in women 55+), is modelled at the point of childbirth in each 3-month cycle, and dependent on one or more condomless partnership (short or long-term), 9 months previous. Risk of mother to child transmission (MTCT) of HIV at childbirth is dependent on the mother's viral load and differentiated according to 4 levels: 40% risk, >100,000 viral copies/ml; 20% risk, 10,00 – 100,000 viral copies/ml; 10% risk, 1000 – 10,000 viral copies/ml; 0.2% risk, <1000 viral copies/ml **(C4, Table 4**). With the exception of factoring in the probability of pregnant women experiencing an additional HIV test at ANC clinics, HIV testing along with PrEP usage, ART initiation, ART interruption, loss to follow up, development of complications (such as resistance, mutation, toxicity) and viral load are not modelled by sex, age and risk group. The effect of age and gender on ART adherence however, is represented in the model.

Optima:

Optima HIV, developed with the objective of aiding national governments and other relevant stakeholders across the globe (including SSA settings) allocate limited resources effectively towards their HIV responses, is a deterministic compartmental model (**C4, Table 3**) [100]. Highlighting horizonal, vertical and injecting-related transmission, Optima is available for MATLAB and Python [100]. Using a system of ordinary differential equations to track people living with HIV across 5 stages of CD4 count, the model partitions the population according to population groups determined by dominant risk [100]. The model allows for incorporation of a large, flexible (usually 8-20, but in theory, unlimited) number of distinct population groups (ex. children, general population individuals, key affected populations such as FSW, MSM etc), and population sub-groups can be stratified by gender and age [100].

The model structure can largely be categorized according to parameters relating to: 1.) Population Demographics (age and gender specific birth and death rates where applicable); 2.) HIV Acquisition [infectiousness of partner group which depends on HIV prevalence and transmission probability

approximated from CD4 count, type of interaction (casual, regular, commercial, injecting), type of intercourse (insertive, vaginal receptive, anal receptive), male circumcision, condom use, PrEP and PEP usage, STI co-infection]; 3.) HIV diagnosis and pre-ART care (HIV testing rate, disease progression according to CD4 count); 4.) HIV treatment (treatment rate, first-line ART, subsequent-line(s) ART, treatment failure, disease progression according to CD4 count). **(C4, Table 4**).

Focusing on horizontal transmission (and omitting injecting-related transmission), sexual behavior is determined by the number of partners across 4 types of interactions (casual, regular, commercial homosexual, commercial heterosexual), along with the intercourse type (insertive, vaginal receptive, anal receptive), and condom use per sex act **(C4, Table 4)**. While age stratification within the model can exist and sexual mixing must be accounted for, as there is specific mention of partnerships formed between individuals of different ages, population groups and categorizations of sexual behavior, they are not outlined in detail [100, 108]. As the model is concerned with HIV transmission (and progression) in various sub-groups, the model framework is best classified as a general aged model, without defined age strata and specific age-related sexual mixing considerations inherent to the model structure. This conclusion is drawn from the fact that definitions of age strata are inconsistently provided in official documentation. Children and adolescent populations are mentioned, but undefined, while definitions for youth (defined as 15-24 years), adult (defined as 25-49 years) and older people (aged 50+) population groups are explicitly stated within the model framework [100, 108]. Additionally, sexual mixing is either represented homogenously across population sub-groups, or fixed according to population sub-groups in the framework, as no mention of mixing matrices accounting for assortative or disassortative mixing preferences among population groups, or description of interaction patterns is discussed. (The one exception being a statement around the force-of-infection being dependent “on the number and type of risk events to which individuals, either in their own population groups or through interaction with other population groups, are exposed to” [100].)

Risk of MTCT is included in the model framework and determined according to three factors: birth rate among women living with HIV; proportion of HIV positive women who breastfeed; proportion of women receiving PMTCT, including ART **(C4, Table 4)**. While not inherent to the structure, similar to above, it stands to reason that the model framework allows the flexibility to differentiate these parameters according to age and/or sub-population, should the modeler so choose.

4.6 DISCUSSION

This narrative review sought to evaluate child and adolescent representation within model frameworks meeting the definition of a 'well-described' and 'frequently used/cited' dynamic mathematical model of HIV. Four models met the inclusion criteria: EMOD and HIV-Synthesis, both individual based stochastic models; Goals-ASM and Optima, both compartmental models. All four model frameworks calculate the probability of horizontal and vertical transmission risk relevant to the SSA setting. Only one model framework, EMOD, explicitly incorporated child HIV dynamics through entry into the model via early infant diagnosis testing, while the Optima framework allowed for the flexibility to incorporate infant and child population groups if needed. Both HIV-Synthesis and Goals omitted children within their framework. Adolescent populations were incorporated into all 4 model's structural considerations.

EMOD is an individual-based model that explicitly tracks age, sexual debut, concurrency, and vertical transmission (MTCT), allowing detailed simulation of adolescent behavior and testing pathways, such as antenatal, symptomatic, and voluntary testing. HIV-Synthesis also follows an individual-based framework, focusing on the natural history of HIV, with long-term tracking of individual outcomes, including ART initiation, adherence, and failure, making it well-suited for exploring adolescent treatment outcomes. Goals-ASM, in contrast, uses a compartmental approach that aggregates populations into age bands and models interventions at the population level. While it captures key dynamics, such as MTCT and youth-targeted interventions, it relies on simplified behavior patterns compared to individual-based models. Lastly, Optima is an optimization model that prioritizes resource allocation, using age-specific compartments to assess the cost-effectiveness of various interventions for children and adolescents. However, its behavioral representation is less detailed, focusing more on optimizing interventions rather than simulating individual behavior.

Comparing these models, EMOD and HIV-Synthesis offer detailed insights into individual-level dynamics, including behavioral risks and treatment cascades, making them ideal for understanding the complexities of adolescent HIV risk and treatment. Goals-ASM and Optima, while less granular in behavioral modeling, are more useful for high-level policy planning, as they allow scenario-based projections and resource allocation. EMOD emphasizes sexual behavior and concurrency, making it particularly useful for studying adolescent transmission dynamics, whereas HIV Synthesis provides deeper insights into long-term treatment adherence and survival outcomes. Goals-ASM is most suitable for evaluating programmatic interventions targeted at different age groups, while Optima-HIV excels in cost-effectiveness analysis, identifying the best allocation of resources for youth-targeted interventions. Together, these models offer varying perspectives for addressing programmatic decisions concerned with

children and adolescents living with or at risk for HIV. However EMOD emerges as the superior model with regards to understanding the impact of tailored interventions targeting children and adolescents, due to the detailed behavior dynamics structural integration, compared to the other models.

Age in EMOD is represented through continuous tracking, with key demographic and behavioral events tied to specific ages [104]. Sexual debut, partnership formation, and testing behaviors are age-dependent [104]. While age is tracked continuously, it is can be grouped in five-year increments for certain simulations [104]. These aggregated age groups align with standard HIV surveillance data formats and allows the modeller greater flexibility in age-stratification decisions, specific to individual research questions and needs for analysis. The most current version of EMOD (v.08) introduces significant improvements to the HIV treatment cascade enhancing its ability to reflect real-world dynamics and inform targeted interventions for children and adolescents in SSA [102]. Key enhancements include the integration of multiple testing pathways – voluntary counseling, antenatal care (ANC), symptomatic, infant, and couples testing—capturing the diverse ways individuals enter the treatment continuum [102]. This is especially relevant for children and adolescents, as early diagnosis through infant testing and regular adolescent testing behaviors are now modeled more accurately. Additionally, v0.8 refines linkage to ART, dropout, and re-enrollment behaviors, reflecting challenges unique to adolescents, such as treatment adherence issues and care retention [102]. These features allow the model to simulate interventions that aim to improve ART coverage and reduce loss to follow-up among youth, which is critical for addressing the gaps in care left by PMTCT programs that missed perinatally-infected children. In settings like Zimbabwe, where adolescent HIV prevalence remains a challenge, these improvements help policymakers assess the effectiveness of youth-focused testing and retention programs, ensuring that resources are allocated to interventions that maximize both coverage and long-term outcomes for vulnerable populations.

Sexual partnership concurrency has been thought to propel HIV transmission in high prevalence settings, as it has the potential to connect otherwise separate sexual networks across both time and location [109]. While the evidence on partnership concurrency as an HIV epidemic driver in SSA is limited, young women in age-disparate relationships are at an increased risk of HIV due to concurrent relationships held by their male partners and increased casual sex [109-111]. While young females in an SSA setting are approximately 4.5 times less likely to engage in concurrent partnerships themselves, compared to young males, females reporting an earlier sexual debut are more likely to report concurrent partnerships [112]. The EMOD model is the only model of those reviewed that includes a concurrency parameterization within the model framework. By accounting for concurrent partnerships, the model better reflects the

complex sexual and social dynamics that shape HIV risk for adolescent females, leading to identify more accurately, critical intervention points to disrupt network dynamics that fuel adolescent infections.

Per the 2024 Global AIDS Monitoring guideline which outlines indicators to assess national HIV response, male circumcision indicators are required only from 15 countries in SSA (including Zimbabwe) [113]. These countries with generalized (heterosexual epidemics) and correspondingly low levels of male circumcision, require male circumcision indicators in adolescents 15 years and older to be reported, disaggregated as follows: 15-19 years, 20-24 years, 25-29 years and 25-29 years [114]. All four models reviewed consider the effect of male circumcision in HIV transmission probability and due to their respective model age strata, and/or flexibility for age-range manipulation, inherently allow for the impact of strategies seeking to improve male circumcision rates to easily feed into measuring and monitoring progress towards achieving targets in these 15 countries, (along with modelling how changing rates of circumcision affect HIV incidence).

In Zimbabwe, the legal age of consent is 16, (however 13-15 year olds are deemed able to consent) [54], and only 5-6% of those aged 15-24 have reported having sex before age 15 [55]. Model structures are highly contextual [56], and research questions interested in assessing trends and interventions pertaining to sexual/horizontal transmission only, are justified in modelling cohorts from age 15 onwards. However, in doing so, the opportunity to accurately capture the full burden of HIV and corresponding epidemic impact are missed. Despite the progress of PMTCT programs in Zimbabwe, 3600 children under 15 were newly infected with HIV in 2023, and notwithstanding the success of the adult population in reaching the 95-95-95 targets, ART coverage in children under 15 was only 63% [57]. Methodologically rigorous models such as HIV-Synthesis and Goals-ASM that capture the dual burden of horizontal and vertical transmission, but do not allow for structural considerations to propagate those newly infected children forward, miss an opportunity to identify and implement instances for something as simple and effective as early infant diagnosis, to more complex evaluations of tailored interventions that address the unique needs of the child population. Integrating children into HIV model frameworks is integral to ensuring equitable care, not to mention, achieving country and global targets.

4.6.1 Strength and Limitations

The quality of the narrative review was assessed using the 6-item SANSRA scale, which was identified by a targeted search for quality assessment tools specific to narrative reviews [101]. The 6 items are 1.) Explicit justification of the article's importance for readership; 2.) Concrete aims or questions formulated; 3.) Literature search described in detail, including search terms and inclusion criteria; 4.) Key statements

supported by references; 5.) Appropriate evidence is present; 6.) Relevant outcome data presented appropriately. This narrative review scored 12/12 on the SANSRA scale strengthening the credibility of this narrative review.

The study also has limitations. Narrative reviews are amongst the most wide-spread and frequently published article types in the scientific literature pool [101]. Yet, the methodology behind a narrative review is not as rigorous as systematic literature reviews [101]. For this reason, narrative reviews can be subject to author bias in search strategy design, article selection and synthesis of evidence, thereby affecting the quality of the review [101, 115]. There are no acknowledged universal guidelines nor standardized methodology for conducting narrative reviews, such as PRISMA for systematic literature reviews [101, 115]. As methodical, structured, transparent and reproducible an approach as possible was taken when constructing the search strategy for this narrative review, along with definition formation, allowing for model inclusion. However, unlike a systematic review, there was no second reviewer involved in this analysis to confer consensus, check and critique decisions made and offset author error and bias.

'HIV Synthesis Mode' and 'Goals HIV Model' had over 10,000 irrelevant hits when they were title searched in Web of Science, such as 'HIV Model output synthesis'; 'goal of this HIV model', etc. To focus the search on relevant hits I added additional terms (i.e. 'HIV Synthesis Model + Cambiano', 'Avenir/Spectrum Goals HIV Model). In doing so, the search strategy was manually manipulated.

The Imperial College London Model from the Lancet paper did not have a name (I have called it the Imperial College London Model for clarity). While that model name did not retrieve modelling related records, the original model (from the Lancet article) was cited more than 65 times, but because it also was a nameless model, the search could not be continued further, as it was impossible to determine how many publications based on this model existed. As a result of all these decisions, which formed the basis of the inclusion and exclusion criteria, relevant models meeting the definition of a 'well-described' and 'frequently used/cited' dynamic mathematical model of HIV may have been missed and omitted.

The quality of the narrative review was assessed using the 6-item SANSRA scale, which was identified by a targeted search for quality assessment tools specific to narrative reviews [101]. The 6 items are 1.) Explicit justification of the article's importance for readership; 2.) Concrete aims or questions formulated; 3.) Literature search described in detail, including search terms and inclusion criteria; 4.) Key statements supported by references; 5.) Appropriate evidence is present; 6.) Relevant outcome data presented

appropriately. This narrative review scored 12/12 on the SANSRA scale strengthening the credibility of this narrative review.

Model comparison studies typically focus on the outputs of models and the impact various interventions might have on epidemic patterns in a population of interest. Rarely is the focus of these comparison studies concentrated to evaluating the differences in model structures, underlying assumptions and varied way in which HIV risk behavior and transmission dynamics are represented, (which of course impact model outputs) [116]. This is both a strength and limitation of these types of comparison studies as it allows for capture of behavioral, epidemic and population variability across SSA [117]. One of the strengths of this narrative review is that it addresses an existing gap in the literature: namely to compare model structural framework and assumptions around the inclusion of children and adolescents as stated in several global reports (UNAIDS, UNICEF, WHO), and specifically age ranges pertaining to children and adolescents.

4.7 CONCLUSION

Mathematical modelling plays a crucial role in understanding epidemics and evaluating the impact of interventions on reducing incidence. HIV modelling is a vital tool for national HIV programmatic planning in endemic settings in SSA especially, as it aids decision-makers to allocate resources efficiently towards interventions which have the greatest impact on reducing and controlling the HIV epidemic. As the burden of HIV resides in the adult population, it is natural that the majority of disease prevention efforts and funding is geared towards reducing transmission in, and improving outcomes among, adults. However this decision-pathway is often at the expense of vulnerable populations like children and adolescents. Decisions making focused on the sub-population are served by the Optima model (as Goals-ASM does not include children within the model framework), but the assessment of impact of interventions targeting this sub-population are best modelled through EMOD as it allows granular insights into the HIV treatment cascade and adolescent behavior.

4.8 CHAPTER 4 KEY TAKEAWAYS

The first study in SSA to investigate child and adolescent HIV transmission dynamics and risk representation in highly visible, peer-reviewed dynamic mathematical models of HIV, this narrative review found that only 4 models met the definition of 'well-described' and 'frequently used/cited' dynamic mathematical models of HIV, of which 2 models, (EMOD and HIV-Synthesis), were individual-based stochastic models, with the other 2, (Goals and Optima), being compartmental models. Only 1 of 4 models explicitly incorporated child HIV dynamics within the framework, while all 4 models incorporated adolescent populations into their model structure, in some capacity. EMOD emerged as the superior model with regards to understanding the impact of tailored interventions targeting children and adolescents due to the detailed and comprehensive dynamics representation within the model structure, while Optima would be appropriate to use in decision-making around resource allocation for the sub-population (**C4, Figure 3**).

WHAT WE KNEW

- Children and adolescents within the HIV response have been inequitably addressed
- Children and adolescents in SSA especially, pose a key challenge for HIV prevention and control measures, as they are a difficult to reach population.
- Modelling studies are used to inform HIV programs in SSA, including interventions targeting children and adolescents
- Due to HIV burden, mathematical models of HIV typically emphasize adult transmission dynamics and omit or oversimply child and adolescent integration into model structure
- Yet decisions concerning children and adolescents are made using these models, without evaluating the appropriateness of these frameworks for this sub-population

WHAT WE LEARNED

1. Current mathematical models of HIV testing strategies are heterogenous and in the minority, in the ways they incorporate both children and adolescents into modelling structures.
2. Amongst the 4 models which met the definition of 'well-described' and 'frequently used/cited' dynamic mathematical models of HIV, only one model (EMOD) explicitly incorporated child HIV dynamics within the framework. All 4 models incorporated adolescent populations into model structure, in some capacity
3. Individual based stochastic models (EMOD and HIV-Synthesis) offer detailed insights into individual behavioral risks and treatment cascade, making them ideal for understanding the complexities of adolescent HIV risk and treatment needs
4. Compartmental models (Goals-ASM and Optima), while less granular in behavioral modelling, are more useful for high-level policy planning, as they allow scenario-based projections and resource allocation among the adolescent sub-population

WHAT'S NEXT

- Addressing a knowledge gap: A critical look at the frameworks behind HIV related programatic decision-making for children and adolescents - are decision-makers allocating resources to this sub-population based on outcomes generated by the most representative models?
- Addressing a knowledge gap: Reviewing publications using the 4 models which met the definition of 'well-described' and frequently used/cited' dynamic mathematical models of HIV to determine: a.) whether these publications focused on HIV testing strategies in SSA; b.) if the impact of these HIV testing strategies were geared towards children and adolescents
- Conversion of this chapter into a manuscript, submitted for publication, to disseminate findings around the variation in ways children and adolescents are represented and included in dynamic HIV epidemic models developed for the SSA context

C4, Figure 3. Results P2 Key Takeaways: What We Knew; What We Learned; What's Next

4.9 IMPLICATIONS FOR THESIS

The overall aim of this thesis is to contribute to the methods of EEs of HIV testing in children and adolescents in a Zimbabwean context. This chapter contributed to achieving this aim by being the first to investigate the inclusion of child and adolescent HIV transmission and risk representation among 'well-described' and 'frequently used/cited' mathematical models of HIV in the SSA context as a whole. In doing so, **Objective 2** of this thesis – to determine how child and adolescent HIV transmission dynamics are represented in popular, peer-reviewed dynamic mathematical models of HIV in the SSA context– was fulfilled. In answering **Objective 2**, an important implication for this thesis was uncovered: concrete proof that children are not routinely represented in model structures, despite these frameworks being used to inform decision making within this sub-population. A secondary implication of this chapter, for this thesis, is that moving forward, a critical look at the appropriateness of methods and models informing resource allocation is needed, especially with regards to funding the HIV prevention and treatment needs of children and adolescents. This is of relevance to not only this thesis, but future EE research and literature. The practicality of the findings of **Objective 2** (along with the previous objective) will be built on, and demonstrated later on in this thesis.

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68&date=2015&title=The+Lancet.+HIV&atitle=Cost-effectiveness+of+community-based+strategies+to+strengthen+the+continuum+of+HIV+care+in+rural+South+Africa%3A+a+health+economic+modelling+analysis.&aulast=Smith&pid=%3Cauthor%3ESmith+JA%3BSharma+M%3BLevin+C%3BBaeten+JM%3Bvan+Rooyen+H%3BCelum+C%3BHallett+TB%3BBarnabas+RV%3C%2Fauthor%3E%3CAN%3E25844394%3C%2FAN%3E%3CDT%3EJournal+Article%3C%2FDT%3E.

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CHAPTER 5 – RESULTS PAPER 3 (P3) – A COST ANALYSIS OF ILHIVT FOR CHILDREN AND ADOLESCENTS IN ZIMBABWE

Overview of Chapter 5 (Results P3)

This chapter is the last of three results chapters for this thesis and presents the findings of a cost analysis of B-Gap; an ILHIVT initiative, delivered via three modalities, to children and adolescents aged 2-18 years in urban (Bulawayo) and rural (Mangwe) Zimbabwe.

Evidence Before this Study

There is a growing body of literature concerned with evaluating the costs and cost-effectiveness of existing and emerging HIV testing strategies. Alternative HIV testing strategies such as HIVST have been costed in multiple settings. No cost analysis of ILHIVT thus far has been conducted in SSA.

Added Value of this Study

Irrespective of setting and population in SSA, this analysis is the first to evaluate the cost of ILHIVT, a targeted HTS strategy proposed by the WHO to expand the efficiency of HTS. The information presented in this chapter is of value to researchers and policy makers alike as it highlights the role of HIV testing uptake as a driver of unit costs, along with the role that personnel and (often times unconsidered) transaction costs have in research and services implemented in the community setting.

Contribution to the Larger Body of Evidence

Alternative, cost-effective HIV testing strategies are needed, as current approaches are not sufficient to identify undiagnosed children and adolescents, and HIV case finding will only become more difficult and costly as knowledge of HIV status and treatment coverage increase. This paper illustrates that the current iteration of ILHIVT, both the format and setting, need to be reconsidered prior to scale-up. A more efficient method or configuration of ILHIVT is needed to approximate a cost-effective strategy for routine implementation. This paper has been published in *BMC Health Services Research*.

5.1 INTRODUCTION

This chapter presents background information on cost analyses relevant to this thesis. In particular, this chapter seeks to determine the cost of delivering an alternative HIV testing intervention – ILHIVT – to children and adolescents in Zimbabwe. The chapter begins by providing a brief overview of costing analyses within the context of EEs, followed by the various costing methodologies. The B-Gap costing analysis (**Results P3**), as published in *BMC Health Services Research* are then presented, followed by a brief discussion and summation of the chapter.

5.2 BACKGROUND

As outlined in chapter 3, EEs provide a basis from which public health decision making around optimal resource allocation for existing and emerging health technologies, interventions, treatments and programs can be made [1]. Estimates of costs are necessary for informing decision making, and costing studies, which examine the costs of an intervention or program compared to another, (without evaluating the subsequent health effects), are considered a partial EE [1, 2]. Costing analyses typically involve three distinct phases: identification of resources in intervention (or program, treatment, technology) delivery; measurement of resources; and valuation of resources. Like all EEs, they are dependent on perspective to inform which resources should be considered for analysis [3].

Economists define cost as the value of resources used to produce a good or service, and costs can be distinguished according to the way in which they are measured: financial and economic costs [4]. Financial costs capture actual monetary expenditure, thereby estimating financing requirements of all inputs involved in service provision, by determining both price and quantity of individual resources consumed, while omitting donated goods and services [2, 4-6]. Economic costs match the impact of resource consumption by valuing resources irrespective of their price (e.g. test kits donated by an external organization), capture not only paid resources along with donated goods and services, but opportunity costs as well; the cost of forgone alternative uses and potential benefits gained for a specified resource [2, 4-6]. The use of financial, economic, (or both), costing approaches is dependent on the objective of analysis; financial costing typically seeks to understand expenditure for service, in the scope of existing budgetary allocation, whereas economic costing is appropriate when considering service sustainability, replication or reproducibility [4-6]. “Analyses using economic costs do not replace those using financial costs, but supplement them with additional information useful for decision-making [4].”

Similar to the delineation between types of costs (financial or economic), two main types of costing analyses exist: full and/or incremental. A full costing analysis estimates all inputs and resources consumed by an existing service [4]. Using HIV as an example, this spans everything from overhead and infrastructural costs such as the monthly rent, utilities and maintenance for physical service delivery space and furniture for a HIV testing waiting room, to the technical needs such as the cost of employing an HIV primary care counsellor to test clients along with HIV test kits, and everything in-between. An incremental costing analysis assesses the major new/additional inputs necessary for delivering the intervention/service, assuming the infrastructure to do so already exists [4]. In short, a full cost analysis

evaluates the entire cost of running an existing service, while an incremental cost analysis determines the surplus cost of incorporating the additional strategy within the existing service's infrastructure [4].

Perspective defines the point of view for a costing analysis and affects the depth and breadth of resource inputs necessary [2]: societal perspective is the most encompassing as intervention (delivery) costs incurred by multiple facets, (the public and private sectors along with individuals) are considered; provider perspective input considerations are costs the entity tasked with financing service provision incur; while patient perspective tallies direct and indirect costs individuals encounter when accessing services [4]. Perspective dictates the inclusion of components necessary to estimate a particular services' cost and are categorized according to input type: *recurrent* (consumed regularly and last for less than1 year) and *capital* (lasting more than 1 year) [5]. There are two main approaches in measurement and valuation of resources: microcosting, gross costing, or both [3]. Microcosting (i.e. bottom up costing) entails detailed collection of all components of resource use in service provision, along with associated price lists. Microcosting is extremely time and resource intensive, typically requires time and motion studies and "customized work as prices are unlikely to be available" [3]. A downside of the bottom-up approach is that results are not entirely generalizable, applicable to specific contexts only [3]. Gross costing (i.e. top-down costing) is a more generalized and blunt approach to costing, dividing a total budget among specific inputs [3]. The strength of a top-down costing approach, simplicity, is off-set by its lack of resolution and specificity [3]. Most cost analyses use a combination of both costing approaches, using bottom-up costing for clearly distinguishable direct costs, and top-down for the remaining inputs [3]. Per the GHCC reference case, the terminology for microcosting vs bottom-up, and gross costing vs top-down is used inconsistently and/or interchangeably in the literature [2]. For the purpose of this chapter and the ensuing costing analysis, the terms are used interchangeably to distinguish between a disaggregated/granular costing approach when accounting for inputs and resources, compared to a bird's eye view of resource and cost delineation across inputs.

The costing analysis of B-Gap presented in this chapter is a dual full and incremental, mixed-methods financial costing analysis conducted from the provider perspective, whose inputs included both capital and recurrent items, for the purpose of answering thesis **objective 3**: measuring the cost of delivering ILHIVT to children and adolescents in Zimbabwe. **C5, Table 1** provides a rationalization for analytical decisions made.

C5, Table 1. Methods Overview for a costing analysis of B-Gap; ILHIVT for children and adolescents in Zimbabwe

Options	Rationale
Type of Costs Estimated	
• Financial • Economic	Financial → The purpose of this analysis was to estimate expenditure related to delivering ILHIVT, leading to a better understanding of financial planning and budgeting needs.
• Full • Incremental	Both → The results of an incremental cost analysis are difficult to generalize without an understanding of the framework prior services are delivered through, along with the existing infrastructure (i.e. a full cost analysis). Additionally, ILHIVT would not replace SoC facility based HIV testing, but considered as an additional testing option. Thus, the purpose of this analysis is to determine the cost of adding ILHIVT into existing service delivery infrastructure, and as a supplement to current services. For this reason, a full costing analysis of SoC facility based HIV testing was conducted, alongside an incremental costing analysis of ILHIVT.
Costing Approach	
• Microcosting (bottom-up) • Gross-costing (top-down)	Both → Where possible, a bottom-up approach was employed, collecting the frequency of consumption of individual components relating to service delivery and use. A top-down approach was employed wherever this was not possible, such as costing components relating to shared infrastructure. (Ex. capital costs such as building and equipment, recurrent costs such as facility maintenance and utilities, etc.) (**C5, Appendix I**, contains a breakdown of all input considerations.)
Perspective	
• Societal • Provider • Individual	Provider → This analysis is conducted from the provider perspective to evaluate costs incurred by the health service provider in Zimbabwe, (the MoHCC), to illuminate potential budgetary needs, if/when considering ILHIVT supplementation to current HTS.

5.3 RESULTS P3 COVER SHEET

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed <u>for each</u> research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1604189	**Title**	Ms
First Name(s)	Arthi		
Surname/Family Name	Vasantharoopan		
Thesis Title	Economic Evaluation Methods for HIV Testing of Children and Adolescents in Zimbabwe		
Primary Supervisor	Dr. Victoria Simms		

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 Health Services Research		
When was the work published?	October 12, 2021		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	N/A		
Have you retained the copyright for the work?*	**No**	Was the work subject to academic peer review?	**Yes**

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

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)	I am the first author of this paper and wrote the first and final drafts. With the oversight and input of my PhD supervisors, I conceptualized the study, developed methods and data collection tools, and analyzed data. I also conducted primary data collection. Additionally, I was responsible for manuscript submission and addressing peer-review comments.

SECTION E

Student Signature	Arthi Vasantharoopan
Date	Jan 11, 2023

Supervisor Signature	Victoria Simms
Date	12 January 2023

5.4 RESULTS P3

A costing analysis of B-GAP: index-linked HIV testing for children and adolescents in Zimbabwe

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Word count, abstract: 280
Tables: 4
Figures: 2

ABSTRACT

Background:

By testing children and adolescents of HIV positive caretakers, index-linked HIV testing, a targeted HIV testing strategy, has the ability to identify high risk children and adolescents earlier and more efficiently, compared to blanket testing. We evaluated the incremental cost of integrating index-linked HIV testing via three modalities into HIV services in Zimbabwe.

Methods:

A mixture of bottom-up and top-down costing was employed to estimate the provider cost per test and per HIV diagnosis for 2-18 year olds, through standard of care testing, and the incremental cost of index-linked HIV testing via three modalities: facility-based testing, home-based testing by a healthcare worker, and testing at home by the caregiver using an oral mucosal transudate test. In addition to interviews, direct observation and study process data, facility registries were abstracted to extract outcome data and resource use. Costs were converted to 2019 constant US$.

Results:

The average cost per standard of care test in urban facilities was US$5.91 and US$7.15 at the rural facility. Incremental cost of an index-linked HIV test was driven by the uptake and number of participants tested. The lowest cost approach in the urban setting was home-based testing (US$6.69) and facility-based testing at the rural clinic (US$5.36). Testing by caregivers was almost always the most expensive option (rural US$62.49, urban US$17.49).

Conclusions:

This is the first costing analysis of index-linked HIV testing strategies. Unit costs varied across sites and with uptake. When scaling up, alternative testing solutions that increase efficiency such as index-linked HIV testing of the entire household, as opposed to solely targeting children/adolescents, need to be explored.

Key words: HIV; index-linked HIV testing; community-based HIV testing; home-based HIV testing; HIV assisted-testing ; costing analysis

BACKGROUND

Since 2010, 1.4 million new HIV infections in children have been averted worldwide, while HIV mortality among children has halved (1, 2). Despite this progress, 150,000 children were newly infected in 2019, falling short of the 2018 target to reduce new HIV infections in children to 40,000 (3). In addition, HIV treatment coverage among children is significantly lower than among adults, likely due to higher levels of under-diagnosis (4). Furthermore, many children present to clinical services and start antiretroviral therapy (ART) in older childhood and adolescence when they have developed advanced disease, with consequent poorer outcomes (5). Notably, adolescents are the only age-group in whom HIV-related mortality has not declined (5-8). HIV testing and counselling approaches aimed at the timely diagnosis and linkage to care of children and adolescents in high HIV prevalence settings are therefore urgently needed.

Index-linked testing refers to screening family, household or other contacts of a case for a disease. Index-linked HIV testing has been widely used to identify higher risk individuals, and thus a high-yielding strategy for HIV testing (9). In sub-Saharan Africa children and adolescents living in households with known HIV-positive adults are more likely to be HIV-positive, and are often untested and untreated (9-11). Index-linked HIV testing (ILHIVT), whereby children living with adults with HIV are targeted for testing, has the potential to identify high-risk, difficult to access children and adolescents, and to improve yield (9, 12, 13).

While WHO guidelines recommend offering testing to children of HIV-positive adults, countries in Eastern and Southern Africa have yet to integrate this policy into routine service delivery (9, 12, 14). The paucity of data on effectiveness, cost and cost-effectiveness of ILHIVT may be one factor preventing its scale up. As there are no costing studies of ILHIVT within sub-Saharan Africa, the cost implications and cost-effectiveness of including this strategy within HIV service delivery programs is unknown.

The Bridging the Gap in HIV testing and care for Children in Zimbabwe (B-GAP) study assessed the effectiveness and cost of a multi-option ILHIVT strategy in both urban and rural settings in Zimbabwe (14). This paper is the cost analysis of B-GAP estimating the cost of providing standard of care (SoC) HIV testing –voluntary, facility based HIV testing and counselling (HTC) – comparing to the incremental cost of different ILHIVT strategies.

METHODS

B-GAP HIV Testing Intervention

In the B-GAP study, individuals with HIV enrolled in and attending care at study clinics, i.e. indexes, were offered HIV testing for any children and adolescents (aged 2-18 years) of unknown HIV status in their household by study staff. Indexes could choose one of three testing options for the

child(ren)/adolescent(s): Clinic-based diagnostic testing using a rapid test; home-based rapid diagnostic testing by a healthcare provider; or home-based, caregiver-provider testing using an oral mucosal transudate (OMT) test. All participants diagnosed with HIV were linked to care at their nearest healthcare facility.

Study Setting

ILHIVT was provided at 9 of the 36 primary health care facilities in Bulawayo and Mangwe district in Matebeleland South province in Zimbabwe, (6 urban, 3 rural) selected based on size and accessibility (14). Adult HIV prevalence in both these provinces is approximately 20% (14). The facilities do not routinely employ ILHIVT. Cost data collection took place at 2 urban facilities in Bulawayo, and 1 rural facility located in the Mangwe, sampled by convenience (*Table 1*).

Table 1. Characteristics of costing study facilities, as of Sept 2018

	Clinic A	**Clinic B**	**Clinic C**
District	Bulawayo	Bulawayo	Mangwe
Setting	Urban	Urban	Rural
Catchment Area Population Total	42,497	31,492	9,137
Catchment Area Population Under 15 yrs	14,433	10,696	4,066
Catchment Area Population 15 years +	28,063	20,796	5,071
Overall Facility Visits in 1 Year*	50,778	77,558	5,118
HIV Tests Conducted in 1 Year*	2,541	3,276	1,860
Number of people on ART as of Sept 2018	4,478	4,625**	960

Notes:

*Based on one year of facility registries: Oct 2017 – Sept 2018

**Due to missing records, this tally is current as of June 2017

Costing Methods

We estimated the provider cost of facility level HIV testing and the provision of index-linked testing, following the Global Health Cost Consortium costing guidelines (15). A combination of bottom-up and top-down costing was employed. First, we estimated the full cost of testing and diagnosis of children and adolescents through SoC facility testing for a 4-month time period before the B-GAP intervention (May–August 2018). We then estimated the incremental cost of ILHIVT and diagnosis of participants (September– December 2018) at the same 3 clinics, provided by the three modalities: clinic, health-care worker testing in the household, and caregiver-testing in the household. Costs estimated included

personnel, consumables, overheads, building, equipment, training, start-up and transaction costs, but excluded any research related costs.

To gauge personnel time, we undertook a combination of direct observation and face-to-face interviews with clinic and B-GAP staff to quantify resources utilized to deliver all HIV testing models. We used prospective time-tracking diaries and direct observation to measure human resource time spent on different activities. Appendix I provides a summarized breakdown of time spent on ILHIVT activities. Prices of test kits were taken from the National Pharmaceutical Corporation of Zimbabwe (NatPharm), as specified by the centralized Matebeleland South pharmacy system. Overheads and other shared clinic costs were allocated to the testing activities based on area of the clinic utilized by each department and patient load depending on the line item.

All resources used were converted into costs using financial data collected from B-GAP project accounts, Bulawayo City Council and the district and provincial medical offices in Matebeleland South. Salaries of study staff who conducted ILHIVT, were substituted with those of facility primary care counsellors who would carry out this work in routine clinical settings. Equipment, building, training and start-up costs were annualized using expected length of life determined by WHO cost effectiveness and strategic planning prices for tradable goods, and discounted at a rate of 3% (16). Due to the instability of the Zimbabwean currency, we estimated costs in US dollars. We converted all real-time gross settlement (RTGS) dollars, the Zimbabwean currency, into USD using the exchange rate at the time when the financial data was provided, using the Reserve Bank of Zimbabwe exchange rates (17). All costs were converted to 2019 constant USD using the GDP deflator for the United States (18). A detailed description of the cost data collection methods is provided in Appendix II and III.

Healthcare Outputs

We used clinic registers to determine the outputs of the standard facility-based HIV testing service including numbers of: tests administered; HIV positive test results; tests administered to 2-18 year olds; positive test results among 2-18 year olds. We used B-GAP study data to determine the outputs of the three ILHIVT modalities, including the number of: index cases screened; children and adolescents identified through index cases; children and adolescents tested by the three modalities; HIV-positive children and adolescents diagnosed.

Data Analysis

Unit cost per SoC HIV test in clinics , and per diagnosis at each clinic were calculated by dividing the total 4 month costs of testing at each clinic by the total number of people tested, and the number identified as positive, respectively. As no additional resources were consumed at clinics to test children/adolescents we assumed the cost per test to be the same as for adults.

The incremental cost of ILHIVT was calculated by assessing the additional personnel time and resources to follow-up cases and test them. To obtain the incremental cost per test, the incremental cost was divided by the total number of children and adolescents who were tested using the respective modality. The cost per diagnosis of a positive child/adolescent was calculated as the incremental cost per test divided by the number who tested positive. The relationship between uptake and unit cost was explored by plotting the incremental ILHIVT cost per test, against uptake per modality

Sensitivity Analysis

A univariate sensitivity analysis was performed on input variables for which there was a degree of uncertainty, or that constituted a significant portion of the total costs including the exchange rate and transaction costs. The impact of the RTGS conversion rate used (1USD:4 RTGS) was assessed by varying the conversion rate to the highest (1USD:1 RTGS) and lowest (1USD: 50 RTGS) observed rates during the study period. The impact of assumptions made around resource use items such as staff salaries (±5-10%,), building (±10-20%), equipment (±10-20%) and overhead costs (±10-20%) and the frequency of the refresher training (1/year – 4/year) were also tested. In addition, HIV prevalence of clinic attendees was varied from 5 – 20%, while yield of ILHIVT was varied from 2 – 7%. Finally, transaction costs defined as management costs incurred through non-governmental organization (NGO) supervision of intervention activities (for study staff), was varied (±10-20%).

Scenario Analysis

HIV self-testing is recommended by the WHO as an alternative HIV testing strategy for scale-up (19-21), and qualitative work conducted after the conclusion of the ILHIVT intervention indicated that lack of exposure to, and acceptability of caregiver-provided testing affected the uptake of this modality across all sites. We explored variations in the uptake of index-linked caregiver provided HIV testing to reflect potential real-world acceptability and implementation scenarios: 1.) equal uptake of all 3 modalities; 2.) a 50-50 split between facility based testing and testing performed by caregivers; 3.) 100% uptake of caregiver-provided testing at all clinics. Additionally, we compared the efficiency of home-based and

caregiver-provided testing (i.e. non facility-based options) by identifying the uptake of caregiver provided tests required to match the unit cost of home-based ILHIVT performed by health care workers.

RESULTS

Cost Composition

Table 2 presents recurrent and capital costs for SoC HIV testing and the three ILHIVT modalities. The total monthly cost of providing SoC testing ranged from US$997 to US$1,410. Across these facilities, personnel costs accounted for 56.9% to 70.9% of total costs; testing-specific consumables accounted for 27.9% to 35.7%; overheads from 1.2% to 9.8%, and less than 1% of total costs were attributable to capital resource items. The total incremental monthly cost of providing ILHIVT ranged from $379 to $400 in clinic; $359 to $420 for home-based testing; $255 to $288 for caregiver-provided testing. Across all three clinics and modalities; personnel costs accounted for 39.7% to 62.4% of total costs; testing-specific consumables accounted for 4.5% to 23.1%; transaction costs from 17.6% to 29.1%; capital resource items for 2.6% to 6.4%.

Table 2. Monthly cost breakdown of providing: 1.) Full SoC HTS at 2 urban and 1 rural clinic in Bulawayo and Mangwe District in Matebeleland South Province, Zimbabwe; 2.) Incremental ILHIVT according to 3 modalities – clinic, home-based and caregiver – at the same 3 clinics

	Clinic A – Bulawayo (Urban)				Clinic B – Bulawayo (Urban)				Clinic C – Mangwe (Rural)			
	SoC	**Clinic**	**Home-Based**	**Caregiver**	**SoC**	**Clinic**	**Home-Based**	**Caregiver**	**SoC**	**Clinic**	**Home-Based**	**Caregiver**
Recurrent	**$1,178.43 (99.4%)**	**$375.71 (93.9%)**	**$385.34 (96.6%)**	**$265.01 (97.2%)**	**$1,401.98 (99.4%)**	**$355.07 (93.6%)**	**$346.30 (96.6%)**	**$280.52 (97.4%)**	**$993.20 (99.6%)**	**$357.15 (93.7%)**	**$407.82 (97.1%)**	**$246.97 (97.0%)**
Personnel	$706.06 (59.5%)	$219.60 (54.9%)	$221.32 (55.7%)	$108.08 (39.7%)	$802.19 (56.9%)	$236.76 (62.4%)	$187.00 (52.2%)	$125.24 (43.5%)	$704.39 (70.9%)	$167.96 (44.0%)	$253.02 (60.2%)	$128.01 (50.3%)
Consumables – (Test specific)	$352.56 (29.7%)	$54.90 (13.7%)	$63.23 (15.9%)	$56.14 (20.6%)	$503.63 (35.7%)	$17.10 (4.5%)	$58.50 (16.3%)	$54.48 (18.9%)	$276.77 (27.9%)	$87.98 (23.1%)	$54.00 (12.9%)	$18.16 (7.1%)
Consumables – (Other)	$3.17 (0.3%)	$27.14 (6.8%)	$26.72 (6.7%)	$26.72 (9.8%)	$2.38 (0.2%)	$27.14 (7.2%)	$26.72 (7.5%)	$26.72 (9.3%)	$0.05 (0.0%)	$27.14 (7.1%)	$26.72 (6.4%)	$26.72 (10.5%)
Overhead	$116.64 (9.8%)	NA	NA	NA	$93.77 (6.7%)	NA	NA	NA	$11.99 (1.2%)	NA	NA	NA
Transaction Costs (NGO Management)	NA	$74.07 (18.5%)	$74.07 (18.6%)	$74.07 (27.2%)	NA	$74.07 (19.5%)	$74.07 (20.6%)	$74.07 (25.7%)	NA	$74.07 (17.6%)	$74.07 (17.6%)	$74.07 (29.1%)
Capital	**$7.55 (0.6%)**	**$24.24 (6.1%)**	**$12.27 (3.1%)**	**$7.59 (2.8%)**	**$7.89 (0.6%)**	**$24.24 (6.4%)**	**$12.71 (3.4%)**	**$7.59 (2.6%)**	**$4.14 (0.4%)**	**$24.24 (6.4%)**	**$12.27 (2.9%)**	**$7.59 (3.0%)**
Equipment	$4.33 (0.4%)	$13.50 (3.4%)	$1.53 (0.4%)	$0.00 (0.0%)	$2.51 (0.2%)	$13.50 (3.6%)	$1.53 (0.4%)	$0.00 (0.0%)	$1.71 (0.2%)	$13.50 (3.5%)	$1.53 (0.4%)	$0.00 (0.0%)
Building	$3.22 (0.3%)	NA	NA	NA	$5.37 (0.4%)	NA	NA	NA	$2.44 (0.2%)	NA	NA	NA
Intervention Start-Up	NA	$10.74 (2.7%)	$10.74 (2.7%)	$7.59 (2.8%)	NA	$10.74 (2.8%)	$10.74 (3.0%)	$7.59 (2.6%)	NA	$10.74 (2.8%)	$10.74 (2.6%)	$7.59 (3.0%)
Total	**$1,185.98**	**$399.95**	**$397.60**	**$272.60**	**$1,409.86**	**$379.30**	**$358.56**	**$288.11**	**$997.34**	**$381.39**	**$420.08**	**$254.56**

HIV Testing Outcomes

From May 2018 to August 2018, 2317 clinic based SoC HIV tests were administered (*Table 3*). The test yield (proportion of test results that were positive), was 12.9% (299/2317 total tested). Across the 3 clinics 11.5% (267/2317) of those tested were 2-18 years of age, and the yield was 3.7% (10/267).

The 3 clinics screened 2087 index-cases, identified 1708 eligible children and adolescents of unknown HIV status, and of those, tested 1263 (74%); 41% in clinic, 48% via home-based testing, and 10% through assisted testing. Uptake of each modality varied by clinic; home-based testing was the preferred option at urban clinics A (45.7%) and B (65.9%), while clinic testing was the preferred option at rural clinic C (56.2%). The yield of ILHIVT at Clinics A, B and C was 0.6% (3/505), 0.3% (1/290) and 1.5% (7/468) respectively. Yield by modality is as follows: 1.3% (7/523) via clinic; 0.5% (3/611) via home-based; 0.8% (1/129) via caregiver-assisted testing (*Table 3*).

Unit Costs

The cost per child/adolescent tested through SoC ranged from US$5.90 to US$7.15. The cost per positive SoC test result ranged from US$ 35.92 to US$61.61. The costs per HIV-positive child or adolescent, 2-18 years of age identified through SoC were US$166.69, US$139.76, US$197.80 at Clinic A, B and C respectively (*Table 3*).

The average incremental cost per child/adolescent tested through ILHIVT at the clinic ranged from US$10.56 (urban clinic A) to US$25.47 (rural clinic C). The incremental cost per modality across all clinics ranged as follows: clinic – US$5.36 (clinic C) to US$31.08 (clinic B); home-based testing by health care worker – US$6.69 (clinic A) to US$8.65 (clinic C); caregiver-provided testing – US$17.59 (clinic A) to US$62.40 (clinic C). The cost per diagnosis of an HIV positive child/adolescent through ILHIVT ranged from US$352.59 to US$1,492.02 for clinic based ILHIVT and US$817.21 to US$1,545.41 via home-based testing by health care worker. Clinic C had the only positive test result from caregiver-provided testing, which cost US$998.41 (*Table 3*). The uptake of ILHIVT via modality and associated incremental cost per test indicates that costs are likely dependent on quantity: the fewer tests administered via modality, the higher the associated incremental unit cost per test, and vice versa (*Figure 1*).

Table 3. Unit cost of the various HIV testing modalities across all three costing study clinics, over a 4 month time-period

Testing Modality	No. Tested	No. Positive	Cost Per Test (USD)	Cost Per Diagnosis (USD)
Clinic A – Bulawayo (Urban)				
Standard of Care (SoC) – Total	804	77	$5.90	$61.61
SoC 2-18 years	113	4	$5.90	$166.69
Index-Linked-Clinic	212	2	$7.41	$785.50
Index-Linked-Home-Based	231	1	$6.69	$1,545.41
Index-Linked-Caregiver	62	0	$17.59	N/A
Clinic B – Bulawayo (Urban)				
Standard of Care – Total	955	157	$5.91	$35.92
SoC 2-18 years	71	3	$5.91	$139.76
Index-Linked-Clinic	48	1	$31.08	$1,492.02
Index-Linked-Home-Based	191	0	$7.18	N/A
Index-Linked-Caregiver	51	0	$21.63	N/A
Clinic C – Mangwe (Rural)				
Standard of Care – Total	558	65	$7.15	$61.37
SoC 2-18 years	83	3	$7.15	$197.80
Index-Linked-Clinic	263	4	$5.36	$352.59
Index-Linked-Home-Based	189	2	$8.65	$817.21
Index-Linked-Caregiver	16	1	$62.40	$998.41

Notes:

1. Unit cost of SoC HIV testing presented for all clinics span May-Aug 2018 period
2. Incremental unit cost of index-linked testing for all modalities, presented for all clinics span Sep-Dec 2018

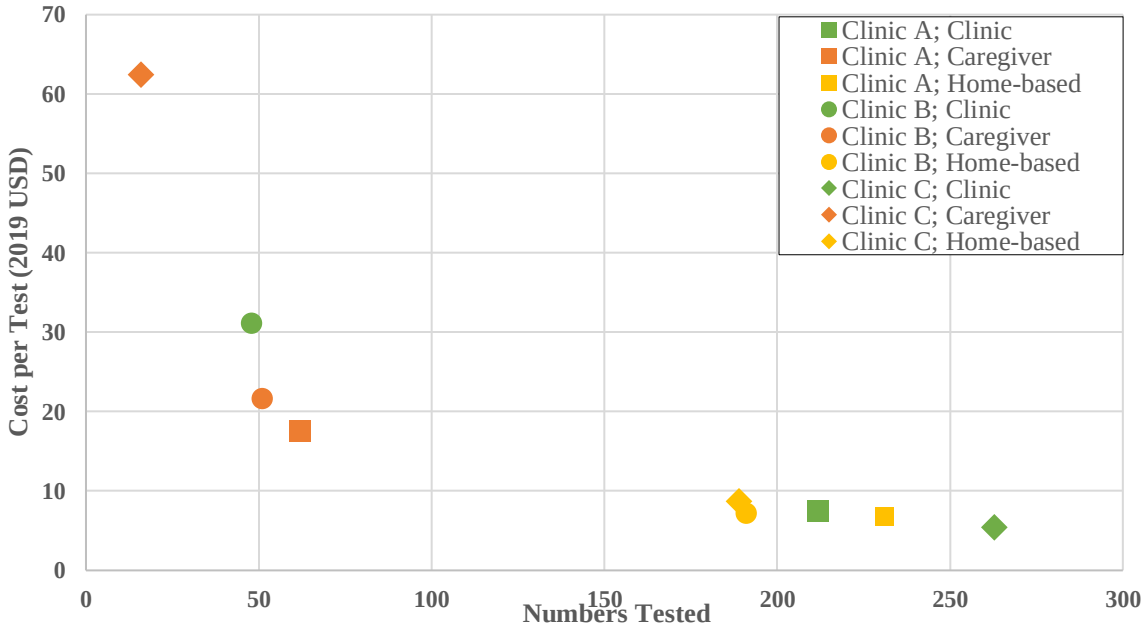

Figure 1. Uptake of *Index-Linked HIV Testing* vs associated *Incremental Cost per Test*, according to modality: Clinic; Caregiver; Home-based

Sensitivity Analysis

All 4 HIV testing unit costs (SoC and ILHIVT via 3 modalities) were most sensitive to changes in the conversion rate. *Figures 2a – 2d* present the results of the sensitivity analysis performed on the remaining variables. With regards to resource use inputs, personnel salaries had the largest influence on SoC unit costs (±3-7%), followed by overheads and the addition of up to 4 refresher trainings. Changes to capital resource inputs had a negligible effect on SoC unit costs. When considering the resource use inputs for ILHIVT across all three modalities, the unit cost per test was most sensitive to changes in clinic attendee HIV prevalence (±9-13%), followed by personnel salaries for all 3 modalities .

The impact of changing the parameters on cost per diagnosis unit costs are presented in Supplementary Figure 1. Cost per diagnoses were most sensitive to changes in the conversion rate. Of the resource use inputs, personnel costs had the largest influence on SoC unit costs, while changes to clinic attendee HIV prevalence as well as testing yield, had the largest influence on ILHIVT related unit costs.

Scenario Analysis

The results of varying modality uptake and the subsequent impact on unit cost per test, compared to observed unit costs for the 4-month period in this study are presented in *Table 4*. If all 3 modalities have equal uptake, the unit cost of home-based testing increases and caregiver-provided testing becomes cheaper than clinic testing at urban clinics. If clinic and caregiver-provided testing have equal uptake, the unit cost of clinic testing decreases at both urban clinics but increases at the rural clinic, while unit costs of caregiver-provided testing at all three clinics decrease substantially. If all index-linked testing is via caregiver-provided testing, the cost per test at Clinic A, B and C respectively, are as follows: US$2.12, US$6.52, US$5.32.

In order for the caregiver – provided testing incremental unit cost per test to equate to that of ILHIVT via the home-based testing modality observed in the same 4-month time period, 163, 241 and 177 caregiver-provided tests would need to be administered at clinics A, B and C respectively. If all participants at clinics A and C who chose home-based testing had opted for caregiver-provided testing instead, it might have been possible to observe the lower situational caregiver – provided testing unit cost per test.

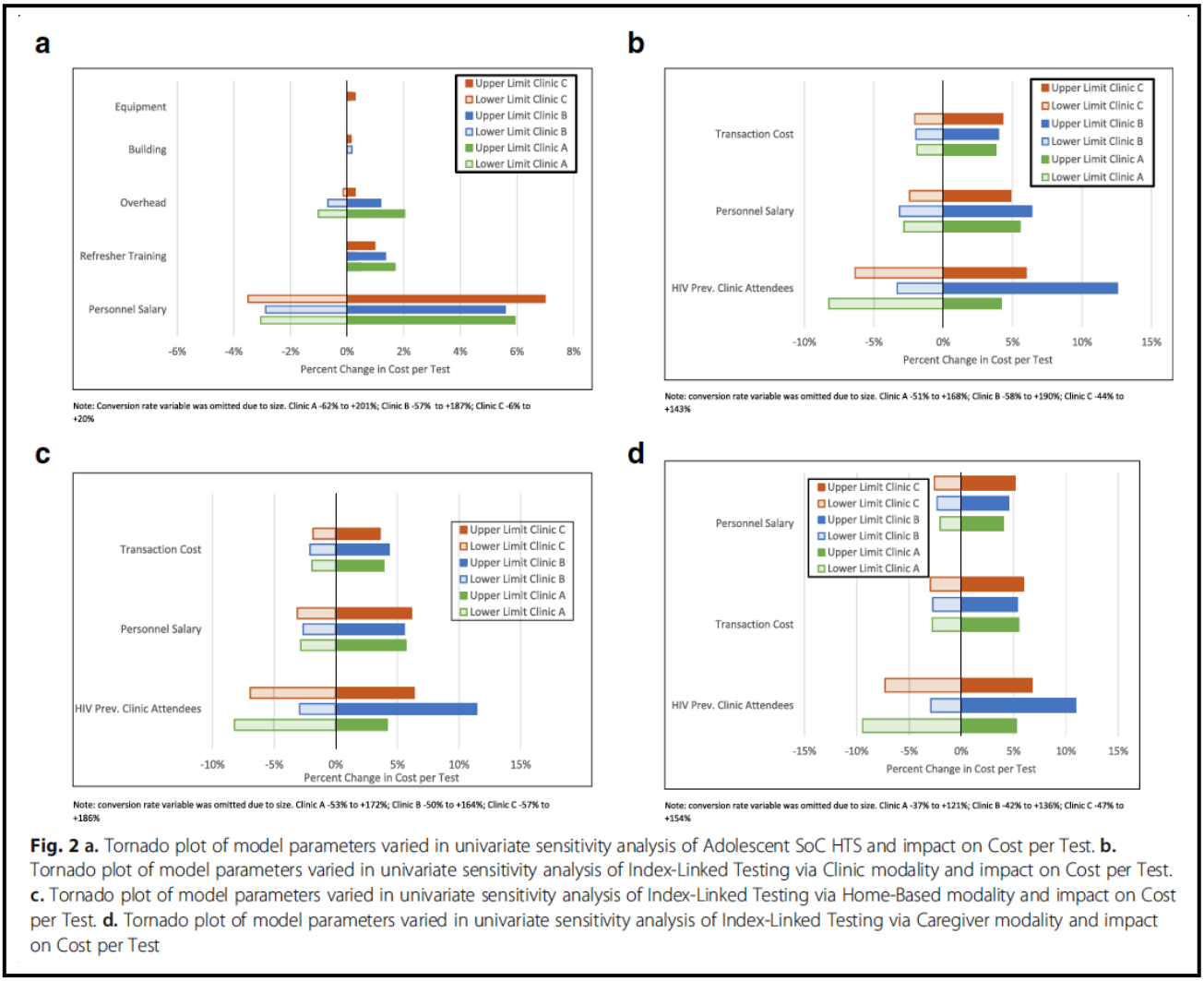

Fig. 2 a. Tornado plot of model parameters varied in univariate sensitivity analysis of Adolescent SoC HTS and impact on Cost per Test. **b.** Tornado plot of model parameters varied in univariate sensitivity analysis of Index-Linked Testing via Clinic modality and impact on Cost per Test. **c.** Tornado plot of model parameters varied in univariate sensitivity analysis of Index-Linked Testing via Home-Based modality and impact on Cost per Test. **d.** Tornado plot of model parameters varied in univariate sensitivity analysis of Index-Linked Testing via Caregiver modality and impact on Cost per Test

Table 4. Scenario analysis of varying index-linked modality preference/uptake across all clinics: change in Unit Cost – Cost per Test

	Clinic	Home-Based	Caregiver
Clinic A – Original Unit Cost	**7.41**	**6.69**	**17.79**
Equal –1/3 Distribution	$9.10	$8.85	$6.36
50:50 –Clinic/Caregiver	$6.37	N/A	$4.24
Caregiver Only	N/A	N/A	$2.12
Clinic B – Original Unit Cost	**31.08**	**7.18**	**21.63**
Equal –1/3 Distribution	$15.89	$13.32	$12.97
50:50 –Clinic/Caregiver	$10.89	N/A	$9.75
Caregiver Only	N/A	N/A	$6.52
Clinic C – Original Unit Cost	**5.36**	**8.65**	**62.40**
Equal –1/3 Distribution	$8.42	$10.29	$9.36
50:50 –Clinic/Caregiver	$5.92	N/A	$7.34
Caregiver Only	N/A	N/A	$5.32

DISCUSSION

Our findings show that 6 times more children/adolescents were tested via ILHIVT compared to SoC HIV testing over the observed period. HIV prevalence among children/adolescents accessing SoC HIV testing (4%), was much higher than children/adolescents (0.7%) tested via ILHIVT. The cost of SoC HIV testing was lower in urban than rural settings, due to a greater number of tests administered at the urban clinics (44%-71% more) and larger catchment populations. The cost of ILHIVT modalities were dependent on, and varied according to uptake. Costs involved in delivering SoC HTS were primarily driven by personnel followed by consumables. Whereas personnel followed by transaction costs were the largest drivers of ILHIVT costs at both urban and rural clinics. While management costs will be an important component of ensuring quality as well as accountability in strategies such as this that rely on identifying potential cases and outreach to the community, the management of this type of service delivery may need to be streamlined in an effort to keep transaction costs low.

The cost of delivering HIV testing through standard clinic-based services in this study ranged from US$5.90 to US$7.15 , and is comparable to recent STAR project estimates from Malawi, Zambia and Zimbabwe (2016 US$4.24 to US$7.65) (22), yet higher compared to the results of a systematic review evaluating the cost of HTC in South Africa (2017/2018 US$3.62) (23). The cost per positive diagnosis through standard clinic services in this study was lower than STAR estimates (US$73.63 to US$178.92) and likely reflects the higher HIV prevalence of those accessing testing among our study population (13%), compared to the STAR project (7%) (22).

In contrast, the high cost per diagnosis associated with ILHIVT was due to a low prevalence of HIV among index-linked children. An estimated >90% of children living with HIV are vertically infected; those who were born prior to the scale up of prevention of mother to child transmission (PMTCT) programs are now likely to be adolescents and would therefore be diagnosed only when symptomatic, resulting in worse outcomes than those diagnosed and initiated on treatment in infancy (13, 24). SoC HIV testing is likely to diagnose children with advanced disease, whereas asymptomatic children may not be brought to the clinic. Other studies of the same age-group in Zimbabwe found higher prevalence (2.6% - 15%) (11, 25), and index-linked testing of sexual partners and biological children in 3 rural provinces found a 30% HIV prevalence (12). A study in Cameroon where only 46.2% of indexes consented to have their children tested, diagnosed HIV infection in 6.8% of children tested (24), while another index-linked study in Lesotho found an HIV prevalence of 1.8% among biological children of indexes (26). The low HIV prevalence among index cases at the B-GAP clinics is likely attributable to recent HIV testing campaigns potentially resulting in saturation of testing, including a large Population Services

International testing campaign operating in the area and exclusion of children/adolescents tested >6 months prior to B-Gap screening.

HIV case finding will become more costly as knowledge of HIV status and treatment coverage increase. Alternative community based HIV testing strategies such as home-based testing and HIV Self-Test have been evaluated using costing studies (19, 27, 28), but this is the first costing study to evaluate index-linked testing, a strategy proposed by the WHO in order to expand HTC (29). Our results provide the first unit costs of the different ILHVIT modalities for sub-Saharan Africa but they do not provide information on the cost-effectiveness of the strategy. While a full economic evaluation is necessary to accurately estimate the cost-effectiveness of ILHIVT, Phillips et al (2019) have shown that cost per diagnosis can be used as a proxy for cost-effectiveness of HIV testing programs, and estimated a value for the cost-effectiveness threshold (2018) US$315 per HIV diagnosis (30). By this definition, none of the index-linked modalities in our analysis would be considered cost-effective as the lowest cost per diagnosis estimated was US$385.35. However, our sensitivity analysis illustrated that when ILHIVT yield was increased from 0.7% to 7%, (as observed in Cameroon (24)), all but two modalities (clinic testing at an urban clinic, and rural caregiver-provided testing), resulted in cost per diagnoses below that US$315 threshold. ILHIVT cost per diagnosis would be more cost-effective if targeted to a higher-prevalence population. For example, a more efficient solution for scaling up ILHIVT could be to test the entire household; costs would be shared across a greater number of tests and yield would likely increase as adults have a higher prevalence of HIV compared to children/adolescents – although measures would need to be in place to ensure services screen out those previously diagnosed and on ART (27), and those testing are effectively linked to HIV treatment or prevention. A scale-up of any version of ILHIVT – in its current format, or expanded to the entire household – to either the regional or national level, requires careful consideration of the implications of potential (dis)economies of scale as well as other cost drivers. While this study explored drivers of cost at the facility level, and expected uptake is critical to this setting, physical capacity and infrastructure investment costs necessitate scrutiny at the regional or national level (31). Furthermore, costs involved in geographical variability with regards to transport, training, management, monitoring and evaluation, quality assurance, as well as socio-cultural variability and acceptability affecting demand, must be considered (32).

HIV self-testing has the advantages of convenience, discretion and confidentiality, compared to clinic based HTS (33, 34). HIV self-test has shown high acceptability and uptake elsewhere which resulted in WHO guidelines recommending scale-up (19-21). In this study ‘self-test’ however referred to caregiver assisted testing of a child/adolescent. Caregiver uncertainty about correctly administering the test to a

child without the aid of a health care professional, as well as fear of how to counsel a child with a positive result, could be factors accounting for the low levels of uptake within this study (35). SoC clinic based HIV testing, when supplemented with HIV self-testing, can be a cost-effective testing option in a population with a high HIV prevalence and has the capacity to extend coverage rates, and therefore diagnoses (28, 33). In this study, because assisted-testing had very low uptake, the incremental unit costs were 3.0 times greater than the cheapest modality (home–based) in an urban setting, and 11.6 times higher than the cheapest modality (clinic) in a rural setting. This low uptake raises questions around the differences of administering a self-test to someone else, compared to self-administration. Exploration into the dynamics and differences between HIV self-test and assisted self-test are needed.

To our knowledge, this study is the first to estimate the cost of ILHIVT in any setting. A limitation is that only 3 clinics were included. Although both urban and rural clinics are represented, showing that the cost and efficiency of each modality varies according to setting, it should be noted that the urban and rural clinics were located in different districts. While Bulawayo is an entirely urban district, and Mangwe an entirely rural district, there may be unique structural and/or district level factors which also influence unit costs. Additionally, the study was conducted within an economically unstable context. Zimbabwe dollarized its economy in 2008 following hyperinflation. In 2018 it introduced its own currency (RTGS), which triggered rapid inflation. In this study all RTGS amounts were converted to USD at the prevailing rate. Costs were highly sensitive to conversion rate as a result of the rapid inflation of RTGS against the US dollar.

CONCLUSION

Innovative and alternative HIV testing strategies above SoC approaches are necessary in order to reach children and adolescents, given the additional barriers they face in order to get tested. The results of our study confirm that both costs and uptake of ILHIVT vary with setting. In addition, while ILHIVT allows for greater access of this difficult to reach population, compared to the standard method, uptake is a key driver of the cost per test. To ensure efficiency when scaling up ILHIVT, acceptability of testing modality needs to be considered and alternative index linked testing solutions that increase yield such as ILHIVT of the entire household, as opposed to solely targeting children/adolescents, need to be explored. Additionally, there is potential to benefit from economies of scope by integrating ILHIVT with other activities, however this would require further consideration and research.

LIST OF ABBREVIATIONS

ART	Antiretroviral Therapy
B-GAP	Bridging the GAP in HIV Testing and Care for Children in Zimbabwe
GDP	Gross Domestic Product
HIV	Human Immunodeficiency Virus
HTC	HIV Testing and Counselling
ILHIVT	Index-Linked HIV Testing
NGO	Non-Governmental Organization
OMT	Oral Mucosal Transudate
RTGS	Real-Time Gross Settlement
SoC	Standard of Care
USD	United States Dollars
WHO	World Health Organization

DECLARATIONS

Ethics Approval and Consent to Participate

Approval for the B-GAP study was obtained from the London School of Hygiene & Tropical Medicine research ethics committee (ref 12263-2), the Medical Research Council of Zimbabwe (ref MRCZ/A/2167) and the institutional review board of the Biomedical Research and Training Institute (ref AP138/2017). Individual patient level data was not presented in this manuscript; written consent to participate was obtained for the parent study.

Consent to Publish

Not applicable.

Availability of Data and Materials

The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing Interests

The authors have no financial or other competing interests to declare.

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Author Contributions

AV, LG, HM and VS conceptualized the study, developed methods and data collection tools, and analyzed data. CDC was parent study coordinator. AV, CDC, TC, RC and KN made substantial contributions to acquisition of data. GN contributed to the conception and design of the parent study. RAF conceptualized the overall project. All authors have read and approved the final draft and declare no competing interests.

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everyone at Bulawayo City Council and Matebeleland South Province offices, involved in procuring the pricing lists.

Figure Legends

Table 1. Characteristics of costing study facilities, as of Sept 2018

Table 2. Monthly cost breakdown of providing: 1.) Full SoC HTS at 2 urban and 1 rural clinic in Bulawayo and Mangwe District in Matebeleland South Province, Zimbabwe; 2.) Incremental ILHIVT according to 3 modalities – clinic, home-based and caregiver– at the same 3 clinics.

Table 3. Unit cost of the various HIV testing modalities across all three costing study clinics, over a 4 month time-period.

Figure 1. Uptake of *Index-Linked HIV Testing* vs associated *Incremental Cost per Test,* according to modality: Clinic; Caregiver; Home-Based.

Table 4. Scenario analysis of varying index-linked modality preference/uptake across all clinics: change in Unit Cost - Cost per Test

Figure 2a. Tornado plot of model parameters varied in univariate sensitivity analysis of Adolescent **SoC HTS** and impact on **Cost per Test**.

Figure 2b. Tornado plot of model parameters varied in univariate sensitivity analysis of Index-Linked Testing via **Clinic** modality and impact on **Cost per Test**

Figure 2c. Tornado plot of model parameters varied in univariate sensitivity analysis of Index-Linked Testing via **Home-Based** modality and impact on **Cost per Test**

Figure 2d. Tornado plot of model parameters varied in univariate sensitivity analysis of Index-Linked Testing via **Caregiver** modality and impact on **Cost per Test**

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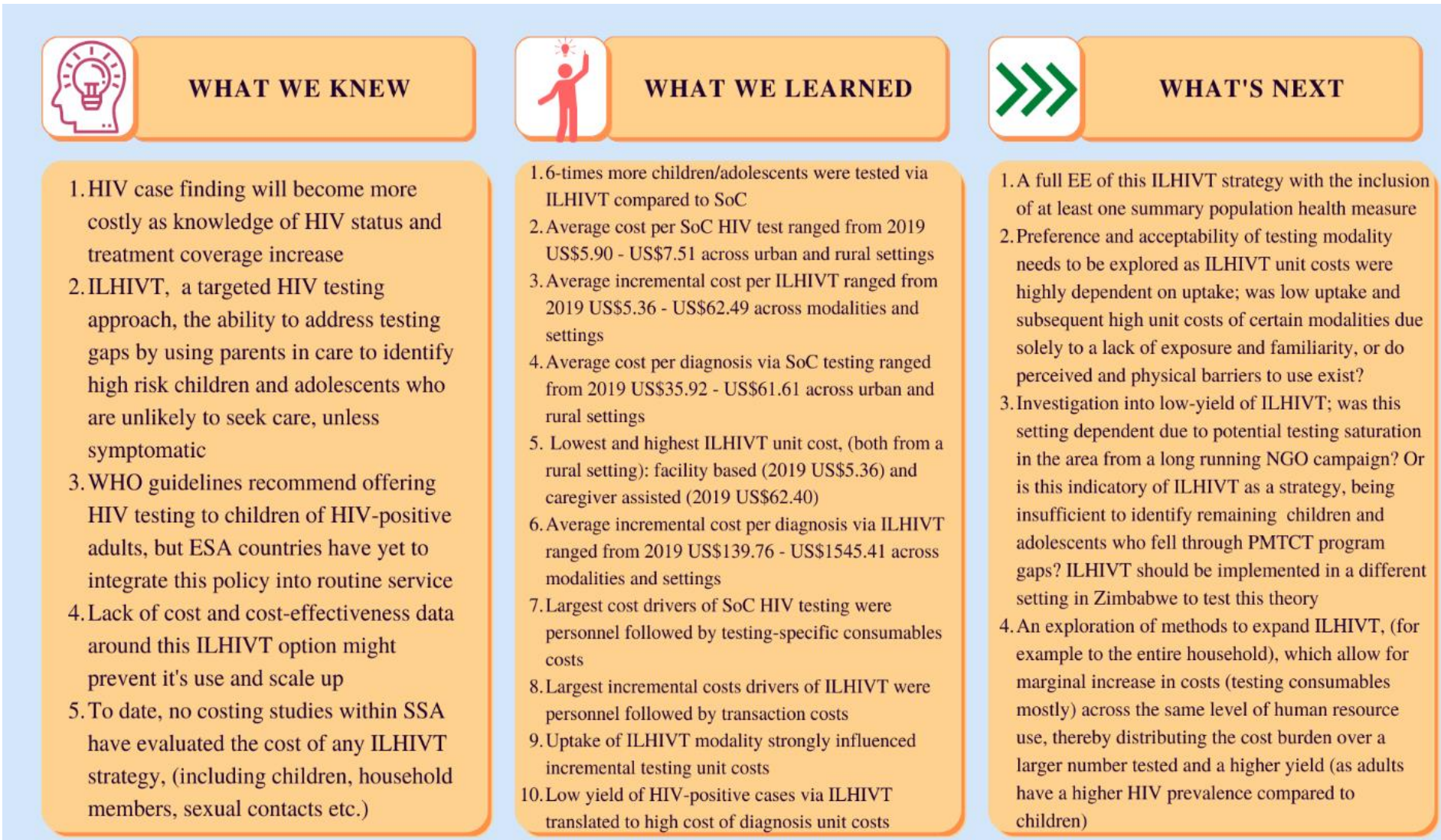
5.5 CHAPTER 5 KEY TAKEAWAYS

The first study in SSA to estimate both the cost of delivering ILHIVT, as well as the first to evaluate the cost of an HIV testing strategy targeting children and adolescents, this analysis highlighted that HIV testing and diagnosis unit costs are highly dependent on uptake and yield, with the largest cost drivers being personnel costs. Despite having tested six times more children/adolescents via ILHIVT (compared to SoC facility based testing), the low yield of HIV positive cases identified translated to high cost of diagnosis unit costs. ILHIVT modality preferences varied across settings and though clinic based ILHIVT was preferred, more index-linked children and adolescents were tested through community, home-based testing. HIVST, usually a preference among adults due to facilitation of privacy and convenience, in this iteration, (assisted self-testing) was the least preferred index-linked testing modality among parents and caregivers (**C5, Figure 1**).



C5, Figure 1. Results P3 Key Takeaways: What We Knew; What We Learned; What's Next

5.6 IMPLICATIONS FOR THESIS

The overall aim of this thesis is to contribute to the methods of EEs of HIV testing in children and adolescents in a Zimbabwean context. This chapter contributed to achieving this aim by being the first to cost (and publish) an HIV testing strategy targeting this sub-population, along with the first to cost (and publish) an ILHIVT strategy in any population in SSA. In doing so, **Objective 3** of this thesis – to measure the cost of delivering index-linked HIV testing to children and adolescents in Zimbabwe – was fulfilled. In answering **Objective 3**, an important implication for this thesis was uncovered: the unit costs of HIV testing interventions targeting children and adolescents can potentially be reduced through brute administration; testing enough (i.e. a large enough) sample of children and adolescents may, from a budgetary perspective, justify intervention delivery. However, the trade-off for this and future interventions is yield; administering HIV testing interventions in underserved areas, so as to identify the remaining HIV positive cases in this sub-population. In the future, as PMTCT programs are strengthened, there may come a time where HIV testing strategies to mop up vertically infected children are no longer necessary. The nature of HIV testing strategies would then morph in this sub-population to specifically target sexual debut in adolescence. This programmatic consideration is not only relevant to this thesis, but to future EE research and literature in this domain. The practicality of the findings of **Objective 3** (along with the previous 2 objectives) will be built on, and demonstrated in the next chapter.

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CHAPTER 6 – PRACTICAL APPLICATION AND FUTURE CONSIDERATION

6.1 INTRODUCTION

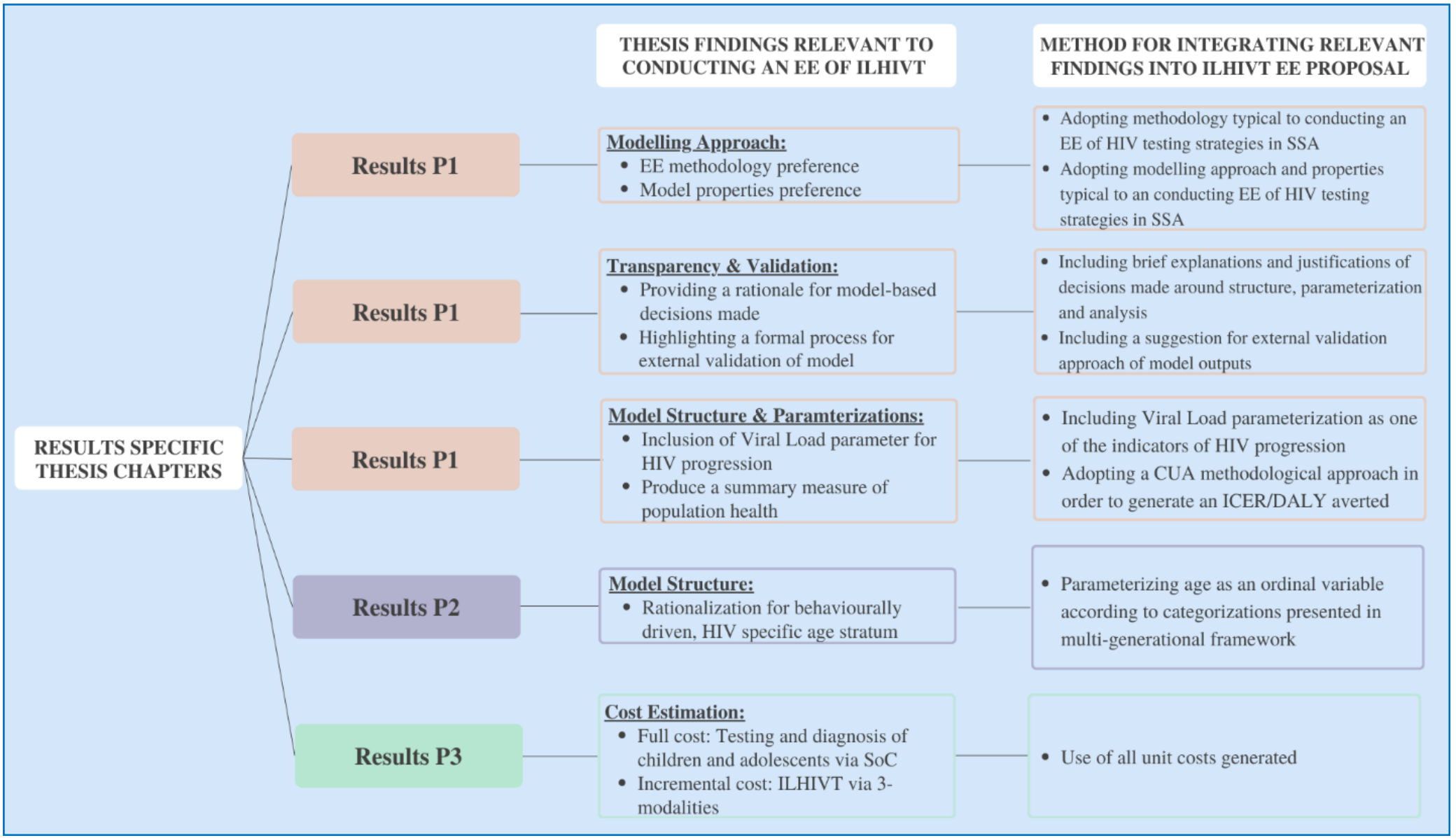
Research is never conducted in a vacuum; the importance and applicability of findings, along with translation of work to a larger context should always be considered. This thesis is no different and it frames chapter findings within the context of '*what's next?*'. This chapter builds on findings generated via **Results P1** (chapter 3), **Results P2** (chapter 4), and **Results P3** (chapter 5), and details how the learnings from the previous three chapters can be combined and extended further. Results P1 provides evidence that full EEs of HIV testing strategies in SSA employ CEA and CUA methodology concerned with *constrained maximization*; i.e. how best to allocate an existing budget [1]. CEA defined by *Drummond et al.,* as "costs related to a single, common effect that might differ in magnitude between the alternative programmes", and its variant CUA, which uses a generic measure of health gain (thereby allowing comparison of programs across the disease spectrum), include the following components [1]:

1. Assessment of the resulting health benefits of the alternative intervention being considered [2];
2. Estimation of the costs of delivery and the subsequent impact on resources [2];
3. Assessment of opportunity costs – benefits forgone – against a cost-effectiveness threshold [2].

Results P3 partially estimates the second of the above 3 components for an ILHIVT strategy in children and adolescents in Zimbabwe. Given that knowledge surrounding the costs of ILHIVT alone is insufficient to understand its impact or answer the question of whether investment into an ILHIVT strategy is even worthwhile, next steps entail executing an EE. This chapter proposes a method for conducting an economic evaluation of ILHIVT based on findings from the previous results chapters (**P1, P2 & P3**) and in doing so, meets **objective 4** to *integrate thesis findings into an actionable format*. This chapter's contribution to future considerations in the format of an EE proposal of B-Gap, is a pathway towards advancing HTAs of HIV programming in Zimbabwe, allowing for informed decision making around the issue of access to children and adolescents potentially at higher risk for HIV. No prior economic modelling work assessing HIV

testing strategy targeting children and adolescents in SSA or ILHIVT in SSA has been conducted.

As such, this chapter outlines a hypothetical proposal for an EE of ILHIVT based on best practices informed by the findings and recommendations of **Results P1** and **Results P2**. The costing data generated from **Results P3**, are transferable and of use as they inform relevant unit costs for the ILHIVT. The specifics of relevant findings and recommendations integrated into the proposal are highlighted in **C6, Figure 1** below.



C6, Figure 1. Future Considerations of this Thesis - Where do we go from here and how?; an EE proposal for ILHIVT
The contributions of each of the results chapters, with relevance to integration into an EE proposal for ILHIVT are highlighted here.

A Proposal for an economic evaluation of B-GAP: index-linked HIV testing for children and adolescents in Zimbabwe

6.2 BACKGROUND

In 2020, an estimated 2.8 million children and adolescents (0-19 years) were living with HIV globally, with sub-Saharan Africa (SSA) bearing 88% of the global burden amongst this group [3]. In the same year, there were 300,000 newly infected children and adolescents, despite as substantial decline in HIV infection (53% and 38% respectively) [3]. Failure to meet any of the 2020 global HIV targets resulted in more than eight fold the number of newly acquired HIV infections in children 0-9 years than anticipated and . The COVID-19 pandemic intensified setbacks to HIV programs already suffering from decreased funding and resources, and served as a exigent reminder that children and adolescents, (along with pregnant women), were amongst the most vulnerable populations [3, 4]. The pandemic severely limited access to maternal and child prevention and health care services: high burden countries reported a decline of approximately 50-70% in infant HIV testing; treatment initiation for children under 14 declined by approximately 25-50%; older adolescents (15-19 years) received the results of their HIV test only 1-25% of the time [3]. Innovative and cost-effective HIV testing modalities are needed more than ever to bridge not only the inequitable gap to HIV diagnosis in children and adolescents, but to also account for the increased difficulty in case-finding among this population due to overall lower HIV prevalence [5].

Children with undiagnosed, perinatally acquired, slow-progressing HIV who survive into adolescence without treatment, generally only present to care when symptoms of advanced disease manifest, resulting in poorer outcomes [6-8]. Additionally, a range of structural barriers (e.g. testing and treatment coverage is lower among children and adolescents compared to adults), physical barriers (e.g. difficulty accessing care without a guardian and poorer care-seeking behaviors in general), and social barriers (e.g. stigmatization), culminate in children and adolescents being underserved by the existing format of HIV care services [6, 8]. Children and adolescent targeted HIV testing approaches aimed at timely diagnosis and treatment can offset some of these barriers.

Index-linked HIV testing (ILHIVT), the provision of HIV testing services (HTS) to household contacts, (e.g. partners, family, children), of known persons living with HIV, has been shown to be a high-yielding strategy among both children and adolescents [9, 10]. Bridging the Gap in HIV testing and care for children in Zimbabwe (B-Gap), conducted in both urban (Bulawayo) and rural (Matabeleland South province) settings, evaluated the uptake and yield of a multi-option ILHIVT strategy among children and

adolescents aged 2-18. However the cost-effectiveness of this strategy is unknown, and whether scaling-up this strategy offers value for scarce resources, remains to be seen.

6.3 AIMS & OBJECTIVES

To determine if ILHIVT of children and adolescents is a cost-effective strategy for implementation into routine practice in Zimbabwe.

1. To estimate the incremental cost per DALY averted from implementing ILHIVT in addition to standard of care amongst children and adolescents in Zimbabwe.
2. To estimate the population-level health impact of a multi-option ILHIVT strategy among children and adolescents (2-18 years) in Zimbabwe.

6.4 METHODS

6.4.1 Analytic Overview

A static, individual based, stochastic model, (i.e. state-transition model – microsimulation), will be developed to explore and project the health impact and cost-effectiveness of a multi-modal ILHIVT strategy for Zimbabwean children and adolescents (aged 2-18 years). 4 HTS strategies will be evaluated using the healthcare provider perspective, under the WHO universal test and treat policy: 1.) Current standard of care HTS (i.e. voluntary, passive, facility based testing); 2.) clinic-based ILHIVT via rapid test; 3.) home-based ILHIVT via rapid test administered by a healthcare provider; 4 .) home-based ILHIVT via oral mucosal transudate (OMT) test administered by a caregiver. The age and sex differentiated model will consider the impact of a positive HIV diagnosis, HIV progression, and ART initiation and retention via 3-month cycles, over a 20 year time horizon. Costs will be presented in 2020 US$, and both costs and health benefits will be discounted at 5%. Methodological problems considered in order to conduct this economic evaluation, subsequent decisions made and the rationale behind these decisions, are presented in **C6, Table 1**.

C6, Table 1. Methods Overview for an EE of B-Gap; ILHIVT for Children and Adolescents in Zimbabwe

Problem	Decision	Rationale
Model Type	State-Transition: Microsimulation (i.e. Static, Stochastic, Individual Model)	The results of a systematic review of modelling approaches in economic evaluations of HIV testing strategies found that HIV testing strategies are modelled in one of three ways: 1. Microsimulations 2. Dynamic Compartmental Models 3. Agent-Based Models The simplest and least resource (data and time) intensive approach of the three (microsimulation), was chosen.
Model Parameters	<u>Demographic Parameters</u> Age and Sex Differentiated: • 0-4 • 5-9 • 10-14 • 15-19 • 20-24 • 25-29 • 30-34 • 35-39 • 40-44 • 45-49 • 50+ *Alternatively -* Age and Sex Differentiated: • 0-2 • 3-9, or 3-14 • 15-24 or 15-19, 20-24	Parameters were chosen based on the results of a systematic review of modelling approaches in economic evaluations of HIV testing strategies. (Please see Table 2, Table S2 and Table S3 of systematic review). Alternate, and 'behaviorally' driven age cut offs are presented based on the theoretical framework found in Chapter 4. Note: Model Structure is depicted in **C6, Figure 2**.

- 25-54
- 55+

Transmission Probability

- Dependent on HIV prevalence, varied by sex and age.

HIV Progression Parameters

1. Viral Load:
    - ≥1000 copies/ml
    - <1000 copies/ml
2. HIV Related Mortality
3. HIV/TB Co-infection

ART

1. Initiation
2. Retention at:
    - 6 months
    - 12 months
    - 24 months
    - 36 months

Parameter Source

- Age and Sex differentiated HIV prevalence, Viral Loads and ART Initiation will be taken from Zimbabwe DHS 2015[11] and ZIMPHIA 2020[12] reports.

	- HIV related mortality data will be taken from UNAIDS 2020[13]. - TB-Co-infection data will be taken from a study analyzing data from Zimbabwe's patient monitoring system[14]. - Retention data will be taken from a 2020 study assessing retention in Zimbabwe's national ART program[15].	
Perspective	Healthcare Payer	The intention of this economic evaluation is to generate evidence which will aid in informing the Ministry of Health and Child Care (MoHCC) around whether index-linked HIV testing should be integrated into routine policy. As such the audience of relevance and interest is the healthcare payer/provider, i.e. MoHCC.
Discounting	5%	Interventions addressing HIV, a chronic lifelong condition will generate costs and health benefits in the future, the value of which diminishes the further in the future they occur [16]. CHEERS recommends that a chosen discount rates should follow local economic evaluation guidelines [17]. In the absence of economic evaluations guidelines for Zimbabwe, a systematic review of modelling approaches in economic evaluations of HIV testing strategies in SSA found that a 3% discount rate was preferred among most evaluations. However an analysis around standard practice of discounting found that the recommended 3% discount rate typically applied in global health – recommended by the second panel on cost-effectiveness, the Gates reference case, NICE (3.5%) – over values future costs and health impacts of interventions, and is inappropriate for low and middle income countries as it is inconsistent with their economic growth rates[18]. As

		such, their calculations and findings based on a social welfare function and projected and historic country economic growth rates concluded that a discount rate of 5 – 6% is appropriate [18].
Time Horizon	20 years	Time horizons should be long enough to meaningfully capture relevant costs and consequences of the decision problem [19], with short enough cycle lengths to represent the frequency of clinical events and corresponding changes in costs [20]. Studies have shown that choice of time horizon is critical to cost-effectiveness estimates of changes to HIV programs [21, 22]. Too short a time horizon might not accurately reflect cost-effectiveness of an intervention as costs of an intervention are initially high and fall over time while benefits accrued, (i.e. DALYs averted) accumulate over time [21]. Incidentally some health economic evaluation guidelines recommend a lifetime time horizon [22]. As a result, a time horizon of 20 years was chosen: 1. In line with findings from a systematic review of modelling approaches in economic evaluations of HIV testing strategies 2. Longer time horizons are subject to greater uncertainty and for an infectious disease such as HIV, the state of the epidemic might change with the ever evolving prevention and treatment strategies and technologies.

Cycle Length	3 months	According to the Zimbabwe ART guidelines, resupply of medicines should coincide with clinic visits every 3 months [23]. Thus a cycle length of 3 months was chosen through which costs and benefits could accrue organically.
Outcomes	<u>Objective 1</u> DALY per strategy <u>Objective 2</u> Cost per DALY averted Evaluated against: • Cost-effectiveness threshold (CET) <50% GDP per Zimbabwe capita[24, 25].	Disability Adjusted Life-Years (DALYs) are favored by the WHO and as a result, (perhaps unintentionally), the preference among LMIC policy makers. A slew of cost-effectiveness measures are applicable and appropriate for an economic evaluation of HIV – e.g. cost per HIV infection averted, cost per HIV death averted, cost per additional positive case identified, cost per Life Year Saved, cost per DALY averted, cost per HYE gained, cost per QALY gained, etc. In line with findings from a systematic review of modelling approaches in economic evaluations of HIV testing strategies, only a limited number of outcomes will be presented. Generic measures of health gain have the widest applicability and facilitates comparability both within and across disease areas [26, 27]. As a health related quality of life questionnaire was not administered to B-GAP participants, cost per DALY averted was chosen. The WHO classifies interventions as very cost effective or cost effective if cost per DALY averted is 1xGDP per capita or 3xGDP per capita respectively. However, this CET has been critiqued for not incorporating health opportunity costs [24, 28]. An analysis of opportunity costs based on variable income countries globally, estimated opportunity costs in

		terms of health forgone, i.e. the amount of money that displaces one DALY/QALY worth of health care investment. CETs for Malawi (low income) and Kazakhstan (high-middle/high income), when factoring opportunity costs were 1%-51% and 32%-59% respectively [29].
Sensitivity Analysis	Inputs to vary in univariate and multivariate sensitivity analysis: 1. Discount Rate: 3% and 6% 2. Time Horizon: 10 years, 25 years, 50 years, lifetime 3. Yield of ILHIVT: 2 – 7% 4. Cost: Unit testing costs of all 4 strategies 5. Costs: varied ART initiation rate/coverage 6. Costs: 2nd line ART treatment regimen Probabilistic sensitivity analysis: 1. To arise depending on individual parameter uncertainty	<u>Deterministic sensitivity analysis:</u> 1. Discount rate, see above. 2. Time horizon, see above. 3. Yield of ILHIVT was surprisingly low in the B-Gap study and did not reflect findings of other studies in Zimbabwe [30], Cameroon [31] and Lesotho [10]. 4. HIV testing unit costs were generated specifically in Bulawayo (Urban) and Matebeleland South (Rural), but will be parameterized for all of Zimbabwe [32]. 5. Children and adolescents especially have lower ART initiation rates [12]. 6. In Zimbabwe, second-line ART is recommended in national pediatric treatment guidelines [23]. <u>Probabilistic sensitivity analysis</u>: 1. It is likely that not all model inputs will be extracted from an applicable source – some parameters might come from other countries, and some might be difficult to find. A probabilistic sensitivity analysis will sample from a relevant distribution (reflecting available evidence), to generate multiple estimates, the range of which will likely cover the correct estimate [27].

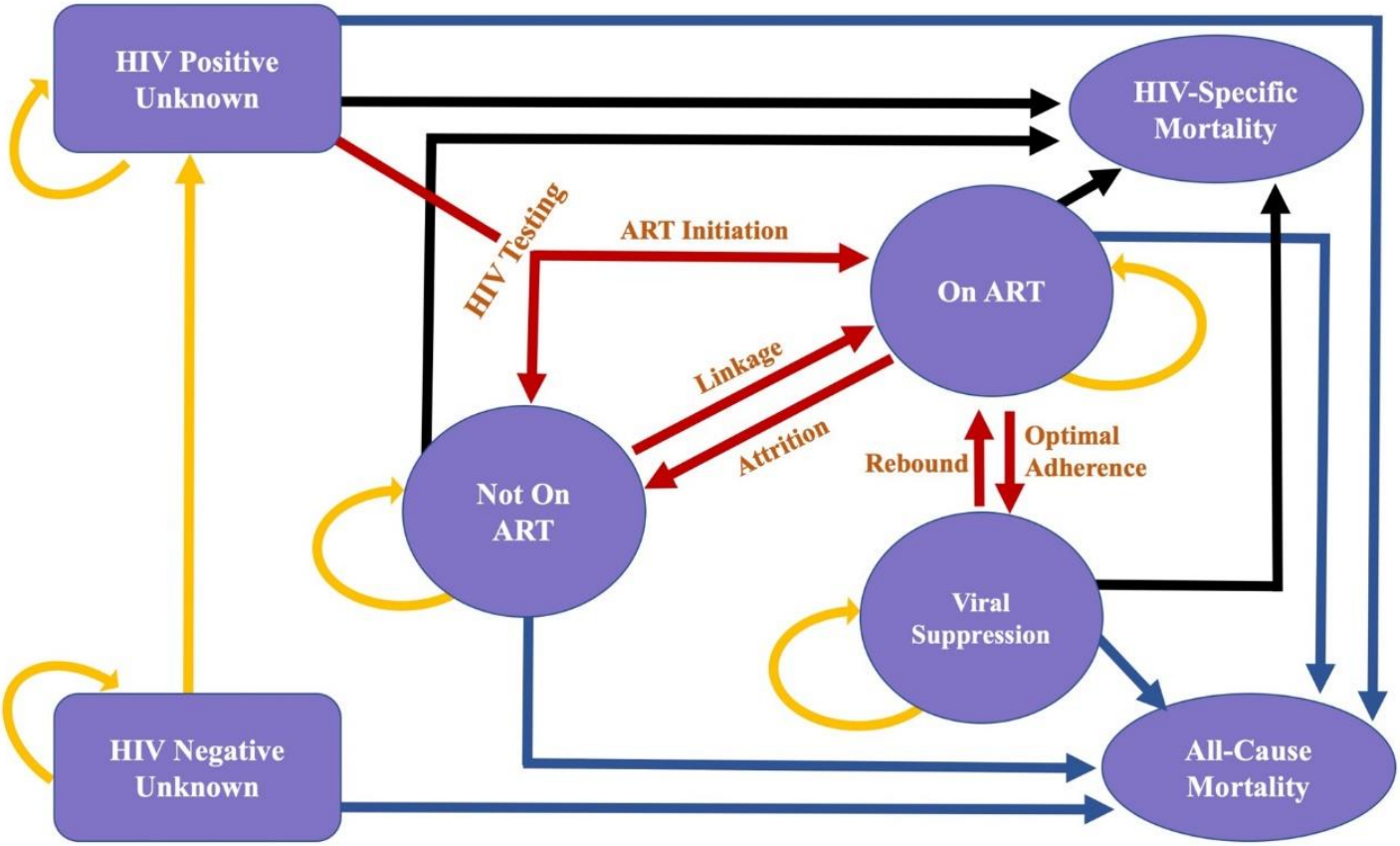
Internal Validation Approach	There are many readily available reports which have compiled observed-data on the real-world Zimbabwean HIV epidemic and the resulting response from the country's ART program over specific reporting periods: • ZIMPHIA 2020 [12] • DHS Zimbabwe [12] • Global AIDS Response Progress Report [33] • Zimstat Census 2012 [34] The following model outputs, over a 30 year period (1990-2020), will be compared to historically observed data to ensure a satisfactory fit: <u>Demographics</u>: • Male population, 0-14 • Male population, 15-49 • Female population, 0-14 • Female population, 15-49 • Death rate, entire population <u>Epidemiology Measures</u>: - HIV Prevalence in Incidence among males, 0-14 - HIV Prevalence in Incidence among males, 15-49 - HIV Prevalence in Incidence among females, 0-14 - HIV Prevalence in Incidence among females, 15-49 <u>HIV Treatment Cascade:</u> - Proportion of children (0-14) on ART - Proportion of adults (15-49) on ART - Proportion of children (0-14) virally suppressed - Proportion of adults (15-49) virally suppressed - HIV related death, entire population	Model calibration is a crucial step as a poor fitting model will generate incorrect and unreliable predictions. Model calibration is the process of specifying exact parameters values from a range of possible values to achieve a satisfactory fit, and can occur in one of three ways: 1. Manual calibration achieved through manipulation of parameter values [35]. 2. Probability distributions for parameters are specified, through which random parameter sets are generated (through a method such as latin hypercube sampling). Eventually incorrect sets are eliminated, leaving only relevant sets [35]. 3. Numerical fitting algorithm which determines ideal parameter values through minimization of absolute or squared error [35]. Once validated, the model may reliably predict the impact of the ILHIVT strategies.

External Validation Approach	Established 'face validity' as the model structure was proposed by incorporating the findings of a systematic review of modelling approaches in economic evaluations of HIV testing strategies. The model output (ICERS) will be compared to other similar published economic evaluations [38].	External validation of models is a process which ensures that a model is behaviorally sound and represents the system or relationship is purports to [39]. External validation is synonymous with generalizability and reproducibility and can be assessed by testing the model in a similar population residing in a different country [40].

6.4.2 Decision-Analytic Model

Microsimulation models simulate the individualized impact of interventions by tracking the progress of (individual simulated) entities through particular disease states as the accrue costs and health benefits over a specified time period, while allowing for individualized disease progression through stochastic variation [27, 41]. This modelling approach is able to differentially account for movement to future states, based on patient history [27]. The costs and effects accumulated by the simulated (large) population is then averaged to estimate the cost-effectiveness of the intervention under investigation [27]. The static nature of microsimulations, (i.e. representing a system at a specific point in time, instead of varying over time), render them unable to describe and account for interaction between individuals [41, 42]. This is a potential limitation of its use in modelling HIV testing strategies, as horizontal transmission risk is dependent on interaction with infectious individuals. However, horizontal transmission is not as large of a consideration among this population (children and pre-sexual debut adolescents), as most cases are perinatally acquired. Furthermore, this limitation is offset by the finding that predicted cost-effectiveness by a static model is replicated in dynamic models also [43].

The microsimulation will be modelled using TreeAge Pro 2021(TreeAge Software LLC, Williamstown, Massachusetts). The model structure contains 5 health states: HIV-negative, HIV-positive not on treatment, HIV-positive on treatment, HIV – associated comorbidities, viral suppression (**C6, Figure 2**). Individuals are simulated through the model based on age and sex, HIV status, ART treatment initiation, ART treatment retention, viral suppression, and death. HIV negative individuals are at risk of becoming infected, while HIV positive individuals are immediately linked to care and start treatment at Zimbabwe's ART coverage rate (per age and sex). Individuals can become virally suppressed, remain on treatment with sub-optimal adherence, or experience treatment attrition at 6, 12, 24 and 36 months. HIV/TB Co-Infection can result from being HIV positive and not on treatment, or sub-optimally adherence on treatment. All cause and HIV-specific mortality, are also possible end points over the 20 year time horizon.



C6, Figure 2. EE Proposal – Model Structure
Abbreviations:
HIV= Human-Immunodeficiency Virus
ART= Antiretroviral Treatment

6.4.3 Scenarios Modelled

The HIV epidemic in Zimbabwe will be simulated until 2020 using existing HIV prevalence and testing data [12]. From 2020, 4 possible scenarios will be projected and compared over a 20 year time horizon: a base-case (i.e. reference scenario according to current guideline-concurrent care) where ILHIVT is not introduced and testing occurs according to current standard of care; introduction of ILHIVT via clinic scenario; introduction of ILHIVT via home-based healthcare provider scenario; introduction of ILHIVT via home-based caregiver scenario. The base-case scenario will simulate existing HIV test rates, ART initiation immediately per routine WHO universal test and treat guidelines adherence in Zimbabwe. Each

scenario will have 5000 executed runs. Estimated total costs and DALYs, (stochastically generated), will average over 10,000 individuals and multiple iterations (5000 runs) for each of the 4 scenarios.

6.4.4 Costs and Outcomes

Details of unit cost per HIV test applicable to all four modelled scenarios can be found in a microcosting study of B-Gap conducted from the provider perspective [32]. Cost parameters needed to calculate each scenario will include HIV and viral load test costs, costs of pre-ART and ART care, costs of 1st line and 2nd line ART treatment regimens, and costs resulting from HIV-associated comorbidity where available.

One DALY is the equivalent of one year of life lost through premature death. Applicable non-age weighted HIV specific disability weights involved in calculating DALYs will include: HIV positive (0.051), HIV positive on treatment (0.053), HIV positive symptomatic (0.221) and HIV/TB co-infection (0.399). (See **Formula 1**).

Incremental cost-effectiveness ratios (ICER) will be calculated by comparing each ILHIVT modality to the base case and also by comparing each strategy to the next least costly option, presented as cost per DALY averted. (See **Formula 2**).

6.4.5 Model Parameter Synthesis

A targeted approach for synthesizing the necessary data inputs for parameterization of model will be employed. Firstly, B-Gap data will be synthesized for parameter inputs and converted to state-transition probabilities where applicable. Next, country wide reports generated from MoHCC, ZIMSTAT, ZIMPHIA, DHS, UNICEF, UNAIDS, WHO will be searched, followed by a search of studies included in a systematic review of modelling approaches in economic evaluations of HIV testing strategies. If the above three steps are unsuccessful at generating the necessary model parameters, a targeted literature review for the remaining parameters will be conducted in Medline. Cost data will be converted to 2020 US$, using the GDP for the United States [29]. Transition probabilities according to a 3-month cycle length will be calculated using a standard approach (see **Formula 3**) [44].

6.4.6 Model Validation

Assessment of internal model validation will be conducted through the Latin hypercube sampling method for model calibration [35]. Calibrated model outputs will be compared to Zimbabwe specific reports highlighting the country's HIV epidemic and treatment program. **C6, Table 1** provides details on data sources and outputs for comparison. Face validity was established by structural adhesion to the findings generated from a systematic review of modelling approaches in economic evaluations of HIV testing

strategies. External validation will be assessed by comparing model outputs to PoPART, a HIV related clinical trial conducted in Zambia and South Africa.

6.4.7 Analysis Plan

To facilitate comparability only one health outcome will be calculated. (See **Formula 1** below). Using the difference in discounted (5%) DALYs and costs between scenarios among all children and adolescents offered testing, ICERs of each ILHIVT strategy compared to the base case, and each strategy compared to the next least costly alternative, will be calculated (See **Formula 2** below). ICERs will be considered cost-effective if <50% GDP per Zimbabwe capita [24, 25].

Formula 1 – Disability Life Years Calculation[45]:

$$\begin{aligned} &Disability\ Adjusted\ Life\ Years\ Calculation \\ &\quad = [Years\ of\ life\ lost\ due\ to\ premature\ mortality\ (YLLs)] \\ &\quad + [years\ lived\ with\ disability\ (YLDs)] \end{aligned}$$

Where:

- YLLs = (Deaths at a specific age) X (standard life expectancy at that age)
- YLDs= (Prevalence) X (DW)
- Disability Weights: Assigned value from 0 (full health) and 1 (death) representing the severity of health loss associated with a particular disease, obtained from the Global Burden of Disease Study.

Formula 2 – Incremental Cost-Effectiveness Ratio Calculation

$$\frac{Cost_{ScenarioX} - Cost_{BaseCase}}{Effect_{ScenarioX} - Effect_{BaseCase}} = {Net\$}/{DALY\ Averted}$$

Formula 3 – Converting Probabilities to Model's Cycle Length[44]

$$p = 1 - (1 - p)^{1/n}$$
$$3\ month\ probability = 1 - (1 - 12\ month\ prob)^{1/4}$$

6.4.8 Sensitivity Analysis

As data for parameters are gathered, it is quite likely that assumptions around inputs will also need to be included in the analysis. A probabilistic sensitivity analysis will be conducted to characterize parameter uncertainty [27].

6.4.9 List of Assumptions Thus Far

1. As this is a static model: HIV incidence remains constant
2. Infants are non-differentially, vertically infected with HIV; HIV prevalence is the same between male and female infants.
3. HIV infection ages up in the 0-14 age range, which encompasses children and young adolescents; HIV prevalence is the same between male and female infants.
4. Older adolescence (15+), is assumed as the threshold for sexual debut; HIV prevalence is variable between males and females
5. Geo-specific urban (Bulawayo) and Rural (Matebeleland South) generated HIV testing costs for all 4 strategies will be representative of all urban and rural areas provinces in Zimbabwe

--- End of Proposal ---

6.5 C6 KEY TAKEAWAYS

There are many possible iterations in which the findings of this thesis could have been integrated into an actionable format. One of the most obvious points of deviation would have been the modelling approach selected for the EE proposal presented in this chapter. The simplest of applicable options (**Results P1**), a microsimulation was chosen due to it being the least resource and computationally intensive options. Age stratification within the model was informed by **Results P1** and **P2**, while costing inputs would carry over from **Results P3**.

6.6 IMPLICATIONS FOR THESIS

The overall aim of this thesis is to contribute to the methods of EEs of HIV testing in children and adolescents in a Zimbabwean context. This chapter contributed to achieving this aim by demonstrating the applicability of the results of this thesis (**Results P1 – P3**). This chapter was an amalgamation of thesis **Objectives 1, 2 and 3** (**C6, Figure 1**), and served as proof of concept and illustration of idealized consideration for EE model criteria reporting using the appraisal tool generated in **Results P1** (found in the Appendix). The output of this chapter achieves **Objective 4** of this thesis: to integrate thesis findings into an actionable format. This was one of possible ways through which thesis findings could have been integrated. The practical application of this chapter lies in executing the outlined proposal to determine the cost-effectiveness of ILHIVT delivery to children and adolescents in Zimbabwe.

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CHAPTER 7 – THESIS DISCUSSION

7.1 INTRODUCTION

This thesis set out to generate and evaluate methods around economic evaluations of HIV testing in children and adolescents within a Zimbabwean. This chapter provides a critical assessment of the major thesis findings, details their contribution to, and scope within, the larger body of evidence and literature, while remarking on both their strengths and limitations. This chapter also discusses future considerations which expands on how the research presented in this thesis might be taken further, along with translational and policy implications, aiming to answer the overarching policy question (**Chapter 1** – **C1, Figure 1**): can provision of index-linked HIV testing to children/adolescents in Zimbabwe, increase the efficiency of the HIV testing services offered in Zimbabwe.

7.2. MAJOR FINDINGS

This section summarizes and presents, according to each of the objectives outlined in Chapter 1 (**C1, Figure 2**), the key findings of this thesis (**C7, Table 1**).

The first objective of this thesis (**Objective 1**) addressed the knowledge gap pertaining to methodology through which EEs of HIV testing strategies in SSA are conducted. A systematic review was conducted to identify the decision analytic modelling approaches these EEs utilized. The approaches ranged from individual agent-based models (33%), microsimulations (29%), dynamic transmission models (24%), and decision trees (14%). The review highlighted a lack of heterogeneity in setting (almost exclusively ESA based) and population (adult population with varying age cut-offs). The second objective (**Objective 2**) of this thesis sought a method to investigate how children and adolescents were incorporated into mathematical models of HIV pertinent to the SSA context, to address the gap of underrepresentation of children and adolescents in mathematical models of HIV testing strategies. Through a narrative review of highly visible, peer reviewed dynamic mathematical models of HIV, 4 'well-described', 'frequently used and cited' models of HIV, deemed influential in the landscape, were reviewed in order to assess their structural features, along with child and adolescent related HIV transmission dynamic representation and inclusion. The third objective (**Objective 3**) of this thesis addressed a gap in literature pertaining to the fact that while it is a strategy recommended by the WHO, ILHIVT service delivery costs remained unknown. Through an incremental costing analysis, the first ILHIVT unit costs related to any setting were published: ILHIVT accessed 6-times more children/adolescents than standard of care, however costs varied highly accordingly to modality and setting and were influenced by uptake. Using the high cost per diagnosis as a proxy for cost-effectiveness, this version of ILHIVT service delivery was unlikely to be a cost-effective strategy for identifying HIV positive children and adolescents. Lastly integrating the output from these three objectives (**Results P1 – P3**) into an actionable format (**Objective 4**), an EE proposal for ILHIVT of children and adolescents in Zimbabwe was generated to illustrate transparency around 'good modelling practice' via 13 modelling criteria.

C7, Table 1. Key Findings of Thesis According to Thesis Objectives

Objective	Methodology	Major Findings/Contributions
Objective 1: Chapter 3 (Results P1)		
Investigate modelling method through which EEs of HIV testing strategies in SSA are conducted	Systematic Review	EEs of HIV testing strategies conducted in SSA: • Were almost exclusively conducted in ESA, a majority of which assessed community based-testing approaches, predominantly from a provider perspective • Did not evaluate any testing interventions focusing on children and/or adolescents • Did not provide a rationale for choice of modelling approach employed • Were typically modelled using dynamic, stochastic and individual properties • Incorporated children and adolescents into model structure less than 25% of the time • Reported poorly across model validation criteria
Objective 2: Chapter 4 (Results P2)		
Determine how child and adolescent HIV transmission dynamics are represented in popular, peer-reviewed dynamic mathematical models of HIV in the SSA context	Narrative Review	Amongst 4 well-described, frequently used and cited models of HIV: • Event split by methodology: 50% individual-based stochastic models; 50% compartmental models • Adolescent HIV dynamics were incorporated in all models, while half of models excluded child HIV related dynamics • Individual-based models allowed for granular insight into adolescent behavior • Compartmental models are better suited for policy planning and resource optimization at the population level
Objective 3: Chapter 5 (Results P3)		
Measure the cost of delivering ILHIVT to children and adolescents in Zimbabwe	Incremental Cost Analysis	• 6x More children/adolescents tested via ILHIVT compared to SoC • Uptake of ILHIVT modality strongly influenced testing unit costs • Both the highest and lowest ILHIVT unit costs were from a rural setting

		○ Facility-based modality: 2019 US$5.36 ○ Caregiver-assisted modality: 2019 US$62.40 • Largest drivers of unit costs: personnel followed by transaction costs • Low-yield of HIV-positive cases via ILHIVT translated to high cost of diagnosis
Objective 4: Chapter 6		
Integrate thesis results findings into an actionable format	Proposal for an EE of ILHIVT	• EE Approach selected based on thesis findings: ○ CUA conducted via microsimulation from the provider perspective • Illustrating 'good modelling practice' by providing a rationale for decisions made around: ○ Model selection ○ Parameter inclusion ○ Perspective and discount rate selected ○ Time horizon and cycle length for analysis ○ Outcomes assessed ○ Sensitivity Analysis ○ Internal and External model validation approach;

7.3. CONTRIBUTIONS TO KNOWLEDGE

The input this thesis makes to the field of child/adolescent HIV research can be denoted according to empirical and methodological contributions.

7.3.1 Empirical Contributions to Knowledge

One of the findings of the systematic literature review (**Results P1**) was that no EE of HIV testing strategies targeting child/adolescent uptake in SSA has ever been conducted. This is troubling given that multi-national specialized agencies such as UNAIDS, UNICEF and the WHO cite the handling of children and adolescents as "one of the most glaring disparities in the AIDS response" [1]. Engaging with HIV testing services is the crucial first step in accessing life-saving ART treatment. Yet in 2021, only 52% of children (0-14 years), and 55% of adolescents (15-19 years) living with HIV in SSA were on treatment, translating to 800,000 children and 400,000 adolescents not receiving treatment despite new and convenient advances in testing such as point-of-care EID and widely available HIV self-tests [1]. While gaps in testing coverage are not the only issue preventing treatment initiation (barriers to linkage to care, along with ART coverage and access contribute also), UNICEF attributes blame largely to a lack of investment in testing [2]. With the increased pressure LMICs face in financing their own HIV responses due to decreased bilateral and international funding [3], blanket testing approaches with the aim of finding and diagnosing the remaining 1.2 million children and adolescents with HIV not on treatment, will inefficiently and indiscriminately consume scarce resources. Targeted and innovative HIV testing approaches need to be considered along with their financial and opportunity costs, which can only be done through cost and cost-effectiveness data. Alongside this empirical finding generated from this thesis, the next step in addressing this gap is that future research proposals attempting to address HTS uptake and diagnosis by children and adolescents should entail a costing component as one of the project deliverables. The opportunity cost of investing into and attempting to scale-up epidemiological and theoretically sound testing strategies for this population, without EE data to support these decisions, is detrimental particularly now in the era of the COVID-19 where unplanned resources were diverted to respond to the pandemic, coupled with a global recession looming on the horizon for 2023 [4].

This thesis contributes knowledge towards informing policy/HTAs of HIV in Zimbabwe by way of a partial EE and was the first costing study of an ILHIVT strategy (in any population) in SSA. And while not a systematic review caliber search, a results chapter of this thesis (**Results P3**) is seemingly the first costing study of an HIV testing strategy targeting children/adolescents in Zimbabwe and potentially SSA. The study contributed SoC HIV testing costs of children/adolescents in Zimbabwe and also incremental unit costs of 3 ILHIVT modalities, highlighting the following:

- Lowest Costing Approach in Rural Setting: Facility Based
- Lowest Costing Approach in Urban Setting: Community Based

- Highest Costing Approach in Rural Setting: Assisted
- Highest Costing Approach in Urban Setting: Clinic Dependent (either Assisted or Facility Based)

The largest takeaway from the study was that factors influencing unit costs were heterogeneity in user preference and uptake and that the low yield of HIV positive children and adolescents were likely to translate to this version of ILHIVT not being a cost-effective strategy. Potential methods to remedy this situation is to attempt the same intervention in a different setting, perhaps a more rural setting where testing saturation due to existing large-scale testing initiatives, would not be a problem. This in turn might potentially increase the yield of ILHIVT, and offset the large diagnosis costs. Additionally, B-Gap was implemented in settings which were easily accessible for research staff; the practicality of this decision may have prevented this ILHIVT strategy from reaching those who would truly benefit from it. There is also a possibility that ILHIVT alone is not sufficient to identify these remaining undiagnosed children/adolescents.

7.3.2 Methodological Contributions to Knowledge

The methodological contributions this thesis made to general EE literature can be summarized as follows:

One of the findings of the systematic literature review (**Results P1**) was that EEs of HIV testing strategies targeting child/adolescent uptake in SSA, methodologically, were evenly split between CEAs and CUAs. However, future considerations in terms of standardizing EE modeling methods, should involve a push to move away from CEAs and towards CUAs so that a population summary measure, (DALY/QALY), can be included in the analysis. In the context of LMICs and countries like Zimbabwe that do not have a formal HTA body in place, CEAs provide insufficient evidence to validate funding and coverage decisions [5]. Advocating for all future EEs conducted around current and emerging health technologies in Zimbabwe to contain a population summary measure, is a step towards establishing HTA comparison guidelines in the country. Given that CBAs are rarely used in HTAs, advocating for all future EEs to be carried out through CUAs will facilitate comparison of interventions both within, and across disease domains and the healthcare spectrum. A first step would be to produce a limited number of cost-effectiveness measures (i.e. cost per DALY or QALY only), to reduce variability within outcomes presented by various modelling approaches, thereby facilitating comparability. A more ambitious next step would entail universal accessibility of datasets (ideally in a repository) to aid in reproducibility of parameter inputs and facilitate a higher research standard.

Viral load is widely considered the most important risk factor in HIV transmission, and a good proxy indicator for ART monitoring, highly sensitive to treatment adherence and failure [6]. However, a review of HIV mathematical models found that only 6% (i.e. 17 of 279) of models incorporated a viral load parameter [6]. This may be in part due to lack of data access, especially in low-income settings where monitoring CD4 count rather than viral load was historically the norm [7]. Only seven of the 21 studies (33%) incorporated a viral load parameter, and three of them were from a single working group using the same model [8-10]. Moving forward, inclusion of a viral load parameter may help homogenize structural/natural history considerations, consequently advancing HIV model standardization.

An ingredients based approach to costing shed light on cost allocation factors and namely the role of transaction costs in the delivery of ILHIVT and as an extrapolation, health interventions in general. Formally defined as the cost of governance of contractual agreements, transaction costs are applicable to both routine service and service delivery as part of a research intervention, especially in settings where existing health service capacity is overwhelmed [11, 12]. Partnering with local NGOs to deliver health services is an approach routinely employed in LMICs to increase coverage and quality of care [12, 13]. Researchers in LMICs routinely enter into agreements with local organizations, leveraging their established community ties, to help execute portions of the research mandate [13]. The role of transaction costs involved in conducting HIV research in SSA are rarely discussed in published costing studies. Notable examples of high-visibility HIV research initiatives conducted in Zimbabwe, where portions of the study interventions were contracted out to local organizations, include the SAFER and STAR projects [14, 15]. When the cost of the services provided through these studies was calculated, both costing analyses included line items for initial research start-up costs and training, along with recurrent training costs, but did not include costing line items for the portions of research executed through local partnerships. The inclusion of transaction costs in the costing analysis of **Results P3** is a novel methodological contribution towards the general field of EE literature within the SSA context, as it is a pervasive, but usually over-looked feature of conducting research in this setting. In the B-Gap study, transaction costs were calculated as all costs associated with partnering with the local organizations, OPHID, in the urban settings and MMPZ in rural settings, for all activities related to conducting the ILHIVT home-visits. Specifically, transactions costs comprised: 1.) the memorandum of agreement contracts held with both organizations for meeting space, study document storage space, (i.e. renting out filing cabinets to store paper copies of documents such as consent and case report forms) and building wifi for B-Gap research assistants and contracted field workers alike; 2.) the cost of administering a home-visit, which encompassed field worker compensation per visit, travel costs, sim card and photocopying allowance. Transaction costs provide a snapshot into understanding the potential increase of cost to Zimbabwe's existing health system infrastructure, should the MoHCC choose to incorporate ILHIVT home visits into HIV service

delivery. Transaction costs were the second largest driver of unit costs in B-Gap. If ILHIVT home visits are adapted into routine service delivery, instead of hiring more personnel, (incidentally, the primary driver of unit costs in B-Gap), to conduct the home visits, the cost of contracting out services to local NGOs is known and understood, and could be a potentially less costly alternate method to increase and expand capacity of HTS in the country.

The inclusion of a detailed *Time Tracking Diary* is a novel and valuable methodological contribution to the field of costing studies for the transparency and accuracy it provides in estimating health intervention delivery (**Results P3)**. Other than WHO Choice (i.e. costing guidelines), no costing study reviewed for this thesis included detailed explanations on how human resources were considered and calculated. Time-tracking diaries are essential tools for costing HIV interventions in sub-Saharan Africa as they improve the accuracy and transparency of cost estimates by capturing human resource use, indirect costs, and contextual variability. These diaries also support cost-effectiveness analysis by providing precise data on time allocation, helping decision-makers optimize resource allocation and improve program efficiency. Given the region's limited healthcare resources and diverse program settings, time-tracking diaries offer a practical solution for insight into ensuring evidence-based budgeting and planning.

7.4 THESIS STRENGTHS AND LIMITATIONS

This section considers the strengths and limitations of the overall thesis and are conveyed according to each objective.

7.4.1 Thesis Strengths

The overarching strength of this thesis is the intersection of economic and infection disease modelling methods, which allowed for a broad perspective and approach in its contribution to HIV testing and children/adolescent literature. The methodological approach for evidence generation for **Objective 1**, a systematic review, is considered the '*gold standard*' when summarizing a substantial body of evidence as it not only identifies, appraises and synthesizes all empirical evidence meeting specified inclusion criteria, but is also a comprehensive search of a wide range of sources which adheres to established and clear guidelines (PRISMA) generated from specialized organizational research bodies [16]. The search strategy employed was also verified by an established process (PRESS) by experts (LSHTM librarians), while the model quality assessment tools was constructed using researched, established and validated reporting (CHEERS) and good practice guidelines (ISPOR), thereby lending confidence to the findings of **Results P1**. Additionally, the tools generated, along with findings and recommendations of **Results P1** are highly transferable and generalizable when conducting EEs of other diseases and contexts (i.e. not just limited to HIV and/or SSA.)

A high standard was achieved for the narrative review, according to a SANSRA assessment, which is a strength of **Objective 2 (Results P2**). The narrative review does not attempt to highlight all relevant or the most appropriate HIV related dynamic models, but instead, looks to understand the most frequently used models because of the impact that they have on current and future policy considerations. Understanding children and adolescent representation in these models directly influences how priorities are set and resources are distributed.

The costing analysis, **Objective 3** (**Results P3**), was conducted using the GHCC reference case, developed to standardize the estimation and improve the quality of HIV (and TB) intervention cost data [17]. As with **Results P1**, the methodological approach utilized in **Results P3** was modelled after an established and vetted guideline, allowing for confidence in the estimates generated. Additionally, as data collection for **Results P3** was conducted at the clinic sites (and the accompanying ministry departments) where the ILHIVT intervention was delivered, the data collected was relevant, complete and reliable; none of the estimates and accompanying costs were borrowed from the literature, (and/or different settings), approximated or imputed. Lastly, the ingredients based micro-costing approach, which shed light on cost allocation factors, and the role of transaction costs, allowed for full transparency and confidence in the results of the costing analysis.

While theoretical in nature, the output for **Objective 4**, a proposal for an EE of ILHIVT in children and adolescents, was constructed from the findings of **Results P1 – P3**. The modelling approach was chosen according to recommended properties (individual and stochastic, **Results P1**) and the accompanying level of detail and transparency illustrated 'best practices' (**Results P1**). The simpler modelling approach (microsimulation), also accounted for some of the data needs and difficulties a more complex structure (**Results P2**) would require, while allowing for the incorporating of first hand cost estimates (**Results P3**).

7.4.2 Thesis Limitations

Thesis limitations were associated with the methodological approaches of each objective. Due to practical considerations, the inclusion criteria for the systematic review conducted for **Objective 1** was restricted to papers in English, (due to comprehension) and papers with full text (needed for abstraction). As a result, search results could have been skewed towards EEs conducted in ESA, thereby omitting WCA based EEs of HIV testing strategies, due to omission of French language papers. Additionally, relevant EEs conducted and presented at for example, conferences (but not published), could have been missed. Lastly, as the grey literature was not searched, the search strategy for the systematic review was not exhaustive, again, allowing for the possibility of missing relevant evaluations.

The definitions, cut-offs and inclusion criteria, upon which the narrative review conducted for **Objective 2**, though systematically determined, were arbitrary in essence. As a result, there may be other models which are 'more accurate representations' of child and adolescent HIV dynamics that were not reviewed because of these arbitrary cut-offs. However, they are unlikely to influence policy, if they are not 'highly visible' or 'frequently used' such as the 4 models included in the narrative review. As a domino effect, these 'better models' would then not be used in policy considerations, when attempting to set the targets and agenda for the child and adolescent sub-populations.

An incremental costing analysis (conducted to answer **Objective 3**) may underestimate the cost of delivering a new health intervention, as the cost of the infrastructure for its delivery is assumed to be completely absorbed within the existing health infrastructure. The reality is that this assumption does not account for overhead costs required to branch, add or create a new space within existing operations. Additionally, the costing study itself (**Results P3**) was limited by the small sample size (n=3 clinics). Ideally, costing all 9 clinics in the B-Gap study would have provided a richer source of data for costs, resource consumption, and strategy uptake, allowing for greater confidence and comparability between rural (n=3) and urban (n=6) settings. However, clinics in the costing study were sampled in the same 2:1, urban to rural clinic, ratio as the parent B-Gap study.

A proposal for the detailed framework of a static microsimulation was presented as a way to answer **Objective 4**. HIV is an infectious disease however, best represented through a dynamic model, capable of capturing onward transmission. Therefore if the proposal was actually initialized to conduct an EE of ILHIVT in children and adolescents in Zimbabwe, it is quite likely that the magnitude of the intervention effect would be underestimated as it does not capture the benefits of preventing onward transmission. However, where a static model estimates cost-effectiveness, a dynamic model most certainly will. Additionally, as the framework for the microsimulation is conceptual, the resulting model has not been initialized, calibrated and validated.

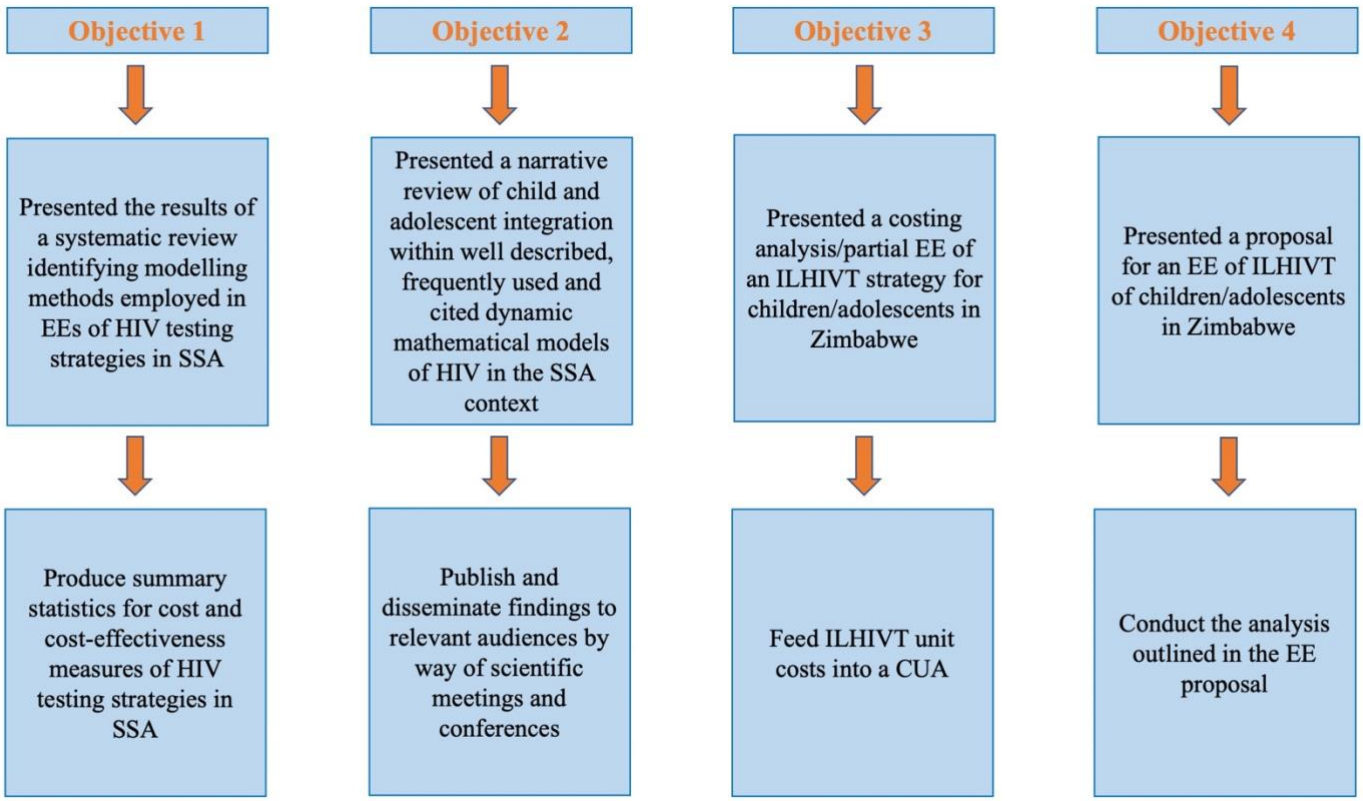
7.5 FUTURE CONSIDERATIONS

Each research objective and its corresponding output helped achieve the overall aim of this thesis: to generate and evaluate methods arounds EEs of HIV testing in children and adolescents within a Zimbabwean context. However, the findings of this thesis can be expanded to contribute further to the economic evaluation literature surrounding children/adolescents and HIV testing strategies (**C7, Figure 1**).

Objective 1 resulted in the synthesis of literature surrounding EEs of HIV testing strategies. For the purpose of this thesis, their modelling methodology was of interest. While outside the scope of this thesis, there is use for researchers and policy makers alike to know the overall unit costs and cost-effectiveness of the HIV testing strategies included in the systematic review, as it may help inform and improve efficiency with regards to how future iterations of testing interventions are structured and strategies delivered. Conducting a meta-analysis of the papers included would not be possible as there is vast heterogeneity in the types of testing approaches included in the systematic review, and therefore a statistical analysis combining the outcomes would be meaningless. However one solution might be to disaggregate summary measures according to testing strategy and present them. Additionally, assessing the quality of the EEs included may add further insight and recommendations for 'best practices'.

Objective 2 resulted in a narrative review of child and adolescent integration within well described, frequently used and cited dynamic mathematical models of HIV in the SSA context. Next steps would entail publishing findings, and disseminating results to relevant audiences via meetings, conferences and symposiums. It is important to collaborate and eliminate replication of efforts when conducting research in SSA and Zimbabwe, where resources are over-taxed and available pools of grant funding are reprioritized and diminishing. When sophisticated mathematical models, revised and fine-tuned over decades such as EMOD and Goals exist, it is beneficial for researchers to work within an existing, expert framework, instead of investing resources to reinvent the wheel again.

Objective 3, provided estimates of unit costs for an ILHIVT strategy targeting children and adolescents in Zimbabwe, while **Objective 4** presented a proposal for an EE of the ILHIVT; next steps would be to conduct the CUA outlined in the proposal, feeding the estimated unit costs into the model. The high-cost-per diagnosis accompanying the ILHIVT strategy was a proxy indicator for low cost-effectiveness, however actually conducting the evaluation might serve three purposes: 1.) contribute a full EE of ILHIVT to HTAs of HIV testing strategies in Zimbabwe; 2.) to conduct sensitivity and scenario analyses highlighting the threshold at which this strategy becomes feasible and cost-effective; 3.) to serve as a comparison for future EEs of ILHIVT in similar settings.



C7, Figure 1. Future Research Considerations
Potential ways in which the research conducted in this thesis can be furthered.

7.6 POLICY IMPLICATIONS WITHIN THE ZIMBABWEAN CONTEXT

UNAIDS has stated that a priority for the next five years should be expanding ILHIVT to families and households, in order to bridge testing gaps and diagnose HIV positive children and adolescents who fell through PMTCT programs, and as a result, were not identified during post-natal care visits [18]. The results of B-Gap, an ILHIVT strategy targeting children and adolescents however, were mixed. While ILHIVT facilitated access to HIV testing for far more children/adolescents than SoC facility-based testing, it yielded far fewer diagnoses, resulting in high cost-per-diagnosis unit costs [19, 20]. Using cost-per-diagnosis as a proxy for cost-effectiveness, ILHIVT in its current iteration is unlikely to be cost-effective [8]. This research result, while not enough to provide a definitive answer to the policy question attributed to this thesis, provides a minute piece of the necessary evidence snapshot and an impression that this version of ILHIVT service delivery for children and adolescents is unlikely to increase the efficiency of HTS in Zimbabwe.

Additional HIV policy implications extrapolated through the findings of this thesis is that messaging surrounding ILHIVT and especially one of the delivery modalities, HIVST, is insufficient in

Zimbabwe. While ILHIVT did increase testing uptake among children and adolescents (compared to SoC) in B-Gap, 40% of eligible children were not tested [20]. Additionally, the low uptake of ILHIVT via HIVST resulted in high unit costs for this particular modality [19], despite the easing of fear, stigma and access related barriers, while allowing for both privacy when testing and more control over the testing process [21, 22] . The MoHCC should consider holistic, seemingly benign campaigns to improve the messaging around the importance of both family testing of index cases, as well as the testing of children and adolescents, along with HIVST. The involvement of children in messaging campaigns for other diseases have resulted in success at addressing problems. (One such example; the involvement of children in Community-Led-Total Sanitation and Hygiene (CLTS) programs, can potentially be transferred to the way HIV messaging around ILHIVT and the importance of testing children and adolescents is conveyed. Open defecation, considered shameful and taboo when addressed by adults, was reduced through advice and actions conveyed by children [23, 24]. Adults were not as offended that their practice of open defecation resulted in poor hygiene, when received by children, as opposed to when the message was conveyed by a peer [23, 24]. Additionally, the whistle blowing initiatives (groups of children walking around drawing attention to open defecators by whistling), was comical enough to promote behavior change [23, 24].) While AIDS education is compulsory in primary and secondary schools in Zimbabwe, the MoHCC in partnership with the Ministry of Primary and Secondary Education (MoPSE) may need to consider revamping and updating its curriculum as HIV strategies and recommendations evolve [25]. For example, school curriculums could be utilized to translate messaging around HIVST and ILHIVT of children and adolescents, to parents/caretakers. It could be something as simple (and lower-resource consuming) as circulating a one-page handout about HIVST and ILHIVT, for a student to then take home to their families. To something far more involved, such as enacting structural change into the sexual health modules of the primary and secondary school curriculum, to including conversations around HIVST and ILHIVT. One such example could be a required lesson in each yearly school cycle, where teachers are instructed to produce prompts for their class, and have students perform skits demonstrating a conversation between a child and their parent(s), around the ease of HIVST and the need for the entire household to be tested for HIV. While requiring significantly more resource input then simply circulating handouts, messaging delivered in an interactive manner such as ‘drama class’, requires pupil ‘buy-in’, increasing the chances that the message is not only memorable, but leaves the child excited to share learnings with parents/caregivers at home.

According to the findings of a recent study from 5 high HIV prevalence Southern African countries including Zimbabwe, 30% of children with untreated perinatal HIV infection survived into adolescence, while 40% of adolescents living with HIV were undiagnosed [26]. Among adolescents living with HIV aware of their status, most had been diagnosed after age 10 [26]. These findings are alarming as they highlight the continued inadequate case-finding and gaps in HIV testing services

along a growth continuum: missed opportunities for early testing in antenatal care, transitioning to limited availability and offering of testing in pediatric care, culminating in a lack of adolescent-friendly HIV testing services [26]. Untreated perinatal HIV infection has long-term, detrimental consequences, resulting in a higher likelihood of comorbid conditions and increased mortality rate [26-29]. While Zimbabwe has made substantial progress towards addressing the public health burden of HIV, evidenced by the country's progress in meeting the 2030 markers, most of its successes have been geared towards the adult population, (understandably so, as the onus of the country's epidemic resides within this population). However, as more than 30% of infected children and young adolescents (0-14 years) are unaware of their status, the gaps in HIV testing services specific to this sub-population across the country, are evident [30]. HIV testing services in Zimbabwe must be adapted and strengthened in order to identify this difficult-to-reach subpopulation. This thesis highlighted the paucity of data around the inclusion of children and adolescents in the overall conversation of effective HIV testing strategies in SSA (i.e. lack of representation in EEs of HIV testing strategies); an issue generalizable to Zimbabwe as well. We must identify how available resources can be efficiently allocated to improve their impact on the prevention and treatment of disease in this vulnerable sub-population.

Per the MoHCC's 2021-2025 National Health Strategy, Zimbabwe must "*provide, administer, coordinate, promote and advocate for the provision of equitable, appropriate, accessible, affordable, and acceptable quality health services and care to Zimbabweans while maximizing the use of available resources"* [31]. While this statement, in theory, lends credence and bolsters the need for institutionalized HTA in Zimbabwe, the reality is quite different. HTA is increasingly used to inform decisions in the UHC context. Zimbabwe has adapted the universal health coverage political declaration in 2019 and aims to achieve UHC by 2023 [32]. UHC requires critical information on the range of health services to be provided, the population to be covered and financial protection: Zimbabwe must define its own UHC pathway by generating data based on the health needs of the population and available resources [32].

As one of the goals of the Zimbabwe MoHCC policy for 2021-2025 is to integrate more evidence from economic evaluations into their decision making process. This thesis provides evidence to inform this goal by the following:

- Looking at the most appropriate methodological ways to conduct EEs of HIV testing strategies, strengthening a call to future researchers in the space;
- Identifying that children and adolescents are poorly represented in EEs of HIV testing strategies;

- Highlighting that amongst the most known and used dynamic mathematical models of HIV implicated in decision making in SSA, children and adolescents transmission dynamics must be refined and improved;
- Evaluating the cost of an HIV testing strategy not routinely used in HTS;
- Putting forth an EE proposal for the aforementioned HIV testing strategy

These contributions push forward the EE agenda for Zimbabwe's MoHCC enabling more informed decision making processes from a methodological perspective.

7.7 THESIS CONCLUSION

Children and adolescents are falling well behind global HIV markers of progress. Despite the value proposition economic evaluations contribute towards policy considerations and implementation, and the known and demonstrated impact HIV testing interventions have on halting HIV transmission, children and adolescents are underrepresented in economic evaluations of HIV testing interventions. Though well described, frequently used and cited dynamic mathematical models of HIV transmission have a robust representation and integration of the adolescent sub-population within their structural frameworks, improvements to child HIV modelling considerations in the SSA context are needed, especially considering that the impact of HIV testing interventions targeting children and adolescents are infrequently the focus of published modelling studies, (compared to the adult sub-population). As HIV case identification becomes more difficult and costly in the child and adolescent sub-population, especially passively via current standard of care due to poor and under-utilized care seeking behaviours, the need for effective HIV testing interventions targeting children and adolescents becomes paramount. The regional or national level policy implementation of effective HIV testing interventions are dependent on the demonstrated value of these interventions, with a substantial piece of contributory evidence being the cost-effectiveness of these interventions. Yet, the body of available evidence is lacking substantial inclusion of children and adolescents. This thesis aimed to contribute to the literature around economic evaluation methods for HIV testing in children and adolescents by addressing empirical and methodological knowledge gaps. The findings of this PhD contribute to the testing and child/adolescent HIV literature by addressing: 1.) investigating child and adolescent integration within EEs (of HIV testing strategies) and well-described, frequently used and cited mathematical modelling frameworks of HIV; 2.) the lack of EE literature focused on HIV testing strategies targeting children and adolescents through a partial EE of ILHIVT. The main methodological contribution of this thesis is a model reporting appraisal tool to facilitate understanding and transparency in EE reporting. This model reporting tool is transferable beyond HIV and can be generalized to other conditions. The findings of this thesis can help shape and guide the delivery of future ILHIVT intervention strategies, while also providing a foundation for future ILHIVT related policy implementation in Zimbabwe.

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