Demographic Determinants of Paediatric HIV In Generalised HIV Epidemics

Camilla Vere Marston

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Department of Population Health

Faculty of Epidemiology and Population Health

LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

Based on research part funded by: UNAIDS and the Wellcome Trust

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

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Abstract for whole thesis

Background

Estimates of Paediatric HIV are essential for planning national HIV programs. Although there is a large amount of empirical data on the prevalence of adult HIV from antenatal clinics and national surveys there is very little HIV data for children, necessitating estimates based on knowledge of: HIV infection in pregnant women; transmission rates among pregnant and breastfeeding women according to their treatment status; and survival of infants infected in different ways. It is essential that these inputs into estimating paediatric HIV are as accurate as possible as there is little empirical data to calibrate the final estimates of prevalence of paediatric HIV. Currently there are gaps in the understanding of some of the inputs needed to estimate paediatric HIV and a potential to improve estimates as new data become available, particularly as more widespread availability of antiretroviral treatment changes the circumstances in which children become infected.

Aims and Objectives

The aim of the research is to improve and fill gaps in knowledge about the HIV epidemic and thereby improve estimates of paediatric HIV. Objectives include improving estimates of survival of infected children, exploring the acquisition of HIV by women in relation to incidence during pregnancy, furthering understanding of the impact of HIV on fertility and understanding the biases inherent in different data sources.

Implications

The new empirical evidence and rigorous methods developed to evaluate the inputs needed to estimate the number of children born to HIV positive women and the prevalence of paediatric HIV will produce more reliable HIV epidemic projections, and will improve information available to policy makers and programme planners.

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List of acronyms

ANC	Antenatal Clinic
AIDS	Acquired Immune Deficiency Syndrome
AIM	AIDS impact module
AIS	AIDS Indicator Survey
AHRI	African Health Research Institute
ALPHA	Analysing Longitudinal Population-based HIV/AIDS data on Africa
CTC	Care and Treatment Clinic
DHS	Demographic and Health Survey
DSS	Demographic Surveillance System
FRR	Fertility Rate Ratio
HIV	Human Immunodeficiency Virus
HRR	Hazard Rate Ratio
IeDEA	International Epidemiology Databases to Evaluate AIDS
LSHTM	London School of Hygiene and Tropical Medicine
MTCT	Mother-to-Child Transmission
NIMR	National Institute for Medical Research
PCR	Polymerase chain reaction
PMTCT	Prevention of Mother-to-Child Transmission
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
UNAIDS	Joint United Nations Programme on HIV/AIDS
VCT	Voluntary Counselling and testing
WHO	World Health Organisation

Acknowledgements

This PhD is dedicated to Basia Zaba (1949-2018) who has not only been my PhD supervisor but also my line manager for the past 17 years. I'd like to thank her for her energy, enthusiasm and sense of humour. I am hugely grateful to her for her invaluable guidance and advice over the course of the thesis. I will miss her greatly and count myself extremely lucky to have been mentored by her for so long.

There are many other people who I need to acknowledge for their help and support over the course of this PhD. Over the years it has been a pleasure to work with all the sites involved in the ALPHA network. Without their hard work and enthusiasm the data for much of this PhD would not have been available. A particular thanks to Mia Crampin, Tom Lutalo, Simon Gregson, Mark Urassa, Marie Louise Newell, Jessica Nakiyingi-Miiro and Nuala McGrath.

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A special thanks to Emma Slaymaker, my office mate since time began for all her help and support over the years which has helped me no end. Thank you to all those in room 148 Clara Calvert, Rachel Scott and Melissa Palmer for letting me tap into their recent knowledge about PhD structure and procedure. Additional thanks goes to Clara Calvert for reading through final drafts of parts of the thesis. There are so many colleagues at the school that I have at some point received help and advice from over the years, that I have been very grateful for, but I would like to acknowledge particularly Sian Floyd, Jim Todd, Carine Ronsmans and Judith Glynn.

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A final thanks to my partner Chris for all his support. He now probably knows more about the demographic determinants of paediatric HIV than he wanted.

1 Introduction to thesis

1.1 Background

Estimating the number of children born to HIV positive mothers and living with HIV is essential for providing reliable estimates of the magnitude and trend of the paediatric epidemic. These estimates are needed for national programme planning, policy formulation and resource allocation [1, 2]. Most populations with a generalised HIV epidemic in sub Saharan Africa have very limited population-based data to estimate paediatric HIV. HIV prevalence is usually measured using data from antenatal clinic surveillance and, where available, national HIV surveys such as Demographic Health Surveys [3]. Best estimates of age specific fertility within a country come from the United Nations, Department of Economic and Social Affairs, Population Division, who fit trend lines to data sources that are available for each country, such as census data and demographic and health surveys, and, in more developed countries, vital registration data. From these starting points, in order to estimate the number of children born to HIV positive women, we also need to understand differences in fertility between HIV positive and negative women. To estimate the number of infected children born to HIV positive mothers, mother to child transmission probabilities are required. Finally, to estimate the number of children living with HIV by age who were infected through MTCT we need to know their survival pattern from time of infection. These estimates are needed to estimate and project the HIV epidemic and are used in models such as the UNAIDS Spectrum model which is used by national programs and UNAIDS to prepare annual estimates of the status of the HIV epidemic worldwide [4].

Through my work prior to this PhD on both paediatric and adult survival from HIV, with colleagues at the London School of Hygiene and Tropical Medicine [5-7], I became involved with the UNAIDS reference group on estimates, modelling and projections[8]. What quickly became evident at that time was the paucity of empirical evidence on which to base the estimates and projections of the HIV epidemic, particularly for paediatric HIV. I have been involved with ALPHA (Analysing Longitudinal Population-based HIV/AIDS data on Africa), a network of HIV longitudinal surveillance studies[9] (see page 21) from its inception in 2005, which opened up a new pool of data that could help provide empirical data on the HIV epidemic. My involvement with the ALPHA network and other work using large nationally representative surveys[10, 11] led me to the work in this PhD which aims to improve and update empirical evidence to inform the estimates and projections of the HIV epidemic.

This PhD will focus on the three distinct aspects of paediatric HIV calculations: paediatric survival from HIV; mother to child transmission rates and differences in fertility by HIV status.

1.2 Overarching Rationale

Inputs into the estimates of the number of children born to HIV positive women and the prevalence of paediatric HIV have often been based on very small amounts of empirical evidence. Over the years more data have become available which gives the opportunity to update, improve and assess levels, patterns and changes over time. It is particularly important to capture change, as since around 2005 antiretroviral treatment began to be rolled out in sub-Saharan Africa, with some countries now having very high coverage. Fertility of HIV positive women compared to HIV negative women is a key input into estimates of the number of children born to HIV positive women, but there is no consensus on the impact of ART on fertility. It is essential to try to measure any changes and understand the underlying dynamics in order to be able to provide accurate estimates for national HIV programs of the number of children born to HIV positive women and the prevalence of paediatric HIV.

1.3 Overview of Data

This section highlights the new data that became available prior to this PhD that underpins this PhD and gave rise to the objectives set out in section 1.4 of this chapter

1.3.1 Pooled Clinical Trial and cohort study data

This dataset is a pooled dataset of clinical and cohort study data from sub Saharan Africa prior to the introduction of infant antiretroviral treatment. It is a child based data set with follow up from birth, including timing of HIV infection and survival status along with the HIV status of the mother and breastfeeding patterns. At the time of creating the pooled dataset, the trials represented the vast majority of the clinical research studies performed since the mid 90's on the African continent on the prevention of mother-to-child transmission of HIV (PMTCT).

The dataset was prepared by the University of Bordeaux and is described in detail elsewhere[12, 13] (chapter 3, page 52). In brief, data from 12 clinical trials and cohort studies in Southern, Eastern and Western Africa were combined into the same dataset. Interventions in these studies included various peripartum antiretroviral prophylactic

regimens[14-22], vitamin A[23], and birth canal cleansing[24]. Most of the study sites (n=8) were located in reference hospitals of capital or large cities; three studies were based in antenatal care clinics, or a mixture of the two, and one in a mixture of both urban and rural settings. The median follow up time ranged from 300 to 1096 days, and studies tested for HIV infection in children at regular intervals in the first 18 months.

1.3.1.1 Candidate's role in data preparation

All the data in this data set are secondary data. I was part of the preliminary talks about preparation of the pooled dataset and contributed to the discussions about what needed to be included. Bordeaux University collated the dataset and produce the final version. I prepared the dataset for the analysis in this PhD.

1.3.2 ALPHA network data

The ALPHA network is a network of ten community based, longitudinal HIV studies in Eastern and Southern Africa[9]. Data for this PhD comes from six of the study sites from Uganda (2), Tanzania (1), Malawi (1), Zimbabwe (1) and South Africa (1) (Figure 1.1). Table 1.1 summarises the study sites. Study start dates range from 1989 in Masaka to 2002 in Karonga.

Figure 1.1: ALPHA network study sites, green circles are the study sites used in this PhD

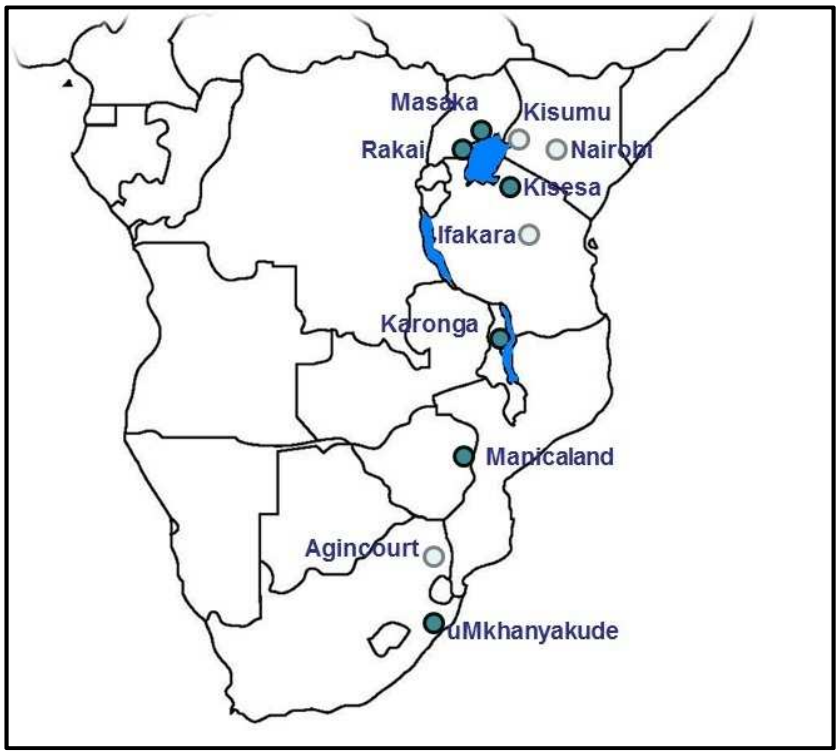


Table 1.1: Description of the ALPHA Network study sites used in this PhD (Abridged from Reniers et al[9])

Name	Short Name	Institutional affiliation URL
Kyamulibwa General Population Cohort	Masaka	MRC/UVRI Research Unit on AIDS http://www.mrcuganda.org/research/research-site/kyamulibwa-field-station
Rakai Community Cohort Study	Rakai	Rakai Health Sciences Program, Uganda Virus Research Institute / Makerere University http://www.rhsp.org
Magu Household Demographic Surveillance System	Kisesa	Tazama Project, Tanzania National Institute for Medical Research http://www.tazamaproject.org/
Karonga Health and Demographic Surveillance System	Karonga	Malawi Epidemiology and Intervention Research Unit (MEIRU), London School of Hygiene and Tropical Medicine http://www.lshtm.ac.uk/eph/ide/research/kps/
Manicaland HIV/STD Prevention Project	Manicaland	Biomedical Research and Training Institute (Harare), and Imperial College (London) http://www.manicalandhivproject.org/
Africa Centre Demographic Information System (ACDIS)	uMkhanyakude	Africa Centre for Population Health www.africacentre.ac.za/

Name	Location, Country	Demographic surveillance: start/frequency	Serological survey: start/frequency
Kyamulibwa General Population Cohort	Kalungu District (formerly Masaka), Uganda	1989: Annual	1989: Annual. Every 2 years from 2012
Rakai Community Cohort Study	Rakai District, Uganda	1995: Every 12-16 months	1995: Every 12-16 months
Magu Household Demographic Surveillance System	Magu District (Mwanza Region), Tanzania	1994: 1-2 times per year	1994: Approx. every 3 years
Karonga Health and Demographic Surveillance System	Karonga District, Malawi	2002: Continuous	Annual survey from 2007 to 2011. New residents and individuals with long test interval since 2012
Manicaland HIV/STD Prevention Project	Manicaland Province, Zimbabwe	1998: Every 2-3 years	2002: Every 2-3 years
Africa Centre Demographic Information System (ACDIS)	uMkhanyakude (formely Hlabisa) Discrict, South Africa	2000: bi-annual	2003-2004: Annual

1.3.2.1 Overview of Study sites

This section gives a brief description of each of the study sites used in this PhD outlining the main features of each study site in relation to the collection of demographic and HIV testing data.

Karonga

The Karonga Demographic Surveillance Study (DSS) is located in rural northern Malawi; it was established in 2002 and has a total population of around 35,000. The demographic surveillance data have been continuously collected using key informants, who are trained to record vital events and movements within their cluster of households[25]. Population-based HIV testing in the DSS based on voluntary counselling and testing (VCT) was undertaken in four annual rounds from 2007-2011 [25] and average adult HIV prevalence between these dates was 8% [26].

Kisesa

The Kisesa DSS is located in Mwanza in north western Tanzania and was established in 1994. It is predominately rural with a small trading centre on the main road from Mwanza City to the Kenyan border and has a population of around 34,000. The average HIV prevalence between 1994 and 2010 was 6% [27]. The frequency of the DSS has varied but is approximately once or twice a year. HIV surveys are done separately to the demographic surveillance rounds, with the data linked afterwards using unique identifiers. Temporary village clinics are used to which people are transported from their homes. Prior to the availability of antiretroviral therapy, testing protocols used informed consent without disclosure, so that participants did not learn the results of the HIV research tests, however with the advent of ART, sites began to offer full pre-test and post-test counselling to the participants during the data collection round. Participants are still not obliged take part in the counselling or to learn their results.

Manicaland

The Manicaland study in Zimbabwe was established in 1998. A prospective household census (population size approximately 37,000) and general population cohort survey (10,000-12,000) were initiated in 12 geographically distinct study sites spread across three districts, with follow-up rounds conducted every 2 or 3 years. The Manicaland study sites comprise of two small towns, four agricultural estates, two roadside settlements and four subsistence farming areas. Overall adult HIV prevalence was around 25% in the late 1990s and has declined steadily to around 15% in 2012-13 [28]. HIV testing is conducted only for research purposes [29].

Masaka

The Masaka DSS is located in rural south west Uganda and was established in 1989. Its initial population was around 10,000 which then increased to 18,000 when 10 villages were added to the census area[30, 31]. Average HIV prevalence between 1989 and 2011 was 8% [32]. DSS data are collected through an annual household census, and through key informants who register births and deaths on a monthly basis. HIV testing was undertaken annually until 2011, with biennial surveys conducted subsequently. HIV test results are reported back to respondents if requested.

Rakai

The Rakai Health Sciences Program runs the Rakai Community Cohort Study (RCCS), with an adult population of between 12,000-16,000. Data were collected from 1999 with adult HIV prevalence in 2002/03 reported to be 11.4 % [33]. In Rakai the HIV surveys were done separately to the demographic surveillance rounds. Samples were taken in the home and tested at the field laboratory then returned by a community based counsellor to those participants requesting the results. The data were linked afterwards using unique identifiers.

uMkhanyakude

The African Health Research Institute (AHRI), formally known as Africa Centre, demographic surveillance study was established in 2000 in uMkhanyakude, in rural KwaZulu-Natal, South Africa; each round covers approximately 90,000 resident and non-resident household members in approximately 12,000 households, with a key-household respondent [34]. Individual HIV surveillance for resident adults (≥15 years) was added in 2003 and adult HIV prevalence in 2012 was around 28% and annual incidence in the 15-50 year age group for women was about 5% [35]. DSS data are collected every six months, and the HIV serosurveys are conducted every year. Participants can obtain their HIV test results from counselling centres in the research area [34].

1.3.2.2 ALPHA Data format

Each study site provides standardised data that conforms to data specifications provided by ALPHA. Specifications used in this PhD are as follows (See appendix 1)

1. **DSS residency episodes:** entry and exit date, entry type (baseline, birth or in-migration) and exit type (still present in study site, death, out-migration, loss to follow up) for calculating person-years of observation and dates of death
2. **HIV test data**: dates and results of HIV tests for the classification of individuals by HIV status and tracking of any changes in this status over time
3. **Birth Records:** Dates of delivery of lives births (and stillbirths if recorded)

1.3.2.3 Candidate's role in data preparation

I did not play any role in collecting primary data but was the lead in the ALPHA team involved with producing the data specifications sites needed for harmonising data. I translated the Kisesa site data into the standard format and also advised other ALPHA sites on the production of the ALPHA specifications. I pooled the site specific standardised data from the ALPHA sites and prepared it for analysis.

1.3.3 Demographic and Health surveys

Demographic and Health surveys (DHS) and AIDS indicator surveys (AIS) are nationally representative surveys that use standard questionnaires to collect data over a large range of countries within and outside sub-Saharan Africa[36]. Data collected include data on fertility, family planning, maternal and child health, gender, malaria, and nutrition along with socio-demographic background characteristics. Since 2001 HIV testing has been undertaken in selected DHS surveys. The HIV testing was on a sub sample of the DHS and was generally done so the power was adequate to measure HIV prevalence in 15-49 year olds disaggregated by sex and urban and rural residence. Details of the survey methodology for HIV testing is provided elsewhere[37].

Table 1.2 shows the DHS and AIS from Sub-Saharan Africa used in this PhD along with the sample number and HIV prevalence.

1.3.3.1 Candidate role in data preparation

I did not play any role in collecting primary data or producing the final country datasets. With permission from the DHS program I download the data for multiple surveys, standardised and pooled them and prepared the final dataset ready for analysis.

Table 1.2: DHS and AIS used in PhD

Region	Survey	Year	n	HIV prevalence Women 15-49 (95% CI)*
Southern Africa				
	Lesotho	2004	3030	26.3 (24.5-28.2)
	Lesotho	2009	3778	26.7 (25.0-28.6)
	Lesotho	2014	3175	29.7 (27.7-31.8)
	Namibia	2013	4051	16.9 (15.4-18.4)
	Swaziland	2006-07	4424	31.1 (29.4-32.9)
	Zimbabwe	2005-06	6947	21.1 (19.7-22.6)
	Zimbabwe	2010-11	7313	17.7 (16.6-18.8)
	Zimbabwe	2015	8667	16.7 (15.6-17.8)
East and Mid Africa				
	Burundi	2010	4533	1.7 (1.4-2.1)
	Kenya	2003	3151	8.7 (7.6-10.0)
	Kenya	2008-09	3641	8.0 (6.8-9.3)
	Malawi	2004	2686	13.3 (12.0-14.8)
	Malawi	2010	7091	12.9 (11.8-14.1)
	Malawi	2015-16	7737	10.8 (9.9-11.7)
	Rwanda	2005	5641	3.6 (3.1-4.2)
	Rwanda	2010	6917	3.7 (3.3-4.2)
	Rwanda	2014-15	6752	3.6 (3.2-4.1)
	Tanzania	2007-08	8179	6.6 (5.9-7.4)
	Tanzania	2011-12	9756	6.2 (5.6-6.8)
	Zambia	2007	5502	16.1 (14.7-17.5)
	Zambia	2013-14	14719	15.1 (14.2-16.0)
West and Central Africa and Ethiopia				
	Burkina	2003	4086	1.5 (1.2-2.0)
	Burkina	2010	8298	1.2 (0.9-1.5)
	Cameroon	2004	5128	6.6 (5.9-7.4)
	Cameroon	2011	7221	5.6 (5.0-6.3)
	Chad	2014-15	5656	1.8 (1.4-2.2)
	Cote Ivoire	2005	4413	6.4 (5.5-7.5)
	Cote Ivoire	2011-12	4509	4.6 (3.9-5.4)
	DRC	2007	4492	1.6 (1.2-2.2)
	DRC	2013-14	9264	1.6 (1.2-2.2)
	Ethiopia	2005	5736	1.9 (1.4-2.4)
	Ethiopia	2011	14695	1.9 (1.5-2.3)
	Gabon	2012	5459	5.8 (4.7-7.1)
	Gambia	2013	4089	2.1 (1.6-2.8)
	Ghana	2003	5097	2.3 (1.9-2.8)
	Guinea	2005	3742	1.9 (1.4-2.6)
	Guinea	2012	4622	2.1 (1.7-2.6)
	Liberia	2007	6382	1.8 (1.4-2.1)
	Liberia	2013	4397	2.0 (1.5-2.8)
	Mali	2006	4528	1.4 (1.0-2.0)
	Mali	2012-13	4806	1.3 (1.0-1.8)
	Niger	2006	4406	0.6 (0.4-0.9)
	Niger	2012	5000	0.4 (0.2-0.5)
	Sao Tome	2009	2378	1.3 (0.8-2.0)
	Senegal	2005	4229	0.7 (0.4-1.0)
	Senegal	2010-11	5326	0.6 (0.4-0.8)
	Sierra Leone	2008	3448	1.7 (1.3-2.3)
	Sierra Leone	2013	7695	1.7 (1.3-2.0)
	Togo	2013-14	4737	3.1 (2.6-3.7)

1.4 Overall aim and objectives

The overall aim of this research is, in light of the availability of new data, to make use of empirical evidence to improve estimates of the number of children born to HIV positive women and hence improve estimates of the prevalence of paediatric HIV in populations with generalised HIV epidemics.

The objectives are as follows:

Objective 1: describe different patterns of paediatric survival by timing of HIV infection, using data from pooled clinical trial and cohort study data.

Objective 2: investigate population level risk of acquisition of HIV in pregnant women, using longitudinal data from the ALPHA network.

Objective 3: investigate whether there is an impact of ART on fertility at the population level, using longitudinal data from the ALPHA network.

Objective 4: estimate the population impact of HIV on fertility and examine the effect of duration of infection on fertility and whether this is independent of age using longitudinal data from the ALPHA network.

Objective 5: estimate the population impact of HIV on fertility and investigate if there are variations by region, urban and rural residence and ART coverage using cross sectional data from demographic and health surveys.

Objective 6: investigate possible biases affecting the analysis of the impact of HIV on fertility that arise from the use of retrospective data such as DHS or prospective data, such as ALPHA network

Objective 7: identify how behaviour contributes to HIV subfertility to gain a better understanding of the contribution it makes to differences in fertility by HIV status

1.5 Overview of methods

The methods used to answer the objectives of this PhD are described in detail in each chapter. This section gives an overview of these methods by the objectives outlined in section 1.4.

Objective 1: describe different patterns of paediatric survival by timing of HIV infection, using data from pooled clinical trial and cohort study data.

Data from 12 clinical trials and cohort studies in Southern, Eastern and Western Africa with data on child survival in the absence of antiretroviral therapy were included in a pooled analysis where all the data was combined into the same dataset. Along with data on child survival with follow up from birth by timing of HIV infection and survival status each dataset also included data the HIV status of the mother and breastfeeding patterns. Most study sites (n = 8) were situated in reference hospitals of capital or large cities; three studies were based in antenatal care clinics, or a mixture of the two, and one in a mixture of both urban and rural settings. The median follow up time ranged from 300 to 1096 days, and studies tested at regular intervals in the first 18 months.

Kaplan-Meier analysis was used to calculate survival curves of children by timing of infection. Date of infection was taken to be the midpoint between the last negative test and the first positive HIV test (antibody or PCR depending on age). Where there was no negative test for those infected early, the midpoint between birth and first positive test was taken. A sensitivity analysis was undertaken to assess how results varied according to the date imputed.

The net survival probability, $l_A(x)$, if HIV-related mortality is the only operative cause of death, was calculated from the proportions of HIV-infected children surviving to age x, $l_{O+A}(x)$, and the proportion of uninfected children surviving to age x, $l_O(x)$, using the usual relationship for cause deleted life tables:

$$l_A(x) = \frac{l_{O+A}(x)}{l_O(x)}$$

To make the distribution of the HIV-negative children similar to that of the HIV-infected children, the HIV-negative ones were weighted so that their distribution by entry into observation, study group, and timing of start of risk exposure matched those of the HIV-infected children.

The double Weibull provides a good functional representation of paediatric survival curve as it allows for initial high mortality followed by rising mortality at later time points [6, 38], taking the form:

$$l_A(x) = \pi \cdot \exp\left\{-\left[\lambda_1 \cdot x\right]^{\mu_1}\right\} + (1-\pi) \cdot \exp\left\{-\left[\lambda_2 \cdot x\right]^{\mu_2}\right\}$$

Where $l_A(x)$ is the survival at time x from HIV/AIDS. By studying the empirical curves depicting net survival by time since infection we used the double Weibull curve to produce functional representations of the net survival post infection of children for different times of infection, in the perinatal period and during early and late breastfeeding.

Objective 2: investigate population level risk of acquisition of HIV in pregnant women, using longitudinal data from the ALPHA network.

Data from the ALPHA network was used as outlined in section 1.3.2. For this objective I used data from six of the sites Karonga, Kisesa, Masaka, Rakai, Manicaland and uMkhanyukude. Data collection was sufficiently similar to allow pooled analyses, with allowance for unobserved heterogeneity between sites.

Women of reproductive age (15- 49 years old) were eligible for inclusion in the analysis. Person-years of observation for each woman were split into time not-pregnant, pregnant and one year postpartum. For a woman to be included in the analysis she must have had at least two HIV tests, the first of which must have been negative to allow observation of any sero-conversion. Follow-up time started from the date of the first negative test and lasted until exit at the date of their last test or at the date of sero- conversion, if earlier. Time between HIV surveillance tests varies across the different sites ranging from annual to three year inter-test intervals; further, a person might miss a surveillance round thus extending the period between tests. For all study sites, the interval between HIV tests is longer than a full gestation pregnancy, and we cannot be sure whether the sero-conversion occurred before, during or after the pregnancy period. To allow for this uncertainty, the analysis was repeated 100 times, each time with the estimated sero-conversion date assigned at a random point between the last negative and first positive dates, rates and crude and adjusted hazard rate ratios (HRR) were calculated using piecewise exponential regression, so that age (grouped into conventional five year age groups), pregnancy status and calendar time could be treated as time-varying factors. Rates and the log of the hazard rate ratios from the imputations were combined using Rubin's rules [39] to give confidence intervals that reflect the uncertainty about the exact date of sero-conversion. The crude hazard rate ratios converged at around 20

imputations with the adjusted rate ratios taking 30 to 40 imputations to converge to stable values.

Objective 3: investigate whether there is an impact of ART on fertility at the population level, using longitudinal data from the ALPHA network.

Data from the ALPHA network was used as outlined in section 1.3.2. Fertility data that span the pre-ART era and the time of introduction and widespread use of ART that were needed to complete the objective above were available from four of these community-based demographic and HIV surveillance sites: Kisesa, Masaka, Rakai and uMkhanyukude. The population included in this analysis is women of reproductive age (15-44) living in the surveillance areas between the time point corresponding to five years before ART was introduced, to the last date for which data were available for each site up to 2015.

All live births to women aged 15–44 years old while under observation in the study were included in the analysis, classified by mother's age, area of residence and HIV status at time of the birth, and by ART availability in the community. Women aged 45-49 year olds were not included to create the standard fertility analysis grouping of 15-49 years as there were very few births to HIV positive women at this age.

I used Poisson regression to calculate age adjusted fertility rate ratios over time by HIV status, and investigated the interaction between ART period and HIV status to ascertain whether trends over time were different for HIV positive and negative women. I adjust for age and area of residence in this analysis to control for any changes in the composition of the study site that may have occurred between the pre and post ART periods. The analysis was performed separately for each site and pooled across sites where appropriate, the pooled results were adjusted by study site.

Objective 4: estimate the population impact of HIV on fertility and examine the effect of duration of infection on fertility and whether this is independent of age using longitudinal data from the ALPHA network.

Data from the ALPHA network was used as outlined in section 1.3.2. Fertility data from the pre-ART era that were needed to complete the objective above were available from three of the community-based demographic and HIV surveillance sites: Kisesa, Masaka and Manicaland.

Calculating the fertility rate by duration of HIV infection requires data about when a woman seroconverted, which is not exactly observed. I generated 100 imputations for the date of seroconversion for each HIV-positive woman. For women who are observed HIV-negative in one survey round and HIV-positive in a subsequent round ('seroconverters'), I imputed dates of seroconversion from a uniform distribution between the dates of the last negative and first HIV positive test. For women who were already HIV positive the first time they were tested in the cohort ('prevalent cases'), I imputed 100 seroconversion dates from a distribution determined by the convolution of the age-specific HIV incidence rates and the probability of surviving from seroconversion until the woman's latest age at interview.

Person time and live births of women of reproductive age (15- 49 years old) who had ever tested for HIV in the studies were eligible for inclusion in the analysis. HIV negative person-time for women with no subsequent positive test was assumed to last for up to five years past their last negative test, the exact cut-off point was determined by the HIV incidence rates in the sites, defined as the time at which the cumulated probability of becoming infected following the last negative test reached 5%. Data for each cohort were censored at the start of ART introduction (Kisesa March 2005, Masaka January 2004, Manicaland June 2005), in order to estimate the intrinsic relationship between HIV and fertility before the availability of antiretroviral therapy. For women ever testing HIV positive imputed seroconversion dates were used to assign person-time by HIV status. The imputed duration of infection is defined as 0 for HIV-negative, and is treated as a continuous variable in years following sero-conversion. Fertility rate ratios (FRR) by HIV status and duration of infection are calculated using piecewise exponential regression allowing for clustering of births in each women, adjusting for age-specific fertility in each site and a log-linear trend in fertility over calendar time centred on the year 2001. The analysis was repeated 100 times using independently imputed sero conversion dates. The log of the hazard rate ratios from the imputations were combined using Rubin's rules [39] to give confidence intervals that reflect the uncertainty about the exact date of sero-conversion.

Objective 5: estimate the population impact of HIV on fertility and investigate if there are variations by region, urban and rural residence and ART coverage using cross sectional data from demographic and health surveys.

Data from 48 Demographic and Health Surveys (DHS) and AIDS indicator surveys (AIS) conducted in 27 sub-Saharan African countries between 2003 and 2016 were used, in which both full birth histories and HIV testing outcomes were available [40]. DHS and AIS

are nationally representative household surveys [40]. All analyses account for the two-stage cluster sampling survey design and use the HIV weights provided by DHS. In pooled analysis, surveys are re-weighted so that each survey contributes equally toward the analysis.

Each woman respondent was asked birth history questions for up to 20 births, beginning with the most recent. Dates of birth of the women and children are given in months and years, the day of birth was assigned to be the midpoint of the month.

Initially I analysed fertility rates by HIV status during the three years prior to the interview. This cut-off was used in previous studies[41, 42] to balance the benefits of maximizing the person-years of observation while seeking to minimize maternal survivorship bias, recall bias and misclassification of HIV status over the three preceding years[43]. However, I report results adjusted for the first year prior to the survey due to evidence of persistence of these biases when using data from longer than a year prior to the survey (see section 7.2, which shows this analysis). I used the standard demographic definition of age-specific fertility rates (ASFR):

$$ASFR_{x-x+4} = \frac{Number\ of\ births\ to\ women\ aged\ x\ to\ x+4}{Number\ of\ person\ years\ contributed\ by\ women\ aged\ x\ to\ x+4}$$

I then estimated the fertility rate ratios in the general population. Subsequently, I restricted the analysis to person years after first sex to assess the extent to which variation in age at first sex explains fertility differences among HIV positive women and HIV negative women in the younger age groups. I assumed sexual debut occurred on the date corresponding to the midpoint of the reported age at first sex (which is reported as an integer age). Age at first sex was changed to nine months before the reported date of first birth if this was earlier than the midpoint of reported age at first sex.

I used exponential regression to investigate the interaction between HIV status and five-year age group, place of residence, region and ART coverage with respect to their impacts on fertility. Each analysis was adjusted for country and survey year. The analysis was repeated excluding person time prior to first sex. The multivariate Wald test was used to assess significance of interaction terms. The first model includes only the interaction between age and HIV status controlled for country and year of survey. Subsequent models include the effect of place of residence, region and national ART coverage and the interactions between them and age and HIV status.

All models included the three-way interaction between year before the survey, five year age group and HIV status. Results are reported for the first year before the interview date.

Objective 6: investigate possible biases affecting the analysis of the impact of HIV on fertility that arise from the use of retrospective data such as DHS or prospective data, such as ALPHA network.

The methods used for this objective are the same as for objective 5.

Objective 7: identify how behaviour contributes to HIV subfertility to gain a better understanding of the contribution it makes to differences in fertility by HIV status.

I analysed data from 46 Demographic and Health surveys (DHS) and AIDS indicator surveys (AIS) from 26 countries in sub-Saharan Africa that included both HIV testing data and questions about recent sexual intercourse and current contraceptive use. Four surveys with HIV testing (Tanzania 2008 and 2012, Cote D'Ivoire 2005 and Uganda 2011) were excluded as they did not include questions on current contraceptive use.

Outcome variables

Exposure to sex: I created a binary variable "had recent sexual intercourse" defined as reporting having had sexual intercourse in the last four weeks.

Married: Marital status was defined as a binary outcome: currently married (including cohabiting couples) and not currently married.

Modern Contraceptive use: Modern contraceptive use conformed to the DHS definition and included the pill, IUD, injections, diaphragm, condom, female sterilization, male sterilization, implants, female condom, Foam/Jelly and lactational amenorrhea. I restricted lactational amenorrhea to be included only if it was within six months of the birth.

Exposure to pregnancy: A binary outcome "exposure to pregnancy" was calculated as those who reported recent intercourse and reported not to be currently using any modern contraceptive. This definition assumes that current contraceptive use was constant in the 4 weeks prior to the survey.

Condom use: This binary outcome defined as women reporting currently using condoms among women who had reported recent sex and currently using a modern contraceptive.

Fertility Rates: This is measured using the retrospective birth histories and calculated as births per person year in the three years preceding the survey.

Explanatory variables

Other variables included women's HIV status at the time of the survey, five-year age group at time of survey, calendar year, place of residence (urban/rural), geographic region, and national female ART coverage in the year of the survey drawn from UNAIDS estimates[14] and stratified into categories <20%, 20-49%, and >50%. Region was grouped into Southern (Zimbabwe, Lesotho, Swaziland and Namibia), East and Mid Africa (Tanzania, Kenya, Uganda, Rwanda, Burundi, Malawi and Zambia) and West and Central Africa with Ethiopia (Table 1). HIV epidemics in the East and Mid African countries occurred earlier than in Southern Africa. West and central Africa along with Ethiopia have lower prevalence and their HIV transmission is likely to be more concentrated in high risk groups.

Women who were pregnant at the time of the survey (9.0% across all surveys); those infected with HIV-2 (0.04%); and those whose HIV test was indeterminate (0.02%) were excluded from the analysis.

Data analysis

For each outcome variable, I used log Poisson regression[44] to estimate the interaction between HIV status and five-year age group, place of residence, region and national ART coverage for the outcome variables recent sex, recent exposure to pregnancy, and fertility rate[45]. Each model was adjusted for country and survey year. Relative exposure to pregnancy by HIV status were compared to the fertility rate ratios by HIV status in order to estimate how much of the reduced fertility in HIV positive women compared to HIV negative women at the population level could be attributed to less exposure to sex. For regressions of fertility rate, fertility data for the three years before the survey were modelled, with an additional categorical variable for each year before the survey interacted with the age groups below 25 years and above 25 years[45]. Estimated fertility rate ratios by HIV status pertain to estimated fertility rate for the year preceding the survey.

The log Poisson model was chosen for a number of reasons. Normally one might choose a logistic regression model, however this would give odds ratios which I could not have

later compared to rate ratios of fertility, therefore a relative risk was preferable. The literature suggest a number of methods of obtaining risk ratios that can be used when the event is common as it is in the case of this paper. Two suggestions are the log binomial regression model and the other a log Poisson regression model with a robust error variance. In the case of this analysis as stated in the literature, a common problem with the log binomial regression is that the models did not converge so could not be used. An alternative to the log binomial method is a modified Poisson regression first put forward by Zou[44] who suggests using a Poisson model with robust error variances. Since then there has been various literature looking at the reliability of estimates using the Robust Poisson model, concluding that in general it gives reasonable estimates of the risk ratio, although sometimes leads to slightly larger standard errors than the log binomial[46], therefore is in fact more conservative.

I further analysed the outcomes of modern contraceptive use and marital status using the same log Poisson regression models in order to evaluate the extent to which differences in exposure to pregnancy between HIV positive and HIV negative women were mediated by differences in these intermediate outcomes. Finally, I investigate differences in contraceptive type between HIV positive and HIV negative women and the potential implications of this for contraceptive efficacy. I assess differences in type of modern contraceptives used between HIV positive and HIV negative women by analysing differences in condom use among women who reported having recent sex and currently using a modern contraceptive.

1.6 Structure of the thesis

This thesis is presented in research paper style, including five published and one submitted academic papers (A-F), an extract from one academic paper, a report, and three additional chapters including this introductory chapter, a literature review and final discussion.

I present the work in the chronological order in which it was done: first the Paediatric survival from HIV infection in the absence of ART, second whether there are differences in acquisition of HIV in pregnant compared to non-pregnant women which could affect the mother to child transmission rates, finally looking at differences in fertility between HIV positive and HIV negative women, and how this changes in the era of ART.

A short introductory section is provided before each of the papers A-F, briefly outlining the rationale for the paper, and linking it to the findings and material presented in preceding chapters if relevant.

Chapter 2: Literature review on Child survival, HIV acquisition in pregnancy and Fertility and HIV in era of ART

Chapter 3: Research paper (paper A): “Net survival of perinatally and postnatally HIV-infected children: A pooled analysis of individual data from sub-Saharan Africa.” This chapter also includes an extract from another research paper that extends this work and a further unpublished report produced for UNAIDS.

Chapter 4: Research paper B: “Is the risk of HIV acquisition increased during and immediately after pregnancy? A secondary analysis of pooled HIV community-based studies from the ALPHA network”.

Chapter 5: Research paper C: “Measuring the Impact of antiretroviral therapy roll-out on population level fertility in three African countries”

Chapter 6: Research paper D: “The effects of HIV on fertility by infection duration: evidence from African population cohorts before ART availability”

Chapter 7: Research paper E: “The relationship between HIV and fertility in the era of antiretroviral therapy in sub Saharan Africa – Evidence from 49 Demographic & Health Surveys”

This chapter also includes an expanded version of the supplementary materials for research paper E which is an analysis of bias when using cross sectional surveys to look at the impact of HIV on fertility

Chapter 8: Research paper F: “Relative patterns of sexual activity and fertility among HIV positive and negative women – evidence from 46 DHS”

Chapter 9: Final discussion of the work done in the PhD

Table 1.3: Sources of data used in each paper presented in this thesis

	Paper Title	**ALPHA**	**DHS**	**Clinical Trials**
	Brief Literature review on Fertility and HIV in era of ART			
A	Net survival of perinatally and postnatally HIV-infected children: A pooled analysis of individual data from sub-Saharan Africa			**X**
	Research (report for UNAIDS) an update to the paediatric curve		**X**	**X**
B	“Is the risk of HIV acquisition increased during and immediately after pregnancy? A secondary analysis of pooled HIV community-based studies from the ALPHA network”.	**X**		
C	“Measuring the Impact of antiretroviral therapy roll-out on population level fertility in three African countries”	**X**		
D	“The effects of HIV on fertility by infection duration: evidence from African population cohorts before ART availability”	**X**		
E	“The relationship between HIV and fertility in the era of antiretroviral therapy in sub Saharan Africa – Evidence from 49 Demographic & Health Surveys”		**X**	
	Expanded version of the supplementary materials for research paper E which is an analysis of bias when using cross sectional surveys to look at the impact of HIV on fertility	**X**	**X**	
F	“Relative patterns of sexual activity and fertility among HIV positive and negative women – evidence from 46 DHS”		**X**	

1.7 Ethical clearance

Ethical approval was obtained for all studies in the PhD and is highlighted where relevant in each published paper. Copies of LSHTM approvals are found in appendix 2.

1.8 Funding

Research leading to PAPER A was funded by the Epidemiology and Analysis Division of UNAIDS (Geneva, Switzerland).

Research leading to PAPERS B-F was funded by the Wellcome Trust (085477/Z/08/Z).

2 Literature review

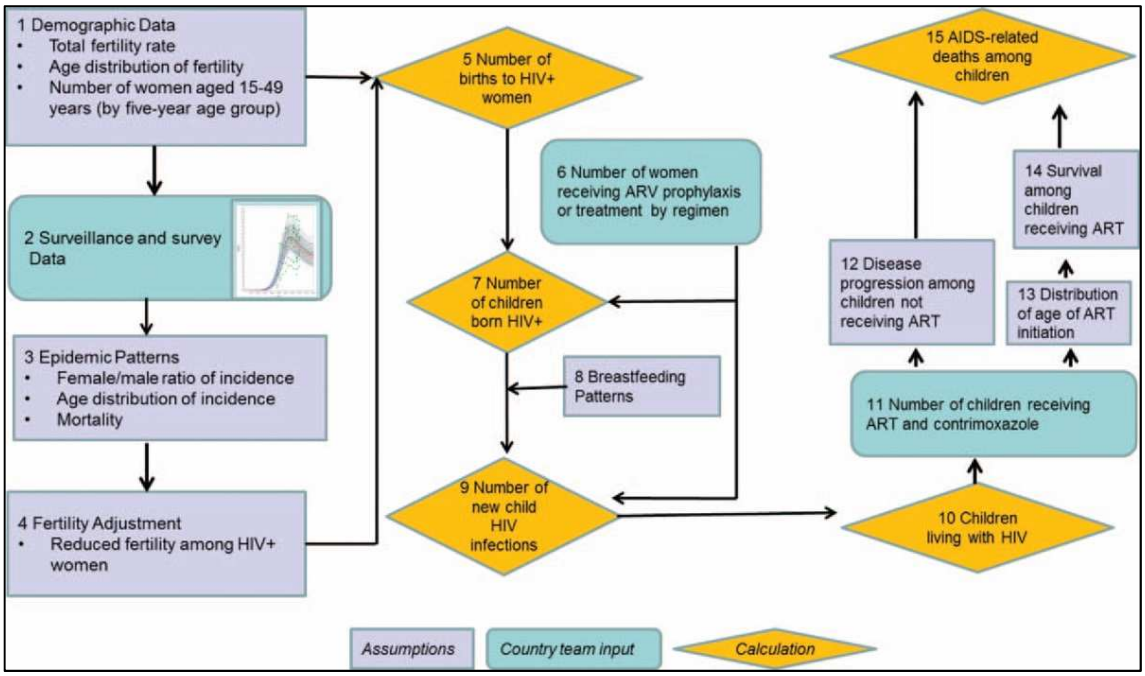
2.1 Introduction

This literature review first describes the Spectrum AIDS impact module (AIM) to give an example of how estimates of paediatric AIDS are calculated. The following sections then go on to describe the current literature that informs the assumptions in these models and evidence that could be utilised to further refine these assumptions.

2.2 The Spectrum AIDS impact module (AIM)

The Spectrum AIDS impact module (AIM) is part of Spectrum, an established model used by UNAIDS that has generated global AIDS estimates since 1999[47]. This module estimates the number of children newly infected with HIV each year and then progresses them through survival schedules as they age to estimate AIDS deaths and numbers of children living with HIV by age, until they reach 15 years old, when they move to the adult model. Figure 2.1 shows the flow of the module highlighting different inputs, assumptions and calculations made, starting from the input of demographic data ending with the number of AIDS related deaths among children.

Figure 2.1: Paediatric HIV Calculations in Spectrum AIDS Impact Module (Reproduced from Mahy et al[48] under the creative commons attribution - Non Commercial – No Derivatives License 4.0.)



The assumptions made in this module and other models that estimate paediatric HIV which are relevant to this PhD are those on fertility adjustments, relating to differences

in fertility of HIV positive and HIV negative women; mother to child transmission rates; and disease progression among children not receiving ART.

2.3 Estimating the survival of HIV infected children

Prior to antiretroviral treatment it was estimated that in breastfeeding populations between 25% and 45% of children born to HIV positive mothers would become infected through mother to child transmission with 30%-50% of these infections occurring during breastfeeding [49]. To estimate the effect that the HIV epidemic will have on population level child mortality, a schedule of age specific "net" mortality - mortality as if HIV was the only cause of death - is needed. This schedule can then be paired with age specific mortality patterns of uninfected children child mortality schedule to obtain expected mortality of HIV infected children given differing background mortality rates.

Survival of HIV positive children infected around birth in the absence of antiretroviral treatment is described by a double Weibul distribution; this distribution is used as it can describe initial high mortality in "fast progressors" directly after birth representing those infected in utero, peri-partum and intrapartum along with "slow progressors", those infected during breastfeeding. This curve has been used in the UNAIDS Spectrum model from 2002 after being recommended by the reference group on estimates, modelling and projections [50]. The curve was originally modelled on data from seven cohort studies that provided survival data on HIV positive children[50], it assumed in the absence of other information that no child HIV infected at birth would survive beyond fifteen years. Following this study, further data from longitudinal studies became available to improve the fitting of this curve, although many of these studies did not have the HIV status of the child but only the HIV status of the mother, necessitating the use of indirect techniques to estimate the survival of children assumed to be infected with HIV. With this later data Marston et al[6] estimated an improved survival schedule, using the same double Weibul function as previously used, retaining the assumption that no child infected through MTCT would survive beyond 15 years.

Later, further evidence emerged from a pooled analysis showing that the mortality two years following HIV infection was lower for children who acquired HIV via breastfeeding compared to those with perinatal infection[51], confirming the slow and fast progressors theorised in previous estimates of net paediatric survival. With this evidence and the newly available data from clinical trials, that provided information on the HIV status of children from birth with accurate estimates of the timing of HIV infection, Marston et al[13] (Presented in this thesis, chapter 3) estimated separate representations of survival for children infected with HIV early; in utero, peri partum and intrapartum and during breastfeeding. Also with increasing evidence indicating children surviving beyond 15

years who were infected through mother to child transmission from national HIV prevalence surveys, assumptions in the updated curves also included an assumption that the "slow progressors" would have a survival pattern similar to that of adults infected at young ages[5, 7] meaning that the slow progressors would be assumed to have a median survival of around 14 years. The resulting estimated net survival schedules gave a median survival of 1.09 years for those infected perinatally compared to 9.24 years for those infected through breastfeeding, this compares to the previous median survival of 2.08 years using the previous schedule that provided only one curve to represent all infected children irrespective of timing of infection. It was agreed later that there was adequate data to break down the survival schedules further by timing of infection through breastfeeding, this resulted in 4 survival schedules, one for perinatal infection as before and three for postnatal infection at 0-180 days, 181-365 days and 365+ days, giving median survival of 1.1, 6.4, 11.5 and 14.1 years after infection respectively[52] (Presented in this thesis, chapter 3).

2.4 HIV Acquisition in Pregnancy

Fertility rates are high in many sub-Saharan African countries and, therefore, a significant proportion of woman-years are spent pregnant[53]. Evidence regarding the risk of acquisition of HIV infection at and shortly after the time of pregnancy is conflicting[54-60]. An increased risk of HIV acquisition in pregnant women has implications for health services as the increased viral load in acute infection would expose the foetus to higher risk of in utero mother-to-child transmission[61]. It would also have implications for HIV epidemic modelling as estimates for paediatric HIV would need to be revised upwards.

A number of prospective studies from Eastern and Southern Africa have assessed the risk of HIV incidence during pregnancy. A multisite study of sero-discordant couples found that HIV incidence was, in univariate analysis, two-fold higher in pregnant than in not-pregnant women; however, after adjusting for age, unprotected sex in last month, and contraceptive use, the risk difference was reduced and was no longer statistically significant[57]. A similar study in Uganda restricted to married sero-discordant couples reported a non-significant increase in the HIV acquisition rate in pregnant women[54]. Other studies included women regardless of the partner's HIV status; in a Ugandan study of sexually-active women the risk of HIV-1 acquisition was doubled during pregnancy[54]. However, in an HIV prevention trial enrolling women from a number of health services and community venues in southern Africa there was no increased risk of HIV-1 in pregnant women[59]. A study in Uganda and Zimbabwe, in which women from family planning sites were enrolled, found no overall increased risk of HIV acquisition in pregnant women in the pooled analysis, and after adjusting for covariates, actually showed some evidence of a protective pregnancy effect in one of the study sites[56].

Further studies have shown a possible increased HIV incidence during pregnancy[62-64], others showed a risk comparable to the general population of a similar age[65, 66]. A number of studies have investigated HIV incidence in the postpartum period, again with somewhat conflicting results. In Malawi, a prospective study of women enrolled after delivery found HIV acquisition was increased in the first year postpartum, decreasing subsequently[60]; this was also the case in Zimbabwe[58] and Rwanda[55]. The authors of the latter study suggested that the decrease could be partly due to a cohort selection bias with those remaining uninfected for longer having a lower risk of infection. Other studies have not reported an increased risk in the postpartum period[54, 67].

The rate of HIV acquisition and differences between pregnant, postpartum and non-pregnant women at a population level will depend not only on the risk of infection per sexual act with an HIV positive partner, but also on the level of discordance in pregnant and non-pregnant couples and the differences in sexual behaviour between these groups. Therefore, results from the studies outlined above cannot be generalised to all women in the population, which are needed for national estimates of paediatric HIV.

To assess the population level differences in HIV acquisition Marston et al[68] (Presented in this PhD, chapter 4) used community based cohort data from six study sites to estimate differences in HIV acquisition by pregnancy status. This study found that HIV acquisition at a population level was lower in pregnant women than non-pregnant women (hazard rate ratio 0.79, 95%CI 0.70-0.89) and that there was no evidence of a difference in HIV acquisition rates in post-partum women compared to women who were not pregnant. These findings were attributed to pregnant women being more likely to be concordant with their partner during their pregnancy and in the post-partum period. A later study from South Africa [69] using updated data from one of the sites in Marston et al[68] (Chapter 4) further corroborated these findings showing pregnancy to have a protective effect on HIV acquisition with no significant difference in the postpartum period when compared to HIV negative women. There has been continued interest in the area of HIV acquisition in pregnancy which often fails to separate the population level from the individual level[70, 71] which will be discussed in the final discussion section (section 9.2)

2.5 Impact of HIV on fertility

In order to estimate the number of children born to HIV positive women, we need to understand differences in fertility between HIV positive and negative women and how this can vary over populations and time. Estimating the number of pregnant women is the first calculation made when estimating paediatric HIV, therefore this directly impacts on all later estimates, PMTCT need, paediatric ART need and numbers of HIV positive children surviving to adulthood. It is widely anticipated that ART scale-up will lessen the

subfertility of HIV positive women, which would lead to an increase in the number of HIV positive pregnant women. This section assesses the current literature on the impact of HIV on fertility and how this might change with the introduction of ART.

2.5.1 Population impact of HIV on fertility

The population impact of HIV on fertility in sub Saharan Africa has been well documented[41, 43, 45, 72]. These analyses have demonstrated that the relationship between HIV and fertility varies with age. Among the youngest women aged 15-19 years, fertility is higher among HIV positive women, due to selection of sexually active women, while above age 25 the fertility of HIV positive women becomes increasingly lower than that of their HIV negative counterparts, termed 'HIV associated subfertility'. Population based studies have also identified differences in HIV associated subfertility by region[43, 45], and urban and rural area[45]

With the increasing availability of ART, studies have sought to estimate its impact on fertility in HIV positive women. A systematic review by Yeatman et al in 2016 [73] concluded that the evidence indicated that fertility increases after the first year on ART but remains lower than in HIV negative women of the same age. The authors exercise caution as the data in the review spans the period of 2005-2010 when ART programs were being scaled up. This systematic review contained studies that can be roughly divided into three types. First, clinic based where the comparison was HIV positive women on ART compared to those not on ART, with no HIV negative controls or comparisons with HIV positive women who have not attended a care and treatment clinic (CTC) groups. Second are general population studies that compare HIV positive women to HIV negative women but do not have individual level data on which women are on ART and instead use comparisons of the two groups in a time when ART was not available and when it was widely available. Both these types of studies have limitations, which are discussed below. Finally, there is a group of general population studies that include individual level data on ART status.

Studies that use clinic based data do not necessarily represent the population experience. HIV positive women who attend a care and treatment clinic may be different to those who do not and may experience different fertility rates. This may be particularly important in the time when ART was being scaled up as there is more likely to be a selection bias in those attending the clinics. One bias that is particularly problematic is that women are often referred to care and treatment through antenatal clinic care: these women are therefore fecund at the time of referral, making them possibly less representative of HIV positive women in the population. Elul et al found in a study of 26 HIV clinics in Kenya and Uganda that women who were pregnant at enrolment into care

were much more likely to be started on ART than those who were not pregnant[74]. As the criteria for ART initiation over time has changed, particularly for pregnant women, this will change the selection effects. Over time WHO guidelines for PMTCT have changed. Early recommendations named option A and option B, suggested that ART should start as soon as a women is diagnosed with a CD4 count of less than 350 and continued for life (option A) or for women with a CD4 count above 350 that ART should be given for a period around the pregnancy (option B). New guidelines were introduced in the form of option B+ recommending that all women found HIV positive during pregnancy should be treated from time of diagnosis for life regardless of CD4 count[75, 76].

This shift in policy implied by option B+ will steadily increase the number of "healthy" fecund HIV positive women in the "on ART group" and likely include more young women of lower parity. Another problem this poses is that in the first six months of initiation on ART a spike in fertility is seen due to women having the babies from the pregnancy during which they were identified as HIV positive and in need of treatment. But if a women's follow up time starts from the time of delivery the bias will go in the other direction as straight after a delivery a woman is less likely to be fecund due to postpartum amenorrhea, lactation amenorrhea and active birth spacing. Elul et al point this out and begin follow up time on treatment from the time of delivery for those who were pregnant at ART initiation then investigate whether there is an interaction between pregnancy status at enrolment in HIV care and ART status with respect to the incidence of pregnancy[74]. They found evidence for a significant effect; in a model adjusting for other factors such as age and time varying CD4 count they found that those women who were pregnant at enrolment in HIV Care and on ART had a higher incidence of pregnancy than those not on ART even though overall they found no difference in the incidence of pregnancy between women in care on ART compared to those not on ART. This study was done at a time prior to option B+, with option B+ the composition on ART will likely increase the proportion of women enrolled on treatment when pregnant.

Three of the studies in the review by Yeatman et al were from general population with an HIV negative comparison group[77-79]. Two of these studies (one of which is presented in this PhD[78], Chapter 7) did not have individual level data on treatment status for HIV positive women so can only infer that any observed narrowing of the differences in the fertility between HIV negative and positive women in the era of ART is due to the impact of ART on fertility. However, this has the benefit of not assuming that the availability of ART has only direct effects on those women receiving treatment. It is possible that with increased availability of ART attitudes and beliefs about HIV infection may change, thereby possibly changing the fertility of HIV positive women not yet receiving treatment. When modelling the HIV epidemic all of these effects must be taken together in order to

get the most accurate estimates. The third population based study was from Gregson et al [77] who used data from a general population survey in Zimbabwe with individual level information on ART status to look at pregnancy prevalence of women who were HIV negative, HIV positive not on ART and HIV positive on ART, at a time after ART was scaled up. They found that the fertility of HIV positive women was 75% lower than that of HIV negative women 15-49 years old and that there was no evidence that the fertility of HIV positive women on ART differed from those not receiving treatment.

Since the publication of Yeatman et al there have been two more studies of note[45, 80] that have looked at the population level effect of HIV on fertility. The first study used data from a demographic surveillance site with HIV testing and clinic data in Malawi[80] enabling, as in Gregson et al[77], comparison groups to be HIV positive women not on treatment in the population, rather than only those in care, and HIV negative women. They found a suggestion of an increase in fertility for younger women on ART compared to those not on treatment but there was not sufficient power to be confident of this result. In this study the fertility of HIV positive women regardless of treatment was nevertheless lower than that found in HIV negative women. The second study by Marston et al[45] (Presented in this PhD, chapter 7) used data from 49 nationally representative surveys from sub Saharan Africa spanning a period between 2003 and 2016 that included times before and after ART roll out and scale up. National ART coverage was used as an ecological measure to see whether there was an impact on fertility, the paper concluded that there did appear to be a slight narrowing of the fertility differences between negative and positive women with high national ART coverage; however, this was not as much as would be expected if the fertility of women on ART was fully restored to that of HIV negative women. The authors also caution that national ART is an ecological measure and could represent other aspects of health and development. Even though many of the DHS surveys were conducted following ART roll-out, only a small number have ART coverage above 50% and so on a population level ART coverage may not be high enough to cause appreciable differences.

Most studies looking at the impact of ART on fertility have not been able to determine whether their results are due to biological or behavioural factors associated with ART.

2.5.2 Determinants of HIV subfertility

The determinants of HIV subfertility are complex and can be both biological and behavioural. This section describes the different possible mechanisms that would tend to lower fertility in HIV positive women, and discusses how these can change in era of antiretroviral treatment.

Biological Mechanisms

There have been a number of reviews assessing the literature on the biological mechanisms of HIV on fertility for females[81] and males[81, 82].

HIV in women could affect their fecundity in a number of ways, due to weight loss and illness caused by AIDS. Kushner and Lewis highlight literature showing lengthened anovulation and amenorrhea, however they state that once adjusting for other factors many studies have found that there is no longer an association[81]. Other studies have looked at differences in the onset of menopause by HIV status, reviews of which in 2007[83] and 2013[84] both found that the literature was conflicting and that it was not possible to distinguish the contribution of HIV to earlier menopause from other risk factors such as smoking, drug use and ethnicity.

HIV positive women are more likely to be infected with another sexually transmitted infection which may also have an impact on fertility. Infections such as Gonorrhoea and Chlamydia which cause tubal blockage can decrease fecundity and if scarring occurs they may cause secondary sterility[85].

A previous meta-analysis by Brocklehurst et al in 1998 found that HIV positive women are more likely to suffer miscarriages and still births, compared with HIV negative women[86]. This was recently updated with a systematic review and meta-analysis by Wedi et al[87] who looked at perinatal outcomes associated with maternal HIV infection in ART naïve women. Wedi criticised the inclusion of some abstracts and poor quality studies in Brocklehurst et al. Wedi et al found that HIV infection in women was associated with stillbirth with a risk ratio of 1.67 (95%CI 1.05-2.66) looking at two studies [88, 89] but found only one study on miscarriage from the USA that found no significant difference in miscarriage between HIV positive and HIV negative women [90]. Higher rates of stillbirths may be due to HIV infection itself or to co-infection with another sexually transmitted infection such as Syphilis[91] which is more prevalent in HIV positive women than HIV negative women due to similar risk factors. There is conflicting evidence on the effect of ART on birth outcomes and very little on miscarriage and stillbirth alone[92, 93]. Some of these differences may be due to different ART regimes, with one study reporting variation in birth outcomes by ART regime, although all outcomes remained less favourable than those of HIV negative women[94].

Male fertility had also been reported to be affected by HIV, with lower semen quality[95-97]. Some studies looked at the association between CD4 count and semen quality and found some parameters to be positively correlated indicating that impairment increases with disease progression[97-99]. There have been conflicting reports on the impact of ART on semen quality[100-103], and the impact may depend on the drug regime[104]. Pilatz at al[101]

found that the semen quality of HIV positive men under stable antiretroviral therapy in an outpatient clinic in Germany was impaired for 25% of their prospective cohort of patients without HIV co-infections when comparing to the WHO 2010 reference values, data that represents distributions of semen characteristics of fertile men for use to evaluate a patient's semen quality and prospect for fertility [105].

Behavioural Mechanisms

Behavioural mechanisms impacting on fertility can occur with or without an individual's knowledge of their HIV status. Prior to the roll out of ART in sub Saharan Africa knowledge of HIV status was rare although even without a test result suspicions of HIV infection due to bouts of ill health or the ill health or death of a partner could impact on behaviour.

Relationship patterns differ between HIV positive and HIV negative women with increased widowhood and marital dissolution in HIV positive women with low rates of remarriage[106, 107] therefore decreasing their chances to have more children. Sexual activity within and outside stable relationships may decline due to illness[108] or, if HIV status is known, a desire not to transmit HIV. If a woman does not know her status but knows or is suspicious of her partner's HIV status, she may try to prevent being infected either through less sexual activity or through use of condoms. If the individual's HIV status is known or suspected within a community, they may also have less access to sexual partners.

Fertility intentions vary by HIV status with many studies reporting HIV positive women less likely to want to have more children compared to HIV negative women[109-114], with this difference increasing with age[114]. However most of these studies do not follow up after recording pregnancies or births to see if this translates into lower fertility rates. Taulo et al[113] found that there was no difference in future pregnancy rates even though there was a lower desire for more children amongst HIV positive women; however, they state that this could be due to the short follow up time in their study. Answers to questions on intentions are subject to social desirability and it is possible that HIV positive women will report intending not to have another child as they feel like that is what they should say. Also there is ambiguity to the meanings of desire and intention; someone who desires a child may not intend to have one and vice versa[115]. With increasing availability of ART, many studies have looked at how this changes fertility intentions among HIV positive women, giving rise to conflicting evidence. Some report after adjusting for socio-demographic factors, women on ART having higher childbearing intentions than those not on ART[116, 117]; however this does not necessarily translate into an increase in fertility[116]. Other studies reported no change[114, 118]. Many of these studies were carried

out when ART coverage was still fairly low, therefore it is likely that they are influenced by the selection biases in the women who are on ART even when controlling for socio-demographic factors and restricting to ever pregnant, sexually active women.

2.5.3 Duration of infection

A number of studies in sub Saharan Africa have looked at disease progression in relation to fertility. A case–control study in Uganda found that high viral load was associated with reduced rates of pregnancy and a reduction in live births[119], even in women who were sexually active and not using contraception. A clinical cohort found that fertility was reduced from the earliest stage of HIV infection with a large reduction in fertility following progression to AIDS[108] – this finding was adjusted for sexual activity but not for contraceptive use. A clinical cohort study in Tanzania also found reduced fertility related to clinical stage of HIV[120] adjusting for social and demographic characteristics. A multisite HIV care and treatment programme analysis showed a strong association between disease progression and a reduction in the incidence of pregnancy[121].

Increased subfertility by duration of infection at the population level could be explained by both biological and behavioural factors. Biological explanatory factors include markers of disease progression in the woman, such as increased viral load or decreased CD4 cell count. Explanatory factors relating to their partners could include reduced semen quality of HIV-positive partners increasing with time since their infection[95, 96, 101], and increased illness could impact on their ability to maintain normal levels of sexual activity. In terms of behaviour, HIV-positive women are more likely to be widowed[106, 107, 122] due to having had an HIV-positive partner. Although voluntary testing and counselling was rare prior to ART introduction, suspicion of HIV status or illness in a partner with HIV may reduce the desire for more pregnancies[115], which may be more obvious at longer durations of infection and it may also increase divorce or separation, and decrease remarriage rates[106, 107].

3 Net survival of perinatally and postnatally HIV-infected children

To address the first objective of the PhD: to describe different patterns of Paediatric Survival from HIV by timing of HIV infection; an analysis of a pooled dataset of clinical trials and cohort studies that provided information on the HIV status of children from birth with accurate estimates of the timing of HIV infection was conducted and published in the International Journal of Epidemiology:

Marston M, Becquet R, Zaba B, et al. *Net survival of perinatally and postnatally HIV-infected children: a pooled analysis of individual data from sub-Saharan Africa*. Int J Epidemiology. Apr 2011;40(2):385-396.

Previous estimates of Paediatric Survival with HIV have relied on direct data from fairly small cohort studies where the HIV status of the child at birth was known along with indirect data from larger cohort studies where the HIV status of the mother was known but not that of the child. Survival estimates of infants and children with HIV grouped all positive children together regardless of whether they were infected in utero, intrapartum or during breastfeeding. More data have become available, mainly from control arms of clinical trials looking at mother to child transmission, where not only is the HIV status of the child known, but also the timing of HIV transmission. Using these data it was possible to improve estimates of paediatric survival with HIV by timing of infection, which improves estimates of the prevalence of paediatric HIV. This work is presented in section 3.1. After the publication of this work, and following discussions with the UNAIDS reference group on estimates, modelling and projections it was agreed that a finer break down of survival patterns by timing of infection was needed. This additional work was published in:

Stover, J., T. Brown, and M. Marston, *Updates to the Spectrum/Estimation and Projection Package (EPP) model to estimate HIV trends for adults and children*. Sex Transm Infect, 2012. 88 Suppl 2: p. i11-6.

The relevant extract from this paper (authored by the candidate) is presented in section 3.2. Finally a further analysis was done to test the assumptions underlying the work on paediatric survival from HIV presented in sections 3.1 and 3.2 and the implications of these assumptions on estimates of paediatric HIV prevalence. This was prepared by the candidate as a report for UNAIDS and is presented in section 3.3.

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

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SECTION A – Student Details

Student	Camilla Marston
Principal Supervisor	Basia Zaba
Thesis Title	Demographic Determinants of Paediatric HIV in Generalised HIV epidemics

If the Research Paper has previously been published please complete Section B, If not please complete Section C

SECTION B

Where was the work published?	The International Journal of Epidemiology		
When was the work published?	April 2011		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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SECTION C – Prepared for publication, but not yet published – *N/A*

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)	The idea for this work came from the UNAIDS Child survival group which I was member of. Data was provided by the university of Bordeaux. I designed the analysis plan, prepared the data for the analysis, did the analysis and wrote the paper with co authors editing and commenting on drafts.

Student Signature: [redacted] **Date:** 27/03/18

Supervisor Signature: [redacted] **Date:** 27.03.2018

3.1 PAPER A: Net survival of perinatally and postnatally HIV-infected children: A pooled analysis of individual data from sub-Saharan Africa

Milly Marston [1], Renaud Becquet [2,3], Basia Zaba [1], Lawrence H. Moulton [4], Glenda Gray [5], Hoosen Coovadia [6], Max. Essex [7], Didier K. Ekouevi [2,3,8], Debra Jackson [9], Anna Coutsoudis [10], Charles Kilewo [11], Valériane Leroy [12], Stefan Wiktor [13], Ruth Nduati [14], Philippe Msellati [15], François Dabis [2,3], Marie-Louise Newell [16,17], Peter D Ghys [18]

1 London School of Hygiene and Tropical Medicine, London, United Kingdom

2 INSERM, unité 897, Centre de recherche "Epidémiologie et Biostatistique", Bordeaux, France

3 Institut de Santé Publique Epidémiologie Développement (ISPED), Université Victor Segalen Bordeaux 2, Bordeaux, France

4 ZVITAMBO trial, Zimbabwe; Johns Hopkins Bloomberg School of Public Health

5 Petra trial, Tanzania, South Africa and Uganda; Perinatal HIV Research Unit, University of Witwatersrand

6 VTS cohort, South Africa, Universty of KwaZulu-Natal, University of Witwatersrand, South Africa

7 Mashi trial, Botswana; Botswana-Harvard AIDS Institute and Harvard School of Health AIDS Initiative

8 Ditrame Plus cohort, Côte d'Ivoire

9 Good Start cohort, South Africa; University of the Western Cape, South Africa

10 Vitamin A trial, South Africa

11 Mitra Plus cohort, Tanzania

12 ANRSa trial, Côte d'Ivoire & Burkina Faso

13 Retro-Ci trial, Côte d'Ivoire; Global AIDS Program, Centers for Disease Control and Prevention, Atlana USA.

14 Nairobi trial, Kenya

15 ANRSb trial, Côte d'Ivoire & Burkina Faso, UMR 145 IRD/Universite de Montpellier 1, montpeillier, France.

16 Africa Centre for Health and Population Studies, University of KwaZulu-Natal, Somkhele, South Africa

17 Centre for Paediatric Epidemiology and Biostatistics, Institute of Child Health, University College London, London, United Kingdom

18 UNAIDS, Joint United Nations Programme on HIV/AIDS, Geneva, Switzerland

3.1.1 Summary

Background: Previously HIV epidemic models have used a double Weibull curve to represent high initial and late mortality of HIV-infected children, without specifically distinguishing timing of infection (peri- or postnatally). With more data on timing of infection, which may be associated with disease progression, a separate representation of children infected early and late was proposed.

Methods: Paediatric survival post-HIV infection without antiretroviral treatment was calculated using pooled data from 12 studies with known timing of HIV infection. Children were grouped into perinatally or postnatally infected. Net mortality was calculated using cause-deleted life tables to give survival as if HIV was the only competing cause of death. To extend the curve beyond the available data children surviving beyond 2.5 years post infection were assumed to have the same survival as young adults. Double Weibull curves were fitted to both extended survival curves to represent survival of children infected perinatally or through breastfeeding.

Results: Those children infected perinatally had a much higher risk of dying than those infected through breastfeeding, even allowing for background mortality. The final fitted double Weibul curves gave 75% survival at five months after infection for perinatally-infected, and 1.1 years for postnatally-infected children. An estimated 25% of the early infected children would still be alive at 10.6 years compared to 16.9 years for those infected through breastfeeding.

Conclusions: The increase in available data has enabled separation of child mortality patterns by timing of infection allowing improvement and more flexibility in modelling of paediatric HIV infection and survival.

Key messages:

1) Children infected perinatally with HIV have a much higher risk of dying than those infected through breastfeeding

2) Differences seen in the survival of children infected perinatally with HIV and through breastfeeding cannot be explained by differences in background mortality, which is much higher in the neonatal period.

3) The use of two separate curves to describe the net survival from perinatal and breastfeeding HIV infection improves the realism of child survival when modeling the HIV epidemic.

3.1.2 Introduction

Until recently, survival of HIV infected children in the absence of causes of death unrelated to HIV has been modelled using a double Weibull curve which represents the mortality experienced by HIV-infected children irrespective of their time of infection from birth [6, 123]. The double Weibull curve has been used as it is one of the few functional forms that can describe high initial mortality along with rising mortality at older ages. However, in a pooled analysis, Newell et al showed that mortality in the two years following infection was lower for children who acquired HIV via breastfeeding (postnatal infection) than those with perinatal infection [51]. To improve modelling of the HIV epidemic a separate representation of children infected early and late was thus deemed appropriate. Indeed, new data have become available from clinical trials which provide information on HIV status of children from birth and allow an accurate estimation of age at infection and sufficient follow up time to allow assessment of the risk of dying, this data is in accordance with the differences shown by Newell et al [12].

It has been suggested that the impact of age at infection may be due to background mortality patterns [5]. Removing background mortality did have a slightly larger effect in those infected at older ages where background mortality is higher but it did not explain the differences in survival from age at infection in adults. However, such effects are more extreme in childhood where the differences between neonatal and post-neonatal mortality is much greater than the difference in mortality rates in adults within one month or 1-12 months after infection. Therefore some of the differences in time since infection shown by Newell el al [51] might be attributable to background mortality in the neonatal period.

This paper investigates the effect of background mortality on survival post-infection of children by time of infection for up to 2.5 years following acquisition of infection. In order to bridge the gap in the data between children and young adults, survival curves are further extended beyond the available data by using survival of young adults and model curves fitted to the net survival of each of these groups for use in HIV modelling.

3.1.3 Methods

Data

Data from 12 clinical trials and cohort studies in Southern, Eastern and Western Africa (Table 3.1) were included in a pooled analysis where all the data was combined into the same dataset. Interventions in these studies were various peripartum antiretroviral prophylactic regimens [14-22], vitamin A [23], and birth canal cleansing [24]. These trials represent the vast majority of the clinical research studies performed since the mid 90's on the African continent on prevention of mother-to-child transmission of HIV. Most study sites (n = 8) were situated in reference hospitals of capital or large cities; three studies were based in antenatal care clinics, or a mixture of the two, and one in a mixture of both urban and rural settings. The ZVITAMBO accounted for 51% of the person years of exposure for HIV infected children. The median follow up time ranged from 300 to 1096 days, and studies tested at regular intervals in the first 18 months. Some studies explicitly stated that they provided free medical treatment at time of follow-up and in between follow-up visits.

Inclusion Criteria

Data collected in time periods when antiretroviral treatment was widely available cannot be used in the analysis as it would not represent the survival from HIV per se. However, it would be incorrect to censor children at time of treatment initiation as this would mean we were selecting out those who were going to die thereby biasing the results to give much lower mortality. Antiretroviral treatment became available in the MASHI trial on the 1st October 2002 so follow up was right censored at this point. Antiretroviral Treatment was not available during the time of the other trials.

Table 3.1: Summary of trials in the analysis with ART interventions for individual site analysis, numbers are for children of HIV positive mothers, number of deaths are in brackets.

Trial	Arm	Mother PMTCT	Child PMTCT*	Total	Infection Status				
					Uninfected	Early	Late	Unknown	HIV Status Unknown/ Indeterminant
ANRS 049a [15]	ANRSA_N2	None	None	78 (22)	55 (4)	15 (14)	2 (1)	5 (2)	1 (1)
	ANRSA_N3	None	None	123 (30)	79 (4)	11 (9)	7 (2)	11 (6)	15 (9)
	ANRSA_T2	ZDV	None	77 (11)	59 (3)	6 (3)	5 (0)	3 (3)	4 (2)
	ANRSA_T3	ZDV	None	123 (25)	88 (3)	6 (6)	8 (4)	10 (5)	11 (7)
ANRS 049b [24]	ANRSB_N	None	None	51 (11)	36 (2)	. (.)	2 (1)	4 (3)	9 (5)
	ANRSB_T1	None	None	53 (15)	35 (2)	1 (1)	3 (1)	4 (4)	10 (7)
ANRS 12010 Ditrame Plus [21]	Diatrame Plus	ZDV+NVP or CBV+NVP	ZDV+NVP	747 (79)	689 (54)	40 (20)	18(5)	0 (0)	0 (0)
Good Start [17]	Paarl	NVP	sdNVP	149 (7)	107 (0)	12 (4)	3 (0)	6 (2)	21 (1)
	Rietvlei	NVP	sdNVP	192 (34)	80 (0)	23 (13)	8 (0)	11 (1)	70 (20)
	Umlazi	NVP	sdNVP	324 (26)	184 (0)	33 (10)	12 (0)	14 (3)	81 (13)
MASHI [20]	MASHI_0	CBV+NVP, ZDV, ZDV+sdNVP	ZDV + sdNVP	600 (42)	551 (30)	26 (9)	11 (3)	4 (0)	8 (0)
	MASHI_1	CBV+NVP, ZDV, ZDV+sdN	ZDV + sdNVP	600 (43)	541 (33)	30 (8)	16 (2)	0 (0)	13 (0)
MB [124]	MB_N	None	None	197 (45)	132 (15)	27 (16)	19 (2)	13 (7)	6 (5)
MITRA Plus [18]	MITRA Plus	ZDV+3TC+NVP	ZDV + 3TC	441 (35)	415 (26)	16 (6)	8 (2)	2 (1)	0(0)
PETRA [19]	PETRA_A	ZDV/3TC	ZDV/3TC	366 (37)	301 (12)	11 (4)	28 (10)	13 (6)	13 (5)
	PETRA_B	ZDV/3TC	ZDV/3TC	371 (52)	294 (21)	24 (8)	21 (9)	14 (8)	18 (6)
	PETRA_C	ZDV/3TC	None	368 (47)	286 (15)	37 (14)	20 (4)	10 (5)	15 (9)
	PETRA_D	None	None	353 (48)	264 (11)	38 (17)	18 (2)	19 (11)	14 (7)
RETRO [22]	RETRO_N	None	None	133 (29)	86 (4)	26 (11)	10 (4)	2 (1)	9 (9)
	RETRO_T1	ZDV	None	128 (10)	96 (1)	15 (8)	13 (0)	2 (0)	2 (1)
VITA [23]	VITA_N	None	None	325 (23)	239 (5)	58 (14)	8 (1)	4 (0)	16 (3)
	VITA_T1	None	None	335 (26)	245 (6)	53 (15)	14 (2)	6 (1)	17 (2)
VTS [14]	VTS	NVP	sdNVP	1422 (198)	979 (40)	127 (77)	70 (20)	52 (29)	194 (32)
Zvitambo [16]	Zvitambo	None	None	4495 (881)	3115 (251)	727 (427)	257 (46)	355 (152)	41 (5)

*up to 7 days postpartum ART antitetroviral therapy CBV = Combivir (ZDV + 3TC) NVP = nevirapine sdNVP = single-dose NVP ZDV = zidovudine

Mortality analysis

Date of infection was taken to be the midpoint between the last negative test and the first positive HIV test (antibody or PCR depending on age). Where there was no negative test for those infected early, the midpoint between birth and first positive test was taken. A sensitivity analysis was undertaken to assess how results varied according to the date imputed.

Children were grouped by infection status (infected and uninfected) and time of infection (perinatal, breastfeeding or postnatal period, status unknown) as defined by Newell et al[51]. Those with unknown timing of infection were not used in the analysis beyond looking at their overall mortality compared to those with known timing of infection. Kaplan-Meier analysis was used to calculate survival curves. Uninfected children of positive mothers were used to estimate mortality from non-HIV related causes when calculating net survival.

Prior to decisions on pooling data the effect on the mortality hazards of the child receiving antiretroviral drugs in the first seven days of life for PMTCT post-exposure prophylaxis and possible regional differences a piece-wise Weibull model was constructed adjusting for duration of follow-up (to allow for changing compostion due to differing follow up times across studies) and study of origin to assess whether data should be excluded or analysed separately.

Calculating net survival

Methods to calculate paediatric survival have been described in detail elsewhere[6]. In brief the net survival probability, $l_A(x)$, if HIV-related mortality is the only operative cause of death, can be calculated from the proportions of HIV-infected children surviving to age x, $l_{O+A}(x)$, and the proportion of uninfected children surviving to age x, $l_O(x)$, using the usual relationship for cause deleted life tables:

$$l_A(x) = \frac{l_{O+A}(x)}{l_O(x)}$$

To make the distribution of the HIV-negative children similar to that of the HIV-infected children, the HIV-negative ones were weighted so that their distribution by entry into observation, study group, and timing of start of risk exposure matched those of the HIV-infected children.

Newell et al showed that infected infants experience different rates of progression through the disease stages leading to AIDS and death, with those who acquired the infection in utero experiencing a more rapid progression than those acquiring the infection around the time of delivery or during breastfeeding.

As noted, the double Weibull provides a good functional representation of paediatric survival curve as it allows for initial high mortality followed by rising mortality at later time points [6, 38], taking the form:

$$l_A(x) = \pi \cdot \exp\left\{-\left[\lambda_1 \cdot x\right]^{\mu_1}\right\} + (1-\pi) \cdot \exp\left\{-\left[\lambda_2 \cdot x\right]^{\mu_2}\right\}$$

By studying the empirical curves depicting net survival by time since infection we produce two functional representations; one for those with perinatal infection and one for those with infection through breastfeeding.

External constraints were introduced to extend the curve beyond the follow-up time provided by the studies, and these data were used until 20 subjects were remaining, which was deemed as a point at which the results could not be seen as reliable due to small numbers. Recently a pooled study has been published[5, 7] showing survival post-infection in adults by age of infection using data from low and middle-income countries. This showed a more favourable survival for those adults infected at a younger age, and similar results were found in studies from higher income-countries in the pre-ART era[125]. A reasonable assumption we could thus consider is that the net HIV mortality rates of infected children at long durations of infection are no higher than the rates experienced by HIV-infected young adults below age 25. The net survival of adults from HIV is described by the single Weibull curve:

$$l_A(x) = \exp\left[-\lambda \cdot x^{\mu}\right]$$

3.1.4 Results

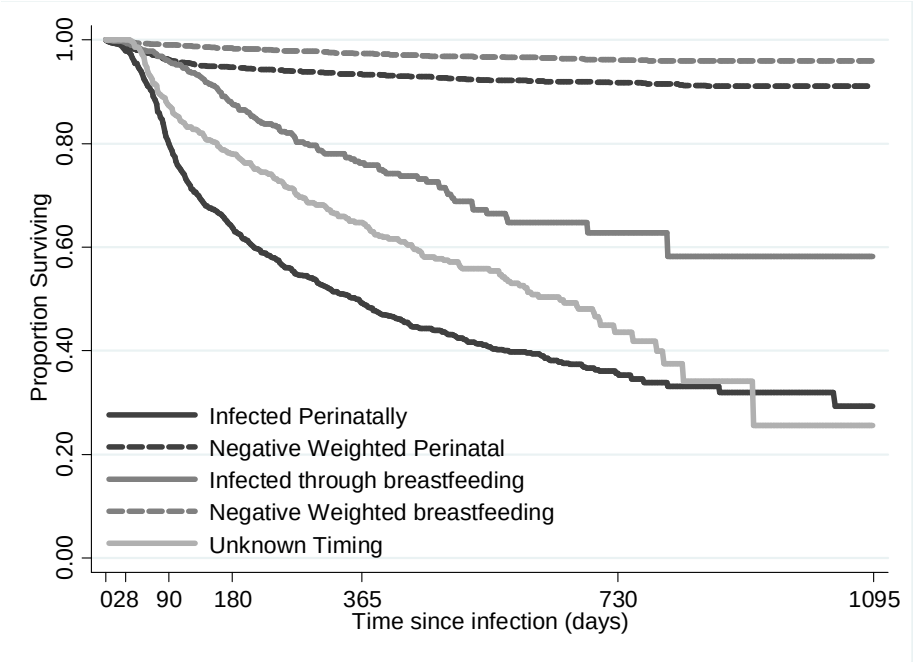
A total of 1930 infected children with known timing of infection were included in the analysis contributing 1576 person years of follow-up. The median age at last follow-up or death was 1.0 years (range: fraction of a day to 4.39 years) for infected children and 1.49 years (range: fraction of a day to 11.39 years) for uninfected children of HIV-positive mothers. Of the 1930 infected children, timing of infection was considered early for 1340, late for 590 and unknown for 615 (Table 3.2).

Table 3.2: Follow up and outcome by child's HIV infection status and timing of infection

	Number at start	Total Person-years	Deaths	Follow Up in years: Median	Follow Up in years: Maximum
Infected					
Perinatally	1340	1095.38	699	0.64	4.39
Through breastfeeding	590	480.66	120	0.65	4.17
Timing unknown	615	590.34	254	0.86	3.77
Uninfected					
Mother positive	8384	11457.84	493	1.49	11.39
Mother negative	1584	2633.18	51	1.83	4.48
Unknown infection Status					
Mother positive	9484	11296.43	250	1.02	3.28

Figure 3.1 shows the cumulative survival of these children by timing of infection. Median age of survival was 348 days for those infected perinatally, but was not reached by 2.0 years when only 20 subjects remained for those infected through breastfeeding, therefore was unable to be calculated. The survival of children for which the mode of infection was unknown was intermediate, suggesting that this category was made up of children infected perinatally and through breastfeeding. The mortality hazards of those children infected through breastfeeding was 0.39 (95% CI 0.32-0.46), lower than for those infected perinatally. The mortality data of uninfected children which are used to compute non-HIV related mortality risks for those infected perinatally, showed, as expected, higher mortality and worse survival than that of the uninfected children used to compute the equivalent risks for those infected through breastfeeding. Mortality of uninfected children included in these trials was very low with an overall infant mortality rate of 4 per 1000, i.e. lower than in most sub-Saharan African populations generally. Changing the imputed infection date for early infection to be birth for children who only had a positive, and no negative, test had almost no effect on the results. This is also true of the later infected children, assuming the date of infection to be the earliest possible date (last negative test) or the latest possible date (first positive test) date.

Figure 3.1: Survival from time of infection by timing of HIV infection and weighted survival of uninfected children.



Differentials by region and peripartum antiretroviral treatment

Differences in survival by region and whether the child received peripartum antiretroviral intervention in the first seven days of life were assessed using piece-wise Weibull models, these were adjusted for study. After adjusting for study, no mortality differences were seen across the regions or between children who received peri-partum preventative antiretroviral treatment in the first seven days of life (Table 3.3).

Table 3.3: Hazard ratios (HR) of survival for HIV Infection perinatally and through breastfeeding

	Perinatal Infection				Infection through breastfeeding			
	Adjusted for duration of follow-up		Adjusted for duration of follow-up and Study		Adjusted for duration of follow-up		Adjusted for duration of follow-up and Study	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Region								
Eastern Africa	1		1		1		1	
Southern Africa	1.60	(1.19-2.16)**	1.54	(0.85-2.82)	0.69	(0.44-1.08)	0.59	(0.20-1.73)
Western Africa	1.39	(0.96-2.01)	1.67	(0.21-13.03)	0.87	(0.44-1.74)	2.19	(0.37-12.92)
Child PMTCT ARV								
No	1		1		1		1	
Yes	1.22	(1.00-1.49)*	1.20	(0.62-2.34)	0.69	(0.47-1.00)*	0.41	(0.16-1.02)

*p<0.05

**p<0.01

ARV antiretroviral prophylaxis

CI confidence interval

Timing of late infection

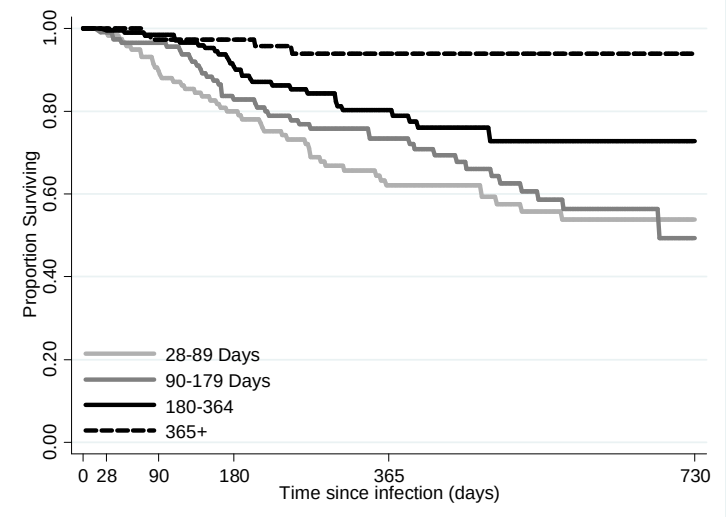
The late infection group was split further into four groups. A Weibull piece-wise model adjusting for duration of follow up and trial showed a decrease in the gross mortality the later the child is infected. Figure 3.2 shows the increasing improvement in survival with later age at infection.

Table 3.4: Hazard Ratios (HR) for those with late HIV infection

	Adjusted for duration of follow-up and trial	
	HR	**95% CI**
Region		
Eastern Africa	1	
Southern Africa	0.57	(0.2-1.67)
Western Africa	2.48	(0.42-14.78)
Peripartum ARV		
No	1	
Yes	0.4	(0.16-1.01)
Age at infection		
28- 90 Days	1	
90-180 Days	0.81	(0.52-1.27)
180-365 Days	0.53	(0.33-0.85)**
365+	0.16	(0.06-0.42)***

**p<0.01
***p<0.001
ARV antiretroviral prophylaxis

Figure 3.2: Survival from time of infection by age at infection for those infected through breastfeeding



Net Survival

Removing all other causes of mortality to give survival as if HIV was the only cause of death only slightly raised survival for both those infected perinatally or through breastfeeding (Figure 3.3). The resulting net survival at one year post-infection for those infected perinatally was 52% and for those infected through breastfeeding 78% (Table 3.5).

Figure 3.3: Net and gross survival from time since infection for infection perinatally and through breastfeeding

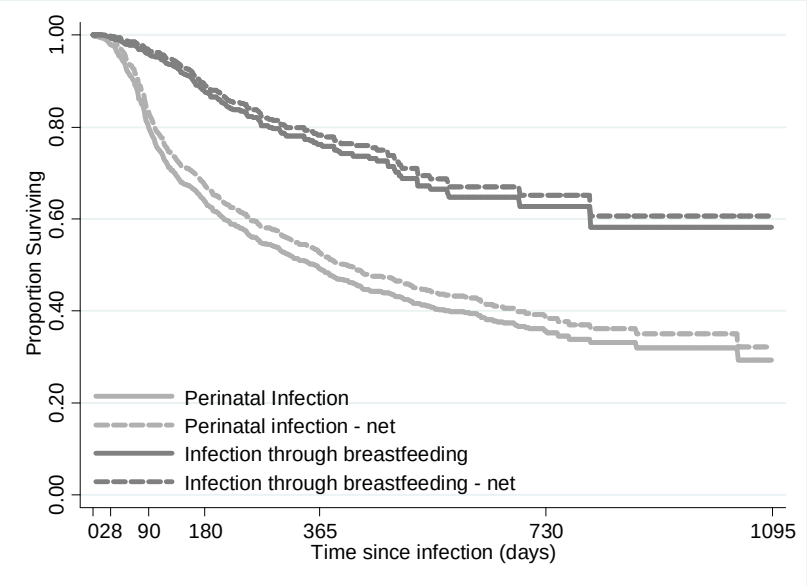


Table 3.5: Probability of survival for HIV infected children and uninfected children to time x by timing of infection.

	Time x							
	1 day	**7 day**	**28 day**	**90 days**	**180 days**	**1 year**	**2 years**	**2.5 years**
Perinatal Infection								
Uninfected (Weighted)	1	1	0.99	0.96	0.95	0.93	0.92	0.91
Infected	1	1	0.98	0.80	0.64	0.49	0.35	0.32
Net Survival	1	1	0.99	0.83	0.67	0.52	0.39	0.35
Net Weibull	0.99	0.96	0.9	0.79	0.69	0.54	0.37	0.32
Infection through breastfeeding								
Uninfected (Weighted)	1	1	1	0.99	0.98	0.97	0.96	0.96
Infected	1	1	0.99	0.96	0.88	0.76	0.62	0.58
Net Survival	1	1	1	0.97	0.89	0.78	0.64	0.60
Net Weibull	1	0.99	0.98	0.94	0.89	0.79	0.63	0.56

Extending the observed net curve

Weibull curves were fitted to the net survival of adults post-infection in East Africa by age at infection which gave a median time of survival of 20 years for 15-24 year olds (λ=0.002 μ=2.195) decreasing to 14 years for ages 35-44 (λ=0.025 μ=1.532) [5]. Assuming that children who survive for 2.5 years following perinatal infection and two years following infection through breastfeeding (the maximum follow up time with greater than 20 subjects remaining) do not have a worse survival than young adults at the equivalent time post-infection the net curve was extended using the probabilities of dying between years since infection x and x+1 for adults at the same point in time. Double Weibull curves were then fitted to the extended net survival (Figure 3.4).

Figure 3.4: Double Weibull curves fitted to extended net survival functions for early and late HIV infection. Curves were fitted using the net probability of survival of adults age 15-24 after 2.5 years of follow up for perinatal infection and 2.0 years for those infected through breastfeeding.

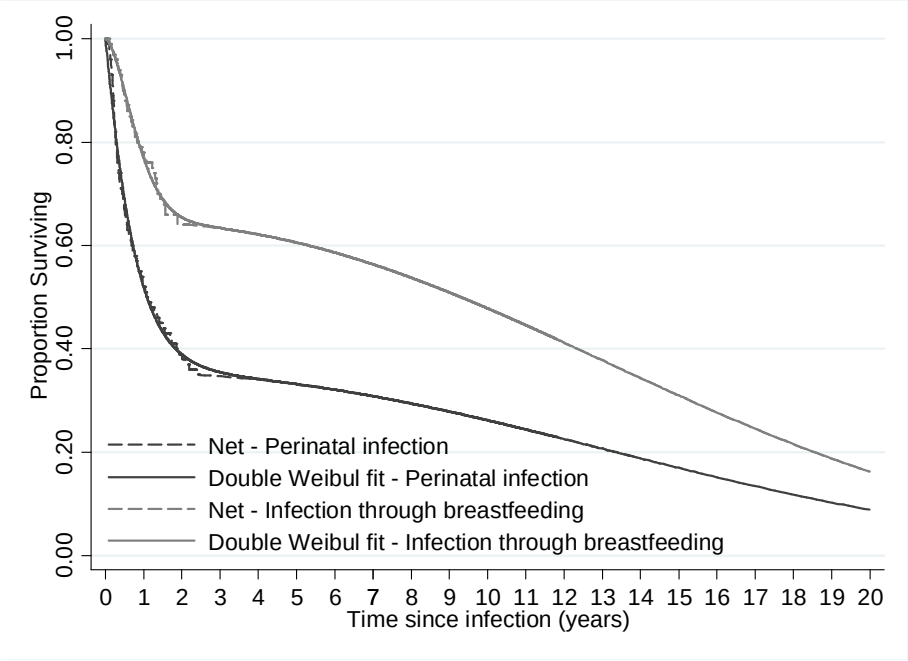


Table 3.6 gives a summary of the curve fits to the extended net survival. The final Double Weibull curves give a median survival at 1.1 years for perinatal infection and 9.4 years for infection through breastfeeding. It predicts a survival of 33% at five years from time of infection for those infected perinatally and 60% for those infected through breastfeeding. At 20 years this is 9% and 16%, respectively.

Table 3.6: Summary of curve fits to the extended net survival (using adult survival) for those infected with HIV perinatally and through breastfeeding from time of infection

Time of Infection	Parameters					Percentiles			Net mortality risks (per thousand)	
	π	λ_1	μ_1	λ_2	μ_2	75%	50%	25%	1q0	5q0
Perinatal	0.65	1.34	1.06	0.06	2.19	0.38	1.09	10.61	481	626
Breastfeeding	0.35	1.03	1.66	0.06	2.19	1.09	9.24	16.91	232	396

3.1.5 Discussion

The current analysis produced separate survival schedules for children infected perinatally and those infected through breastfeeding, with a median survival of 1.1 years and 9.4 years, respectively. The use of these updated schedules in mathematical modelling of the HIV epidemic among children is expected to constitute a major improvement over the past approach with a unique survival schedule applied to all children. This has extended work done by Newell et al suggesting a possible mortality difference by timing of vertical infection by adding new data that has become available and extending the survival curves using the net survival of young adults from HIV. The differences in survival are substantial at five years after infection, with only 33% of those infected perinatally surviving compared to 60% of those infected through breastfeeding. At 20 years after infection the difference is smaller at 16% compared to 9%, this is mainly because in the absence of evidence to suggest that either one should be higher we have applied the same mortality schedule to both groups after 2.5 years.

The analysis further shows that there are also differences in survival within those who are infected through breastfeeding with a more favourable survival the later the time of infection, these differences still persisted after taking into account background mortality.

We found no difference between the survival of those HIV-infected infants treated and not treated with peripartum antiretrovirals to prevent mother-to-child transmission and therefore included these children in the analysis. We do not question the effectiveness of PMTCT interventions to reduce the risk of transmission of HIV. However, our data suggest that where an infant acquires infection in spite of PMTCT exposure, mortality levels are similar to those infants infected without exposure to PMTCT. Regional differences in survival by timing of infection were not seen once heterogeneity between trials was accounted for, therefore with this current data we pooled data from all regions into the same dataset to generate one curve to represent all children. These data are only from sub-Saharan Africa with 51% of the person years of exposure coming from the ZVITAMBO trial in Zimbabwe[16]. Regional differentials between sub-Saharan Africa and

Thailand were seen in adults [7] therefore adding data from other regions would help confirm whether such differences exist for the mortality of HIV positive children, although we acknowledge that fewer HIV-exposed children are breastfed in Asia or South America than in sub-Saharan Africa.

Although breastfeeding is an important factor in child survival [126] we have not excluded those who were never breastfed. Without knowing the breastfeeding trends in the general population we cannot tell how representative this sample is. Even if we had excluded this 12% from this analysis the impact on the overall highly unfavourable survival curve would be minimal.

Background mortality had very little effect on the differences in survival post-infection for both early and late infection. All the data come from clinical trials or research studies within which background mortality, taken from the uninfected children of infected mothers, apparently was much lower than in the corresponding communities. The overall HIV-negative infant mortality rate in the current analysis was 4 per 1000. The Demographic and Health Surveys [127] give infant mortality rates in the 10 years preceding each survey. Estimates for urban areas ranged from 41 per 1000 in South Africa 2003 to 72 per 1000 in Tanzania in 2004-05, all indicating a much higher mortality in the general population in many of the places the trials took place. The difference is evident even if we allow for the fact that the DHS figure includes the mortality of HIV-infected children and that the studies mainly took place at the later end of these periods (i.e. if infant mortality decreases over time we would expect a lower mortality rate in the trial). It strongly suggests that the mortality of uninfected children involved in the trials is lower than that in the general population, possibly due to increased access to health care services due to study participation therefore in the general population one might expect to see a larger difference between net and gross mortality.

We have used the mortality of HIV-negative children of positive mothers as a reference in this analysis. Therefore the resulting net mortality does not take into account the added negative effect of having an HIV-positive mother. There is evidence to suggest that there is a difference in the mortality of HIV-negative children born to HIV-positive mothers compared to HIV-negative mothers. The Rakai study [128] found that overall, for those under two years of age, $C(x<2) = 1.3$ where $C(x)$ is the ratio between uninfected children of infected mothers compared to those of uninfected mothers at age x, but there was some evidence of variation of $C(x)$ with age, with $C(x<1) = 1.1$, and $C(1<x<2) = 1.8$. A study in Kampala [129] showed a similar pattern with the same overall value for $C(x<2) = 1.3$ and a similar increase with age on subdivision of the interval.

The model curves beyond two and a half years rely on what is known about adult survival and assume that children are like younger adults with respect to mortality patterns. Further investigation is needed about whether this is a valid assumption especially for children infected early. The inclusion of more data from other trials might increase our knowledge of net child survival beyond two and a half years and give a more accurate picture and more knowledge on how child survival compares to young adult survival. However this data is currently scarce and with the increase in antiretroviral treatment in children it is unlikely that any further data will become available. It is possible that data on time to treatment need and time to death from treatment by timing of infection might help inform us further.

The aim of this analysis was to improve modelling of the HIV epidemic by providing a separate representation of children infected perinatally and through breastfeeding. This analysis is an update on work done previously[6, 123] and has used more detailed data from studies that can provide the timing of HIV infection of a child.

The increase in data available and the construction of separate survival curves for children infected perinatally and through breastfeeding allows for a clear improvement in the modelling of the HIV epidemic and is being used in the UNAIDS spectrum package to project the HIV epidemic [130].

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Composition of the UNAIDS Child survival group

- ***Coordination***

Renaud Becquet, François Dabis (INSERM, Unit 897, Bordeaux, France); Milly Marston, Basia Zaba (London School of Hygiene and Tropical Medicine, London, UK); Marie-Louise Newell (Africa Centre for Health and Population Studies, University of KwaZulu Natal, South Africa); Peter Ghys (UNAIDS, Epidemiology and Analysis Division, Geneva, Switzerland).

- ***Data management***

Sophie Karcher, Renaud Becquet (INSERM, Unit 897, Bordeaux, France).

- ***Representatives of the participating studies***

Larry Moulton (Zvitambo trial, Zimbabwe); Anna Coutsoudis (Vitamin A trial, South Africa); Glenda Gray (Petra trial, Tanzania-SA-Uganda); Charles Kilewo (Mitra cohort, Tanzania); Jerry Coovadia (VTS cohort, South Africa); Valériane Leroy (ANRSa trial, Côte d'Ivoire); Max Essex (Mashi trial, Botswana); Stephan Wiktor (Retro-Ci trial, Côte d'Ivoire); Didier Ekouevi (Ditrame Plus cohort, Côte d'Ivoire); Ruth Nduati (Nairobi trial, Kenya); Debra Jackson (Good Start cohort, South Africa); Philippe Msellati (ANRSb trial, Burkina Faso).

- ***Investigators and collaborators of the participating studies***

ANRSa Trial, Côte d'Ivoire

Investigators. François Dabis, Philippe Msellati, Nicolas Meda, Christiane Welffens-Ekra, Bruno You, Olivier Manigart, Valériane Leroy, Arlette Simonon, Michel Cartoux, Patrice Combe, Amadou Ouangré, Rosa Ramon, Odette Ky-Zerbo, Crépin Montcho, Roger Salamon, Christine Rouzioux, Philippe Van de Perre, Laurent Mandelbrot.

Other investigators. L Dequae-Merchadou, R Lassalle (Bordeaux Coordination Unit); A Bazie, A M Cassel Beraud, B Dao, L Gautier-Charpentier, FD Ky, B Nacro, O Sanou, I Sombié, F Tall, S Tiendrebeogo, Y Traore, D Valea, S Yaro (Bobo-Dioulasso Centre); and D Bonnard, R Camara, M Dosso, N Elenga, G Gourvellec, J B Kottan, R Likikouet, V Noba, M Timité, I Viho.

Data and safety monitoring board. J-F Delfraissy, D Costagliola, C Chouquet, B Bazin, P Lepage, B Masquelier, K Toure Coulibaly.

ANRSb Trial, Burkina Faso

Biostatistics: R Lassalle, V Leroy, R Salamon.

Epidemiology:M Cartoux, F Dabis (coordinator of the ANRS 049 trial/DITRAME programme), N Meda (coordinator of Bobo-Dioulasso Center), P Msellati (coordinator of Abidjan Center), R Ramon.

Gynaecology-obstetrics: A Bazié, B Dao, R Likikouet, L Mandelbrot (principal investigator), C Welffens-Ekra (principal investigator).

Microbiology: D Bonard, P Combe, M Dosso, L Gautier-Charpentier, F D Ky, A Ouangré, T Ouassa, O Sanou, F Sylla-Koko, Y Traore, P Van de Perre.

Molecular biology: A M Cassel-Beraud, J B Kottan, OManigart, CMontcho, C Rouzioux, A Simonon, D Valea, B You.

Paediatrics: R Camara, N Elenga, B Nacro, F Tall, M Timité.

Trial monitoring: G Gourvellec, O Ky-Zerbo, V Noba, I Sombié, S Tiendrebeogo, I Viho, S Yaro.

Nairobi Trial, Kenya

Ruth Nduati, Barbra A Richardson, Grace John, Dorothy Mbori-Ngacha, Anthony Mwatha, Jeckoniah Ndinya-Achola, Job Bwayo, Francis E Onyango, Joan Kreiss.

Petra Trial, Tanzania - South Africa - Uganda

Trial management committee

J M A Lange (chair), J Saba (study coordinator), G Gray, J McIntyre, F Mmiro, Ch Ndugwa, J Moodley,

H M Coovadia, D Moodley, Ch Kilewo, A Massawe, P Okong, P Kituuka, H von Briesen, J Goudsmit, G Biberfeld, F Mhalu, K Karlson, M Guliano, S Declich, S Clapp, G Haverkamp, G J Weverling, D Cooper, A Grulich, D Bray, J Perriens. Representatives of People Living with HIV: F Ngobeni, G Baguma, S Kyambadde.

Participating clinical centres

Uganda: Mulago Hospital, Mulago, Kampala (F Mmiro, Ch Ndugwa, P Musoke, C Nakabito, P Bakaki, I Kalyesbula, M Lutajumwa, S Mmiro, R Kato, R Byenkya, S Kabenge, R Mulira, R Bagenda, J Matavu, F Kikonyogo, E Kawuki, B Nkoyoyo, N Matovu, C Mukasa, C Dukar, M Mubiru, D Bagenda, K Khantaway); St Francis Hospital, Nsambya, Kampala (P Okong, P Kituuka, K Kayanja, S Kateera, B Sam, B Sabrina, M Ravera, E Omobono, M Magoni).

Tanzania: Muhimbili General Hospital, Dar es Salaam (Ch Kilewo, A Massawe, F Mhalu, E Urassa, F Kalokola, F Phillip, M Giattas, F Temu, K Kallanga, A Mkumbukwa, E Lugaiya, S Nyoni, S Haule,

E Hilbayuded, N Kavugha, I Kayombo, E Lyamuya, E Mbena, V Msangi, C Lema, H Matimbwa, I Semali, K Karlsson).

South Africa: Chris Hani Baragwanath Hospital, Johannesburg (S Johnson, A Violari, L Connell, G Nelson, J Moetlo, A Makhofola, B Jivkov, F Ngobeni, M Kunene, G Ngakane, G Tshabalala, W Saba,

P Khela, N Radebe); King Edward VII Hospital, Durban (J Moodley, H M Coovadia, D Moodley K Naidoo, M Adhikari, T Moniwa, D Moholo, I Mtshali, C Ngubane, A Mlaba, N Mkhize, C Sibiya,

L Shozi, T Ngubane, V Mkhize, L Madurai, V Gopaul, L Thaver, G Swart, J Thomas).

Trial coordination, central data management and statistical analysis

Switzerland, Geneva, UNAIDS (J Saba, J Perriens); and International Antiviral Therapy Evaluation Center (J M A Lange, G Haverkamp, S Clapp, H Huisman, P Hollak, L Hendriks), and Department of Clinical Epidemiology and Biostatistics (G J Weverling), Academic Medical Centre, Amsterdam, Netherlands.

Laboratories

Germany, Frankfurt: Georg-Speyer-Haus (A de Amorim-Nink, H Klunker, L Kurunci, H von Briesen, A Simon). Sweden, Stockholm: Swedish Institute for Infectious Disease Control and Microbiology and Tumorbiology Center Karolinska Institute (G Biberfeld, K Karlsson, E Olausson Hansson, A Östborn). Netherlands, Amsterdam: Academic Medical Centre–Department of Human Retrovirology (J Goudsmit, S Jurriaans, E de Rooy, M Bakker, N Romp).

Retro-CI Trial, Côte d'Ivoire

Stefan Z Wiktor, Ehounou Ekpini, John M Karon, John Nkengasong, Chantal Maurice, Sibailly T Severin, Thierry H Roels, Moise K Kouassi, Eve M Lackritz, Issa-Malick Coulibaly, Alan E Greenberg

Vitamin A Trial, South Africa

Investigators: Anna Coutsoudis, Kubendran Pillay, Louise Kuhn, Elizabeth Spooner, Wei-Yann Tsai and Hoosen M. Coovadia.

Additional members: Gill Sinclair, Anne Mburu, Nolwandle Mngqundaniso, Kerry Uebel, Ingrid Coetzee, Ken Annamalai, Trevor Doorasamy, Ugene Govender, Juana Willumsen, Nigel Rollins, Jagidesa Moodley and Daya Moodley.

Data Safety and Monitoring Board: Salim Abdool Karim, Eleanor Gouws, Jonathan Levin and Immo Kleinschmidt.

VTS Cohort, South Africa

Study investigators: Ruth Bland, Hoosen Coovadia (principal investigator), Anna Coutsoudis, Marie-Louise Newell, Nigel Rollins.

Steering Committee: Janet Darbyshire (chair), Nono Simelela (South African National Department of Health), Victoria Sithole (Community Advisory Board) and the study investigators.

Data monitoring and Safety Committee: Cathy Wilfert (chair, Elizabeth Glaser Pediatric AIDS foundation), Carl Lombard (statistician, Medical Research Council, South Africa), Ames Dhai (Department of Obstetrics and Gynaecology and the Biomedical Ethics Unit, University of KwaZulu-Natal, South Africa), Francis Crawley (Good Clinical Practice Alliance).

Data management: Cookie Govender, Londiwe Mthethwa and team.

Clinical team: Thembi Blose, Nqobile Mkhwanazi, Dumo Mkwanazi and team.

Field team: Zanele Fakude, Samukelisiwe Dube and team.

Laboratory team: Johannes Viljoen, Natalie Graham, Siva Davaviah and team.

Zvitambo Trial, Zimbabwe

Investigators: Peter J. Iliff, Ellen G. Piwoz, Naume V. Tavengwa, Clare D. Zunguzac, Edmore T. Marinda, Kusum J. Nathoo, Lawrence H. Moulton, Brian J. Ward, Jean H. Humphrey

Additional members: Henry Chidawanyika, John Hargrove, Florence Majo, Kuda Mutasa, Mary Ndhlovu, Robert Ntozini and Phillipa Rambanepasi (ZVITAMBO); Agnes Mahomva (AIDS and TB Unit, Ministry of Health and Child Welfare, Zimbabwe); Lucie Malaba (Faculty of Science, University of Zimbabwe); Michael Mbizvo, Partson Zvandasara and Lynn Zijenah (University of Zimbabwe College of Health Sciences); Lidia Propper and Andrea Ruff (The Johns Hopkins Bloomberg School of Public Health, Department of International Health).

ANRS Ditrame Plus Cohort, Côte d'Ivoire

Principal Investigators: Francois Dabis, Valériane Leroy, Marguerite Timite-Konan, Christiane Welffens-Ekra.

Coordination in Abidjan: Laurence Bequet, Didier K. Ekouevi, Besigin Tonwe-Gold, Ida Viho.

Methodology, biostatistics and data management: Gérard Allou, Renaud Becquet, Katia Castetbon, Laurence Dequae-Merchadou, Charlotte Sakarovitch, Dominique Touchard.

Clinical team: Clarisse Amani-Bosse, Ignace Ayekoe, Gédéon Bedikou, Nacoumba Coulibaly, Christine Danel, Patricia Fassinou, Apollinaire Horo, Ruffin Likikouet, Hassan Toure. Laboratory team: André Inwoley, Francois Rouet, Ramata Touré.

Psycho-social team: Hortense Aka-Dago, Alphonse Sihé.

Social sciences team: Hélène Agbo, Hermann Brou, Annabel Desgrées-du-Lou , Annick Tijou-Traoré, Benjamin Zanou.

Scientific Committee: Stéphane Blanche, Jean-Francois Delfraissy, Philippe Lepage, Laurent Mandelbrot, Christine Rouzioux, Roger Salamon.

Good Start Cohort, South Africa

Mark Colvin, Mickey Chopra, Tanya Doherty, Debra Jackson, Jonathan Levin, Juana Willumsen, Ameena Goga, Pravi Moodley

MASHI Trial, Botswana

Investigators: Ibou Thior, Shahin Lockman, Laura M. Smeaton, Roger L. Shapiro, Carolyn Wester, S. Jody Heymann, MD, Peter B. Gilbert, Lisa Stevens, Trevor Peter, PhD, Soyeon Kim, Erik van Widenfelt, Claire Moffat, Patrick Ndase, Peter Arimi, Poloko Kebaabetswe, Patson Mazonde, Joseph Makhema, Kenneth McIntosh, Vladimir Novitsky, Tun-Hou Lee, Richard Marlink, Stephen Lagakos, Max Essex.

Collaborators: Drs C. Anude and J. Chanda, study physicians; L. Makori, nursing diploma, study nurse; J. B. Moorad, T. A. Modise, T. Moyo, and M. Malamba, nursing and midwifery diplomas, study nurses; D. Arbi and K. Koloi, nursing diplomas, nurse recruiters; L. Dube and T. Mmolotsi, health education diplomas, health educators and recruiters; S. Babitseng and D. Mere, nursing diplomas, recruiters (Molepolole site); Dr J. Boyle, study physician; J. Magetse, V. Modikwa, and M. Tsuro, nursing and midwifery diplomas, study nurses; T. Sekoto, family nurse practitioner diploma, study nurse; L. Garebatho, nursing diploma, study nurse; M. Sesinyi and K. Kelebalekgosi, health educator diplomas, health educators and recruiters (Mochudi site); Dr Z. Tedla, study physician; G. Mayondi, K. Sebinang, J. Setswalo, nursing and midwifery diplomas, study nurses; N. Makubate, community health

nursing and midwifery diploma, study nurse; L. Tsalaile, MSc nursing education, study nurse; B. Tsule, nursing diploma, study nurse; I. Thebeetsile, nursing diploma, nurse recruiter; I. Leteane and O. Makgabana, health education diplomas, health educators and recruiters (Lobatse Site); Drs. M. Mogodi, A. Owor, I. Hove, and A. Asmelash, study physicians; T. Kakhu, P. Ramalepa, and J. Lubinda, nursing and midwifery diplomas, study nurses; S. Ndebele, F. Modise, C. Bohule, K. Motshabi, and M. Ntshimane, nursing diplomas, nurse recruiters; (Gaborone site).

MITRA Cohort, Tanzania

Investigators: Charles Kilewo, Katarina Karlsson, Augustine Massawe, Eligius Lyamuya, Andrew Swai, Fred Mhalu, Gunnel Biberfeld.

Physicians: N. Hamud, F. Kalokola, G. Msemo, F. Temce, M. Giarttas, J. Methodi.

Nurses: A. Mkumbukwa, E. Rugaiya, S. Semanini, R. Mwamwembe, N. Makundi, A. Temu.

Laboratory Technologists: E. Mbena, E. Olausson-Hansson, D. Kalovya, V. Msangi, and A. O¨ stborn.

Secretary: C. Lema.

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

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Student	Camilla Marston
Principal Supervisor	Basia Zaba
Thesis Title	Demographic Determinants of Paediatric HIV in Generalised HIV epidemics

If the Research Paper has previously been published please complete Section B, If not please complete Section C

SECTION B

Where was the work published?	Sexually transmitted infections.		
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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)	For the section on child survival presented here I carried out the analysis and wrote the section of the paper.

Student Signature: [redacted] **Date:** 27/03/18

Supervisor Signature: [redacted] **Date:** 27.03.2018

3.2 Extract from "Updates to the Spectrum/Estimation and Projection Package (EPP) model to estimate HIV trends for adults and children"

3.2.1 Child Survival

In the previous version of Spectrum two new survival curves for 'AIDS only' mortality of children were introduced, based on data from 12 sub-Saharan African clinical trials and studies: the first to represent children infected at birth, the second to represent those infected through breast feeding.[13, 130] Further analysis of these data gave strong evidence that survival of children infected through breast feeding improved the later they were infected. Double Weibull curves were fitted to the data allowing for time of infection to give a pattern of survival post infection for four groups: those infected at birth, at 28–179 days, 180– 364 days and after 365. Similar curves representing the survival of HIV negative children from the equivalent time points were used to remove non-AIDS mortality. There is limited information about the survival of HIV infected children beyond 2.5 years, so as with the previous estimates it was assumed that beyond this point the survival for children would be equivalent to that of young adults infected at ages 15–24, with a median survival of 15 years.[5] Survival is described as a double Weibull curve of the form:

$$S_t = (\pi \times e^X + (1 - \pi) \times e^Y) \times 100$$

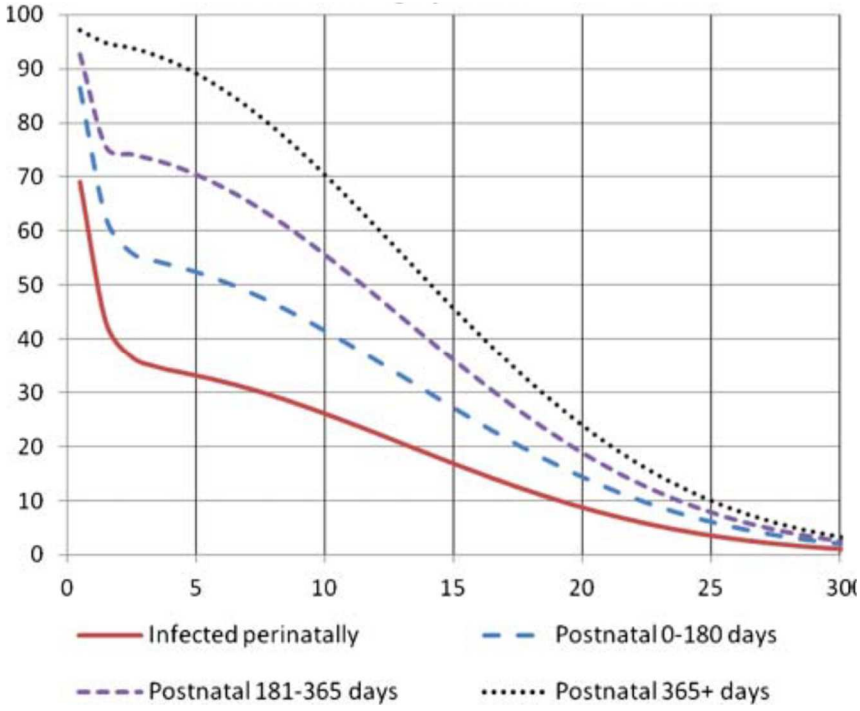
Where $X = -1 \times (\lambda_1 \times t)^{\mu 1}$ and $Y = -1 \times (\lambda_2 \times t)^{\mu 2}$

The parameter values are shown in Table 3.7. The resulting curves give a median AIDS only survival of 1.1, 6.4, 11.5 and 14.1 years resulting in 9% survival at 20 years for those infected at birth and 14%, 19% and 24% for those infected through breast feeding at 28–179 days, 180–364 days and after 365 days (Figure 3.5). These changes provide for greater accuracy in estimating child survival. They will usually result in higher estimates of the number of HIV+ children surviving to age 15.

Table 3.7: Parameter values for child survival patterns

	Time of Infection			
Parameter	Perinatal	Postnatal 0-180 days	Postnatal 181-365 days	Postnatal 365+ days
π	0.646	0.440	0.248	0.048
λ_1	1.336	1.015	1.241	1.873
μ_1	1.062	1.484	2.110	1.708
λ_2	0.058	0.058	0.058	0.058
μ_2	2.195	2.200	2.200	2.200

Figure 3.5: Percentage of HIV+ children surviving by number of years since infection.



3.3 Research report for UNAIDS - an update to the paediatric curve

Changes to the Paediatric Survival Curve

Report for UNAIDS – March 2015

Milly Marston, Basia Zaba, Francesca Cavallaro

Author contributions: MM conceived the analysis. MM prepared and analysed the data using clinical cohorts. FC prepared the DHS data, MM analysed the data. MM wrote the report. BZ commented and edited drafts

3.3.1 Background

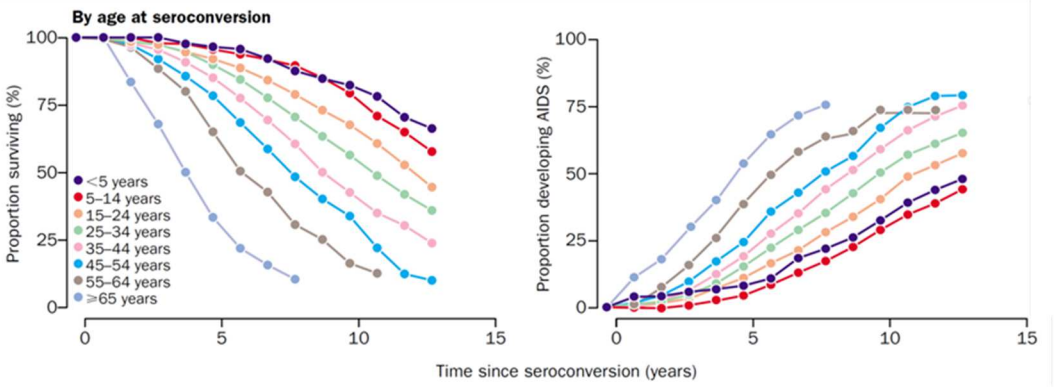
Empirical data on the survival of children post infection from HIV in the absence of ART only exists for up to two or three years post infection. In order to create a survival curve that represents the whole survival pattern for net paediatric survival from HIV we currently make the assumption that the children infected though mother to child transmission have the same mortality hazards post infection as those found in young adults aged 15-24[13, 52]. Data for young adults is taken from Sub Saharan African HIV demographic surveillance cohorts which are part of the ALPHA network[5, 7].

Data from the ALPHA network show a clear increase in median survival post infection with younger age of infection after taking into account background levels of mortality, however these data only include those over the age of 15 so we are unable to see if this increase in survival continues into early adolescence and childhood and whether there is a minimum age beyond which this negative association between age at infection and survival is not observed. Data from Europe, North America and Australia show the same pattern as the African cohorts in adults and also show that 5-14 year olds still seem to have a more favourable survival than those aged 15-24 years. Those infected at ages <5 appear to have a similar pattern to those infected at 5-14 years (Table 3.6)[125]

These findings however may be problematic to apply to populations in Sub Saharan Africa. Firstly although they stem from a time when highly active antiretroviral therapy was not widespread children in developed countries are likely to have received much more HIV related treatment than available in Sub Saharan Africa. Secondly the infected children are nearly all haemophiliacs whereas the older age groups to whom they are compared are more commonly infected through sexual intercourse or injecting drugs,

and there is some evidence that these different routes of infection can lead to different survival times[125]. However studies restricted to Haemophiliacs have shown that age at infection continues to be important and show that <15 year olds have a significantly longer survival than those infected at older ages[131].

Figure 3.6: Survival post infection by age at sero conversion taken from CASCADE Lancet 2000 [125](Permission to reuse license, see appendix 3) , the under 15 year olds are nearly all Haemophiliacs (99%)



3.3.2 Methods

Data Sources

Empirical data of the survival of children infected at birth comes from 12 clinical trials and cohort studies in Southern, Eastern and Western Africa, the data and resulting net paediatric survival from HIV is described elsewhere[12, 13]. Data on adult net survival post infection comes from three East African community based HIV cohorts who are members of the ALPHA network, data and methods are described elsewhere[5, 7]

Analysis

We extrapolate the relationship between age at infection and the parameters of the best fitting Weibul curves representing adult net survival post infection from Marston et al[5] to obtain a Weibul curve that represents the survival of children and young adolescents following infection at ages 5-14.

$$l_A(x) = \exp\left[-\lambda \cdot x^{\mu}\right]$$

We use the new Weibul curve for those infected at ages 5-14 to represent mortality hazards of children after the age point at which empirical data on mortality of children infected through mother to child transmission[13] runs out (With the assumption that those infected at birth should have no worse survival at the point the empirical data runs out than those infected between 5-14 years old at the same time post infection). A double

weibul curve is fitted by timing of infection for perinatal infections, those infected between 0-180 days, 181-364 days and 365 days plus. The double Weibul takes the form:

$$l_A(x) = \pi \cdot \exp\left\{-\left[\lambda_1 \cdot x\right]^{\mu_1}\right\} + (1-\pi) \cdot \exp\left\{-\left[\lambda_2 \cdot x\right]^{\mu_2}\right\}$$

Using the new double Weibul parameters we input the survival estimates into Spectrum to see how AIDS deaths and prevalence change over the age groups compared to the current Spectrum output. We run Spectrum using the no EPP adjustment in order to see the direct effect vertically transmitted infections have in the older ages groups, using the EPP adjustment would mean that Spectrum would make small yearly adjustments to the EPP incidence to match the EPP prevalence therefore essentially forcing Spectrum to give the same prevalence regardless of how many vertical infections are surviving to adulthood.

HIV prevalence in young adults - Demographic and Health Survey (DHS) Analysis

We used data from 44 DHS and AIDS indicator survey (AIS) [132] to calculate prevalence in young people aged 15 to 24 for comparison to Spectrum outputs. We also looked at evidence of vertical transmission and how much it contributes to overall prevalence by calculating prevalence in the 15-19 year olds by whether the respondent had reported ever having sex. We could assume if all reports of never having sex were true and in the absence of other sorts of HIV transmission such as blood transfusions and needles, that the prevalence of HIV positive 15-19 year olds who have never had sex in the population is a minimum for those who were infected at birth.

Data analysis was carried out using the statistical package Stata 13.1 SE.

3.3.3 Results

The extrapolated weibul to represent children infected between 5-14 years old gives a median survival of 16.8 compared to 14.3 in the young adults 15-24 year olds, the curve and parameters are shown in Figure 3.7 and Table 3.8.

Figure 3.7: Weibul curves fitted to net adult survival post HIV infection with projected child net survival curve (for those under 15)

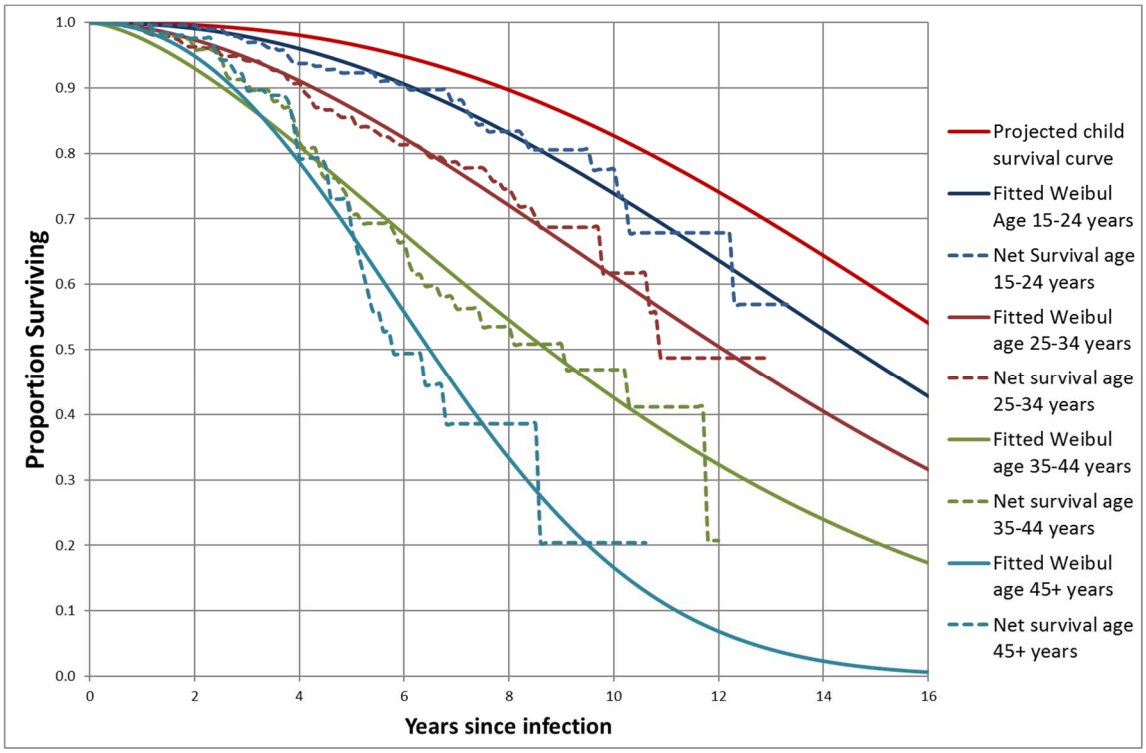


Table 3.8: Weibul parameters for net survival curves of adults and horizontally infected children and adolescents

		Age at infection Adults			
fitted Weibul parameters	Extrapolated curve for 5-14	15-24	25-34	35-44	45+
λ	0.0006	0.0019	0.0075	0.0251	0.0114
μ	2.51	2.19	1.81	1.53	2.20

The parameters for the resulting new double Weibul infant survival curves are shown in Table 3.9 and graphed in Figure 3.8, mortality hazards are shown in Figure 3.9. The new double Weibul curves are very similar to the previous ones but yield a longer median survival time of between 14.0 and 21.9 years from perinatal infection to those infected after their first birthday compared to 10.7 and 19.7 with the curves currently used in spectrum (Table 3.10)

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Table 3.9: Parameters of double Weibuls for paediatric net survival from HIV current in spectrum and for the new curves

Double Weibul parameter	Current Curves by time of infection				New Curves by time of infection			
	perinatal	0-180 days	181-365 days	365+ days	perinatal	0-180 days	181-365 days	365+ days
π	0.646	0.440	0.248	0.048	0.614	0.436	0.251	0.050
λ_1	1.336	1.015	1.241	1.873	1.479	1.033	1.205	1.810
μ_1	1.062	1.484	2.110	1.708	1.132	1.509	2.099	1.691
λ_2	0.058	0.058	0.058	0.058	0.051	0.051	0.051	0.051
μ_2	2.195	2.200	2.200	2.200	2.531	2.531	2.531	2.531

Table 3.10: Quartile survival years by time of infection

Quartiles	Current - Quartile survival by time of infection				New curves-Quartile survival by time of infection			
	perinatal	0-180 days	181-365 days	365+ days	perinatal	0-180 days	181-365 days	365+ days
75%	0.35	0.85	1.65	8.95	0.35	0.85	1.75	10.95
median: 50%	1.05	6.45	11.45	14.15	1.05	8.45	13.65	16.35
25%	10.65	15.65	18.05	19.65	14.05	17.95	20.15	21.85

Figure 3.8: Double Weibul Survival Curves comparing current curves used by Spectrum with new curves

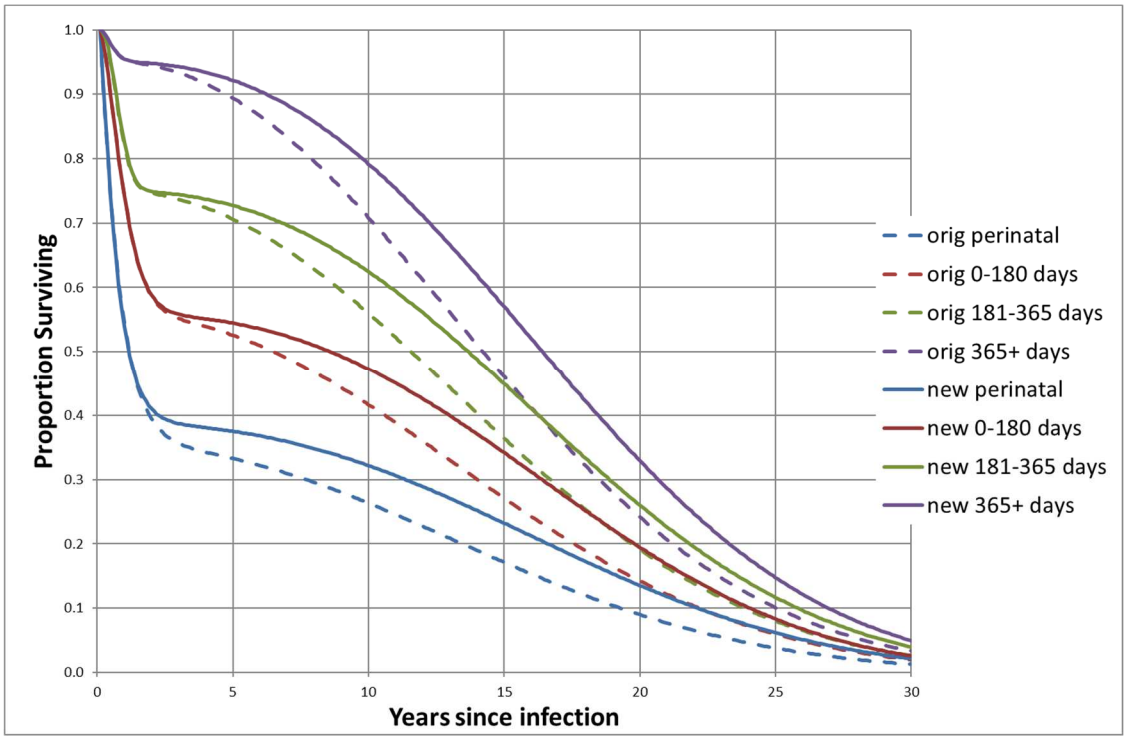
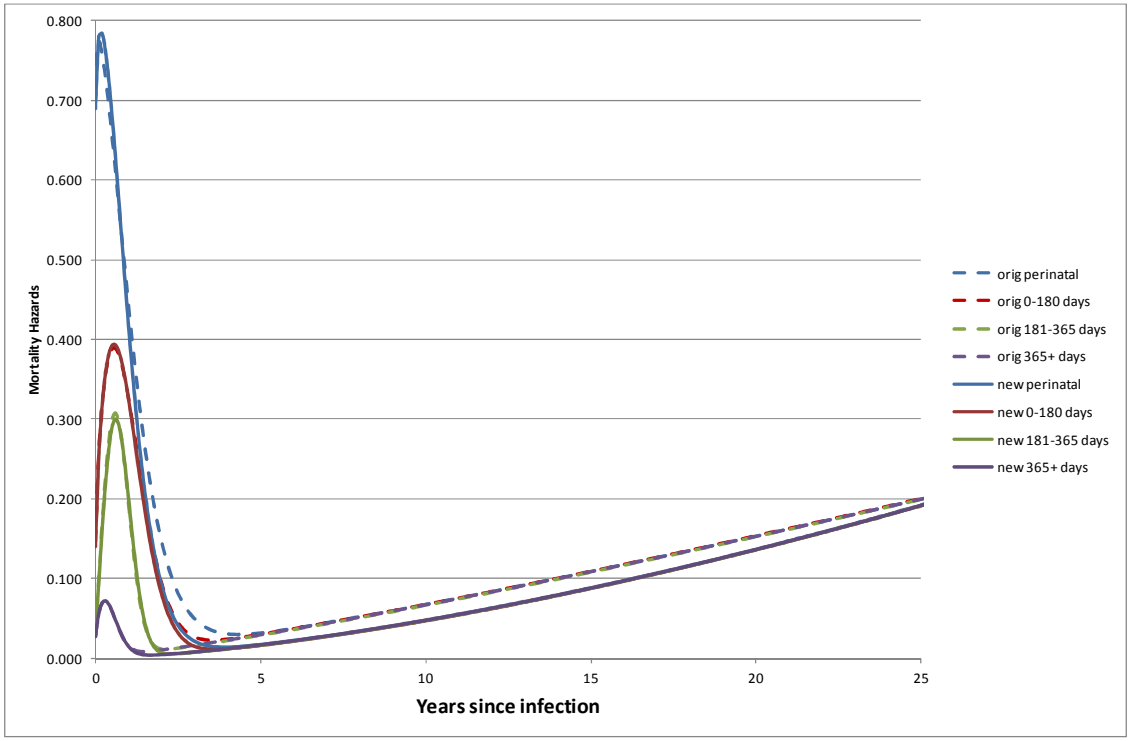


Figure 3.9: Force of mortality comparing current curves used by Spectrum with new curves

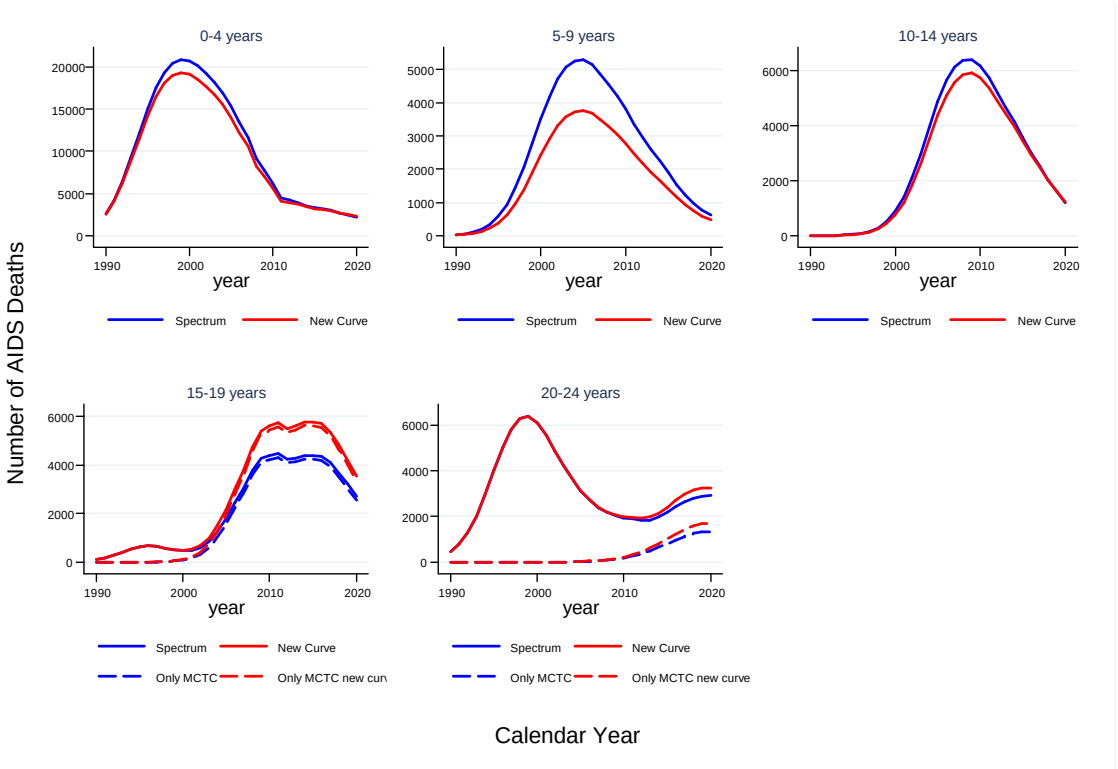


3.3.4 Implication for AIDS Deaths and HIV prevalence in young adults

AIDS Deaths

Using spectrum to project AIDS deaths over time (with the no EPP adjustment) AIDS deaths in the under 15 year olds reduce with the largest reduction in the 5-9 year olds. AIDS deaths then increase using the new curve compared to the old in those 15 plus. This increase is a deferral effect because under the new assumptions more paediatric infections survive to become teenagers. The increase in AIDS death is at its largest in the 15-19 year olds. Figure 3.10 shows the AIDS deaths by age group and time for Kenya which follows a fairly typical pattern, other countries are shown in the appendix in Figure 3.20-Figure 3.30 (Botswana, Lesotho, Malawi, Mozambique, Rwanda, South Africa, Swaziland, Tanzania, Uganda, Zambia and Zimbabwe) For the older age groups the graphs show all AIDS deaths and also AIDS deaths only due to mother to child transmission. It is interesting to note that this predicts that around half the AIDS deaths to 20-24 year olds in Kenya in 2020 will be due to vertical transmission that occurred around the year 2000.

Figure 3.10: AIDS Deaths between 1990 and 2020 by age group from Spectrum using current paediatric survival curve and the new curve. - Kenya



Prevalence

Longer survival of paediatric infections implies increases in HIV prevalence in children and adolescents. Proportional increases in HIV prevalence comparing the new projections with those currently used in Spectrum are highest in the 10-14 year age group at around 1.2 times higher with the differences beginning to fall around 2010 presumably due to falling HIV prevalence in the past and the introduction of ART. For those over 15 prevalence rises to between 1.1 and 1.2 times higher using the new child survival curves (Figure 3.11). In absolute terms the prevalences are very close apart from peak times, which coincide with the age achieved by the cohort of children who were born during peak prevalence years in the population. Prevalence by age group over time is shown in Figure 3.12 for Kenya and for all other countries in Figure 3.31-Figure 3.41 in the appendix.

Figure 3.11: Proportional increase in prevalence by age group in Spectrum comparing projections using the new curves to the current curves – Note that the age groups 15-24 include all HIV infections (sexual as well as vertical transmission).

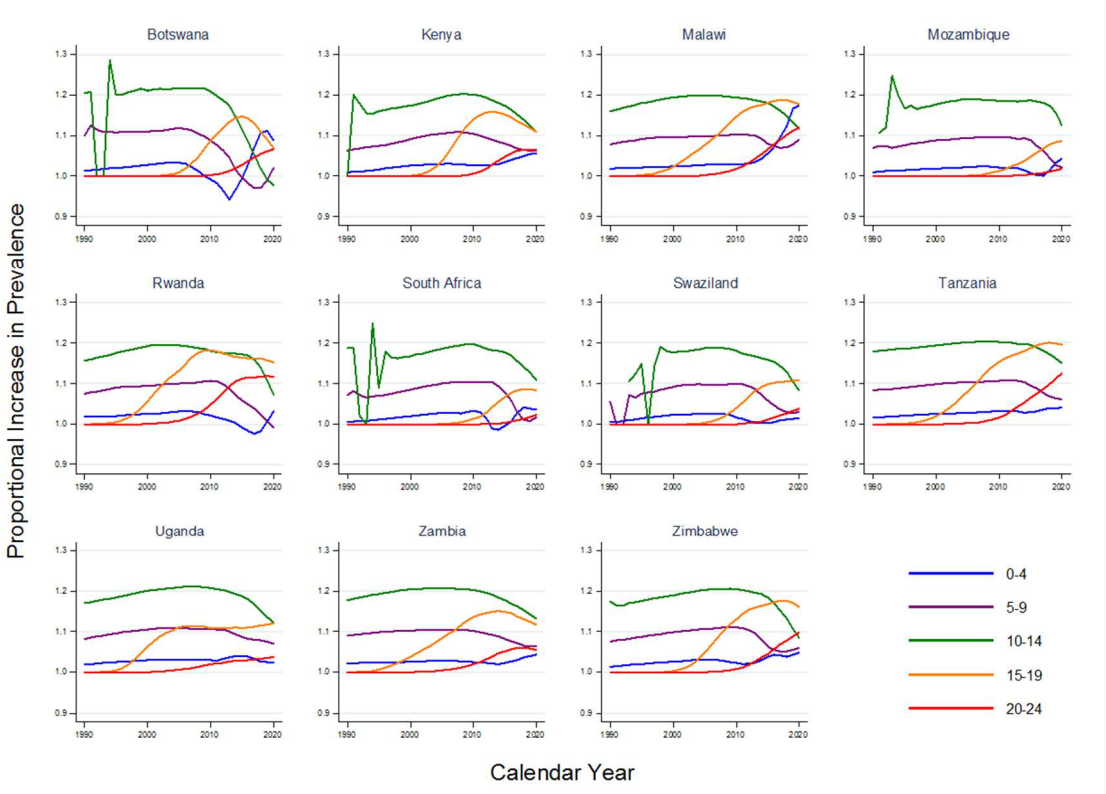
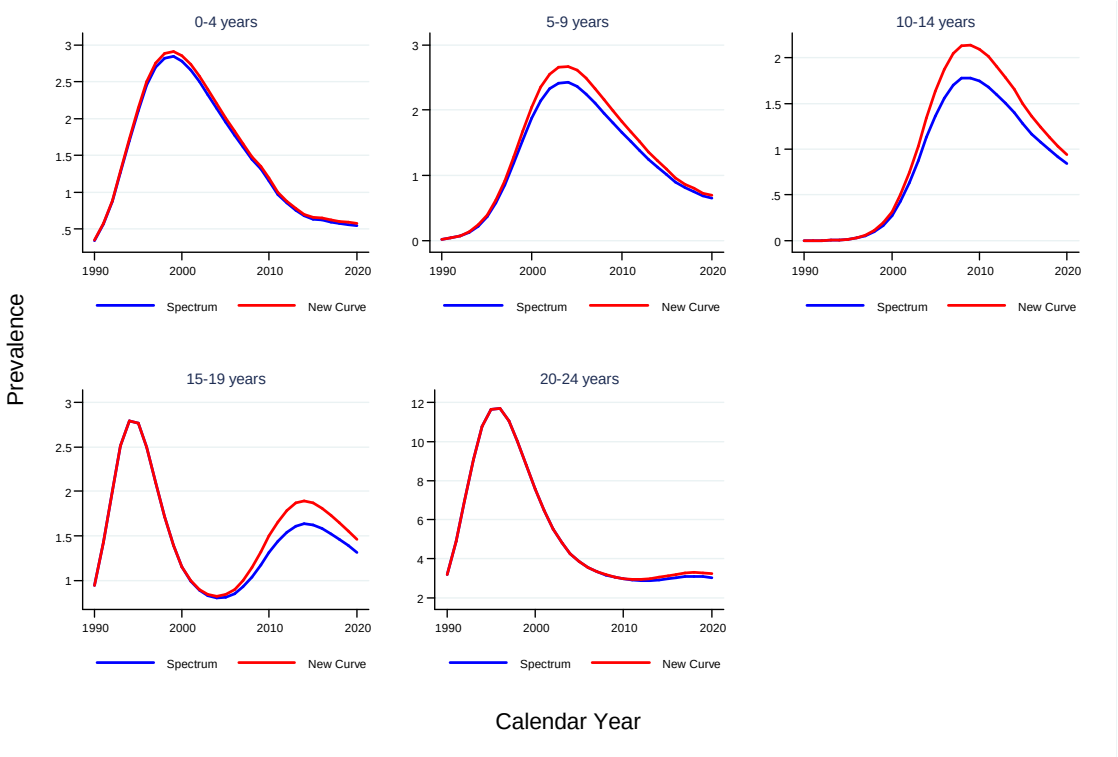


Figure 3.12: HIV prevalence between 1990 and 2020 by age group from Spectrum using current paediatric survival curve and the new curve (using 2014 country files from UNAIDS with no EPP adjustment), note difference y scales. - Kenya



Prevalence comparisons to the DHS

Since the new child survival curves have increased prevalence slightly in all age groups we compared the Spectrum prevalence (without EPP adjustment) to that in the demographic household surveys (DHS). Overall currently in Spectrum the prevalence in most countries in the 15-19 year olds is slightly lower in spectrum than reported in the DHS, for the 20-24 year old age group the differences are very small (Figure 3.13, Figure 3.14).

Figure 3.13: Comparison of Prevalence from Spectrum with DHS for 15-19 year olds (using 2014 country files from UNAIDS with no EPP adjustment)

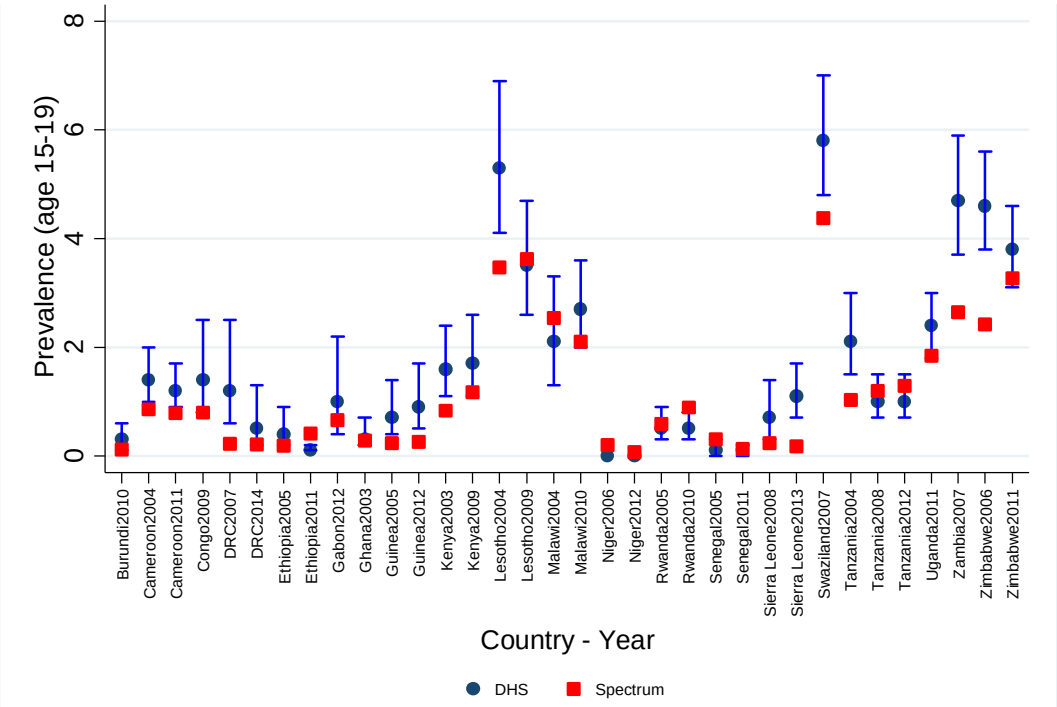
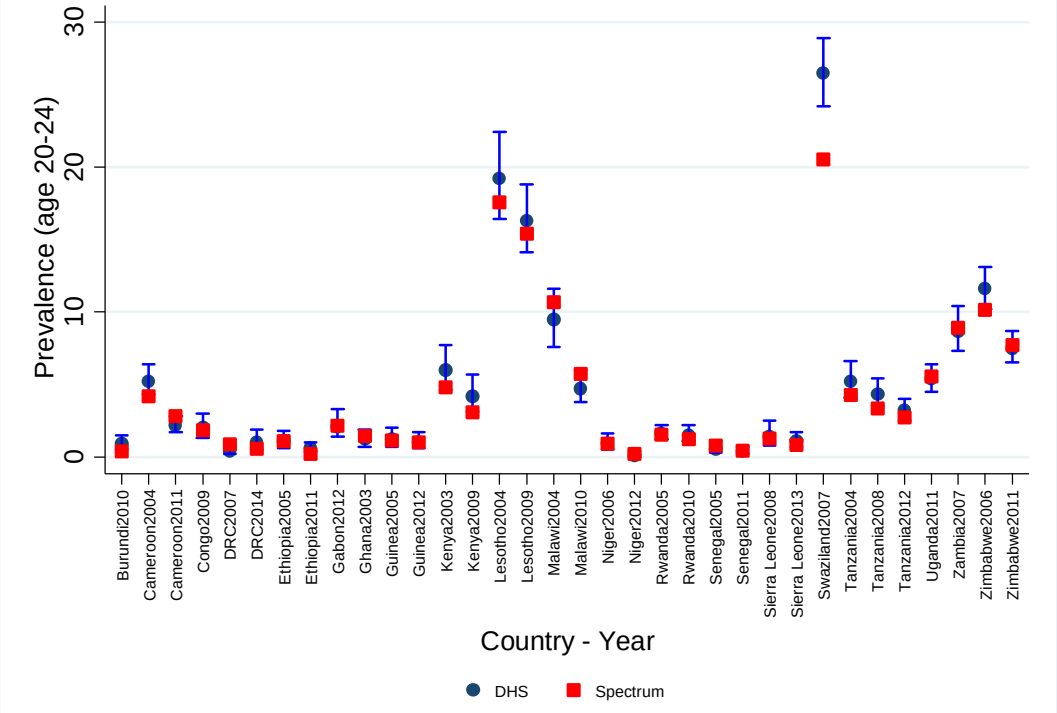


Figure 3.14: Comparison of Prevalence from Spectrum with DHS for 20-24 year olds (using 2014 country files from UNAIDS with no EPP adjustment)



Using the prevalence produced in Spectrum with the new child survival curves for selected countries we can compare whether the new curves generate prevalence estimates closer or further away from the survey data. The number of survey data sources for 5-9 and 10-14 year olds are limited compared to those available for ages 15+. For 5-9 year olds there is little difference in the two estimates from Spectrum for

the years and countries with survey data (Figure 3.15). For 10-14 year olds the new curves bring the prevalence in Spectrum slightly closer to the point estimates from the surveys with the exception of Kenya 2012 (Figure 3.16). For 15-19 year olds there is little difference but in general the new prevalence from Spectrum is marginally closer to the point estimate (Figure 3.17) and for 20-24 year olds there is very little difference (Figure 3.18).

Figure 3.15: Comparison of Prevalence from Spectrum and the prevalence given by the new curve compared to survey data for 5-9 year olds (using 2014 country files from UNAIDS with no EPP adjustment)

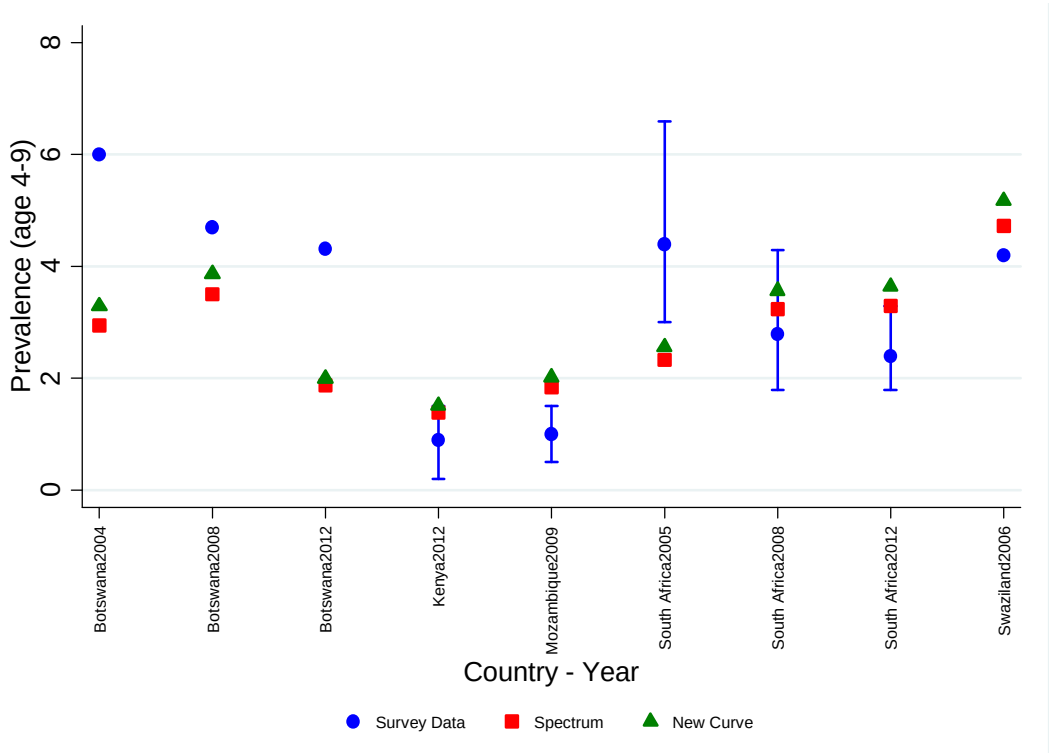


Figure 3.16: Comparison of Prevalence from Spectrum and the prevalence given by the new curve compared to Survey data for 10-14 year olds (using 2014 country files from UNAIDS with no EPP adjustment)

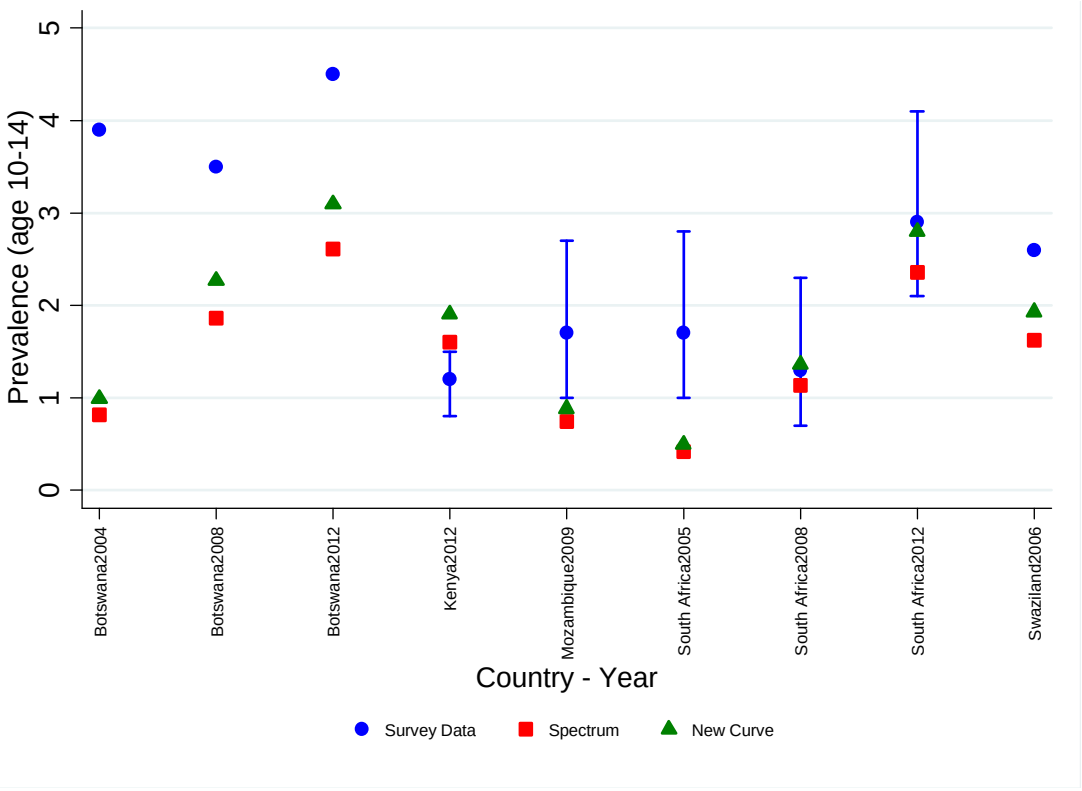


Figure 3.17: Comparison of Prevalence from Spectrum and the prevalence given by the new curve compared to DHS for 15-19 year olds (using 2014 country files from UNAIDS with no EPP adjustment)

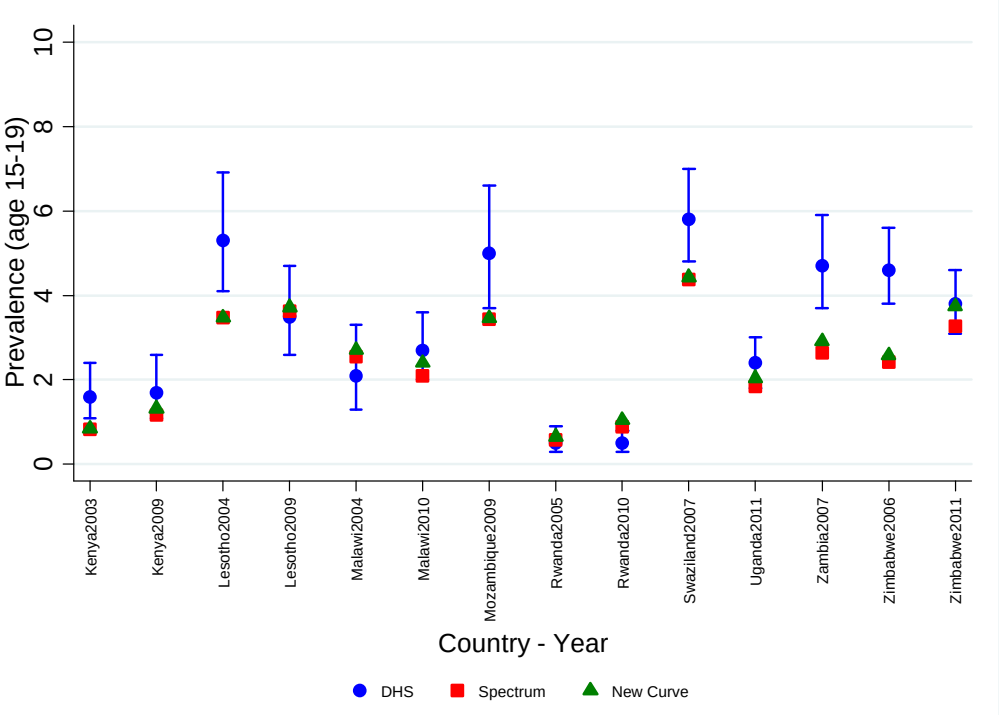
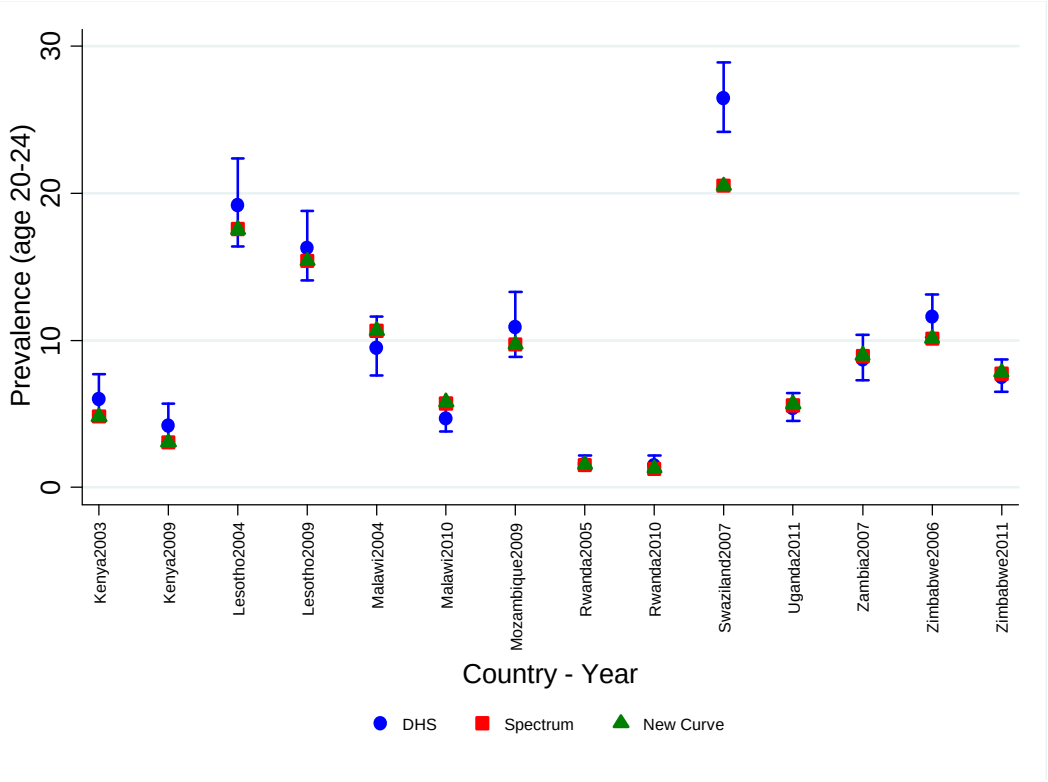


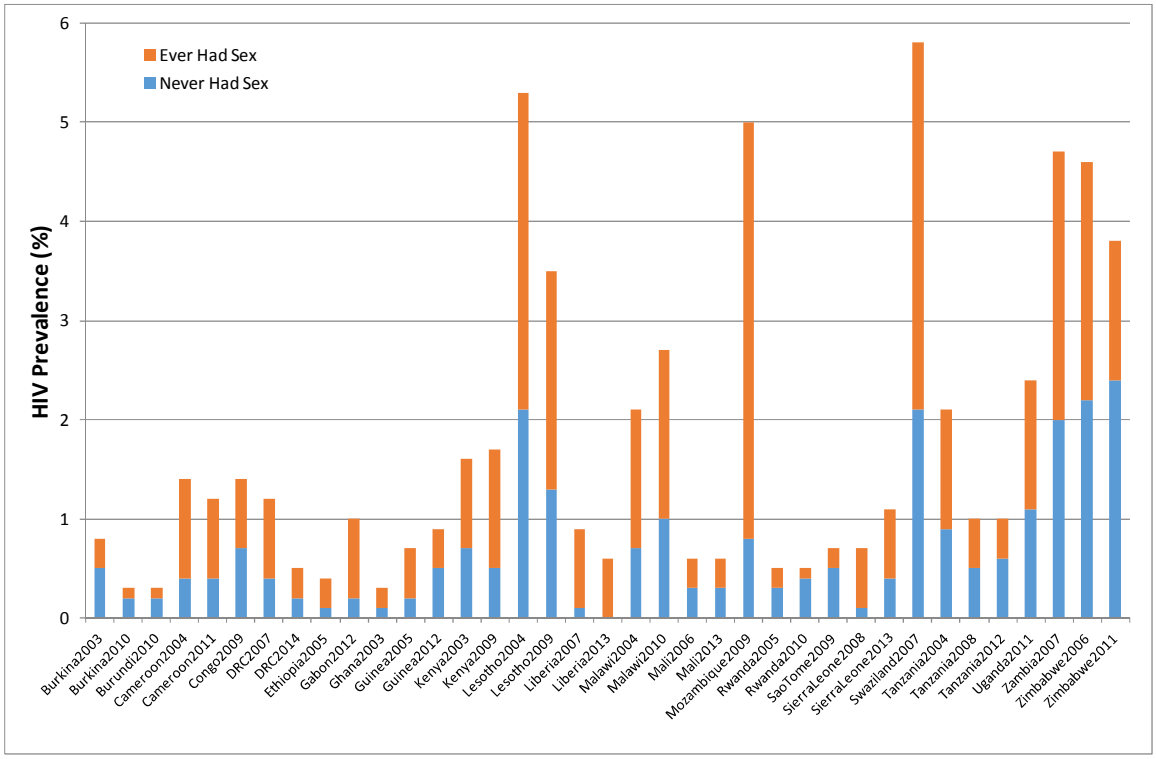
Figure 3.18: Comparison of Prevalence from Spectrum and the prevalence given by the new curve compared to DHS for 20-24 year olds (using 2014 country files from UNAIDS with no EPP adjustment)



Prevalence in young adults by sexual experience

Sample size was small when looking at HIV prevalence by whether the respondent reported ever having sex. Figure 3.19 shows the HIV prevalence in 15-19 year olds by whether they report ever or never having sex (A possible measure of the minimum contribution of vertical transmission to HIV prevalence), corresponding numbers with confidence intervals are found in Table 3.11 in the appendix. Between 4.6% (95% CI 0.9-20.8%) of HIV positive 15-19 year olds in Liberia 2013 to 78.9% (95% CI 49.6-93.4%) in Ethiopia 2011 reported never having sex.

Figure 3.19: DHS HIV prevalence in 15-19 year olds by whether they have ever or never had sex. NB Sample size is small see Table 4 in appendix for confidence intervals.



3.3.5 Discussion

We have experimented with a small change to the Paediatric survival curves, retaining the same basic assumption that once the empirical data runs out, HIV-related child mortality is assumed to follow the same pattern as is seen in adults, however we have extrapolated improving survival by age at infection to include children and adolescents under 15. The question still remains, how far do we go back in age before the survival post infection becomes less favourable as shown by the empirical evidence for those infected under the age of one?

For those infected after the perinatal period there is an initial short increase in mortality followed by a decrease in the empirical data, this could be a biological effect (incubation of disease following infection) or an artefact due to the slight uncertainty about the exact timing of infection.

The new curves give a lower number of AIDS deaths in the under 15 year age groups but increase the AIDS deaths in the 15-19. The resulting prevalence of HIV is no more inconsistent with the DHS prevalence estimates than before and overall bring them marginally closer together.

Looking at those who are HIV positive in the DHS but have reported never having sex is evidence that a large proportion of 15-19 year olds are infected vertically. The prevalence of those HIV positive and reporting never having sex in the population gives an estimated minimum contribution of vertical infected 15-19 year olds, however no further conclusions or estimates of the actual contribution to prevalence those vertically infected make can be made due to a number of reasons; small sample size, knowing how many of those who have had sex were infected vertically and the uncertainty around whether the report of never having sex is true or not.

3.3.6 Appendix

Mortality graphs comparing spectrum with new curves

Figure 3.20: AIDS Deaths between 1990 and 2020 by age group from Spectrum using current paediatric survival curve and the new curve. - Botswana

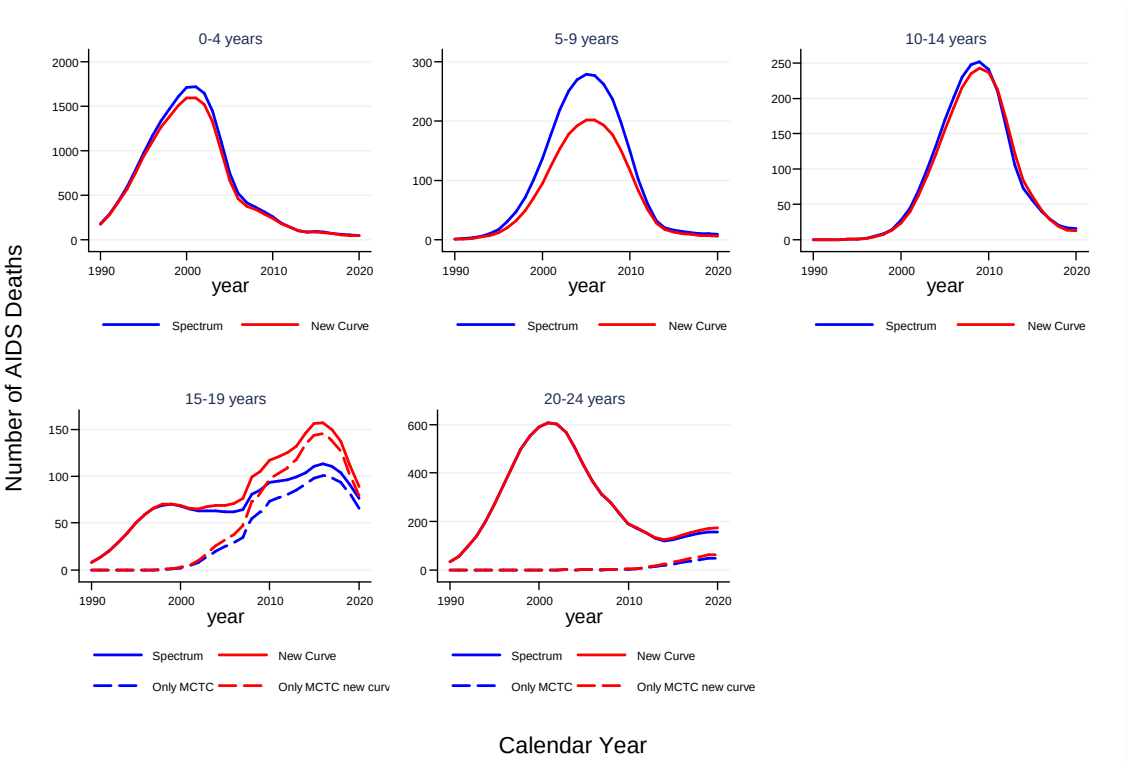


Figure 3.21: AIDS Deaths between 1990 and 2020 by age group from Spectrum using current paediatric survival curve and the new curve. - Lesotho

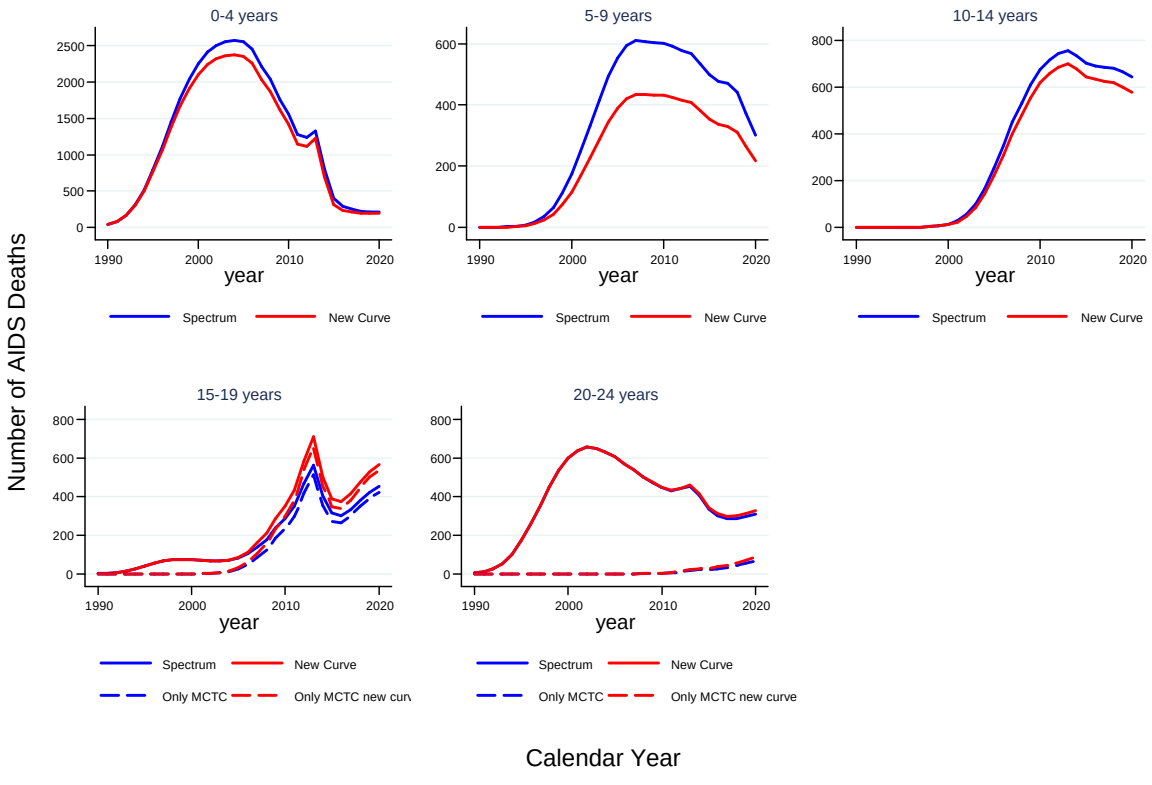


Figure 3.22: AIDS Deaths between 1990 and 2020 by age group from Spectrum using current paediatric survival curve and the new curve. - Malawi

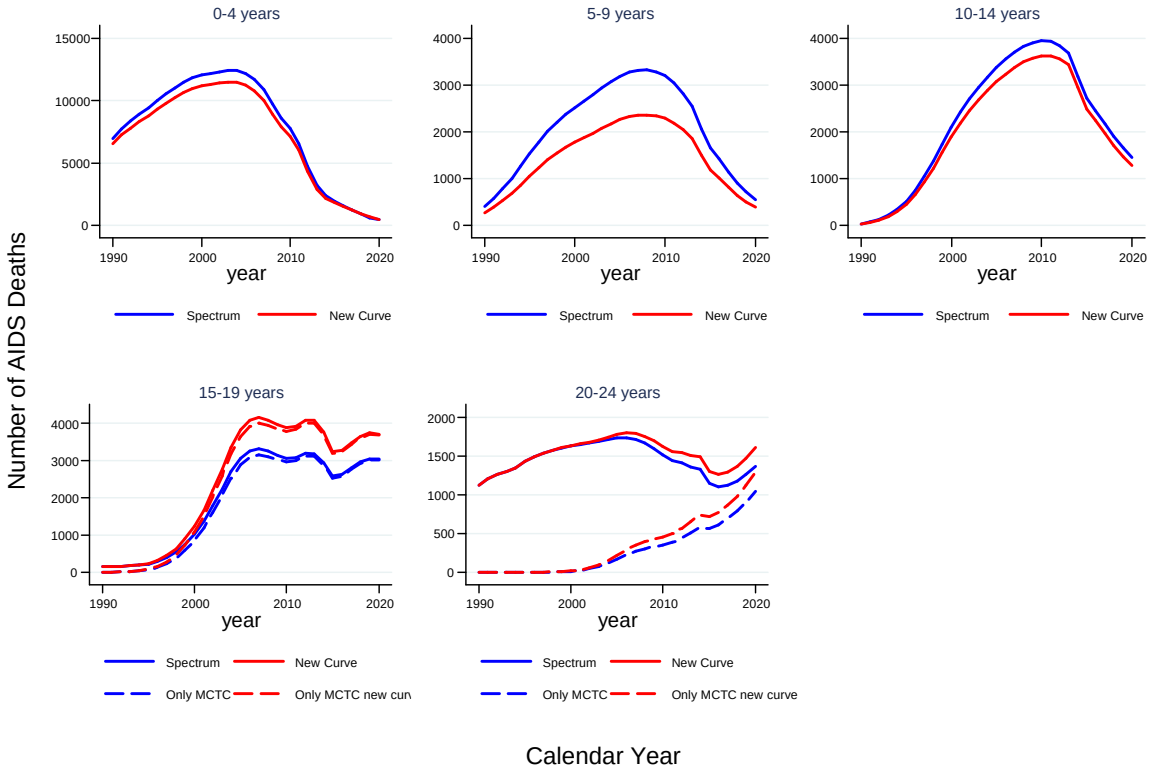


Figure 3.23: AIDS Deaths between 1990 and 2020 by age group from Spectrum using current paediatric survival curve and the new curve. - Mozambique

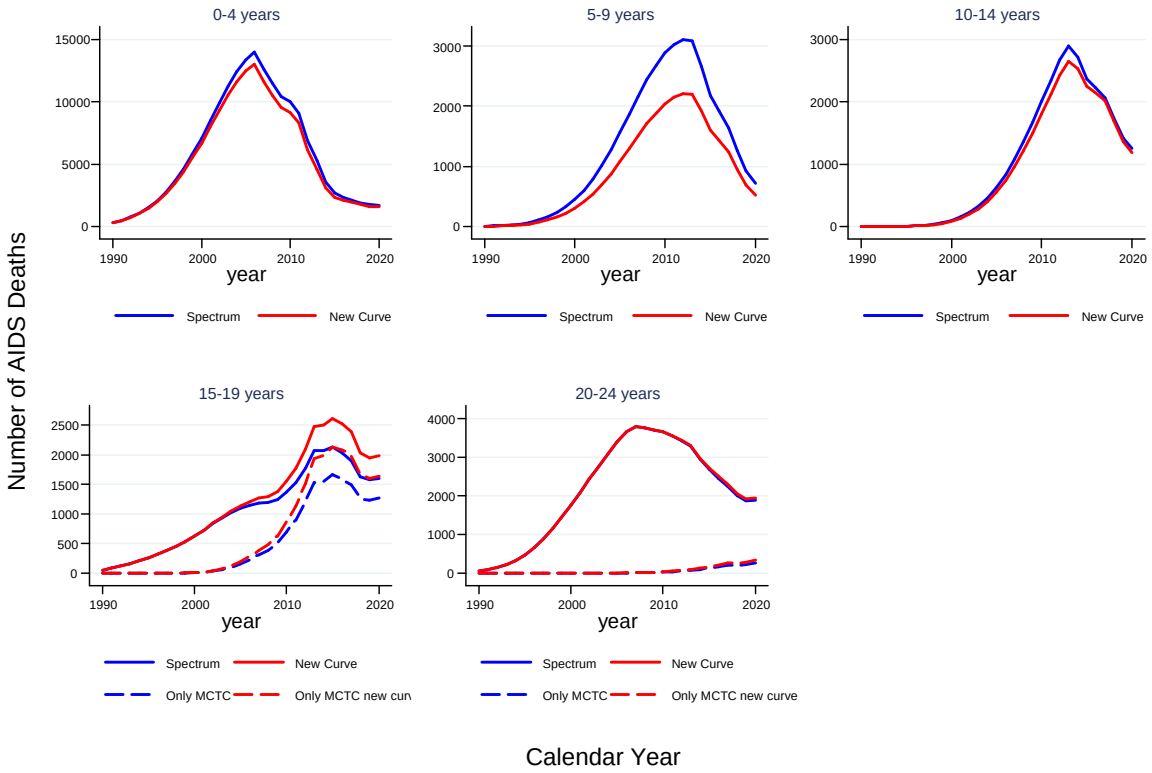


Figure 3.24: AIDS Deaths between 1990 and 2020 by age group from Spectrum using current paediatric survival curve and the new curve. – Rwanda

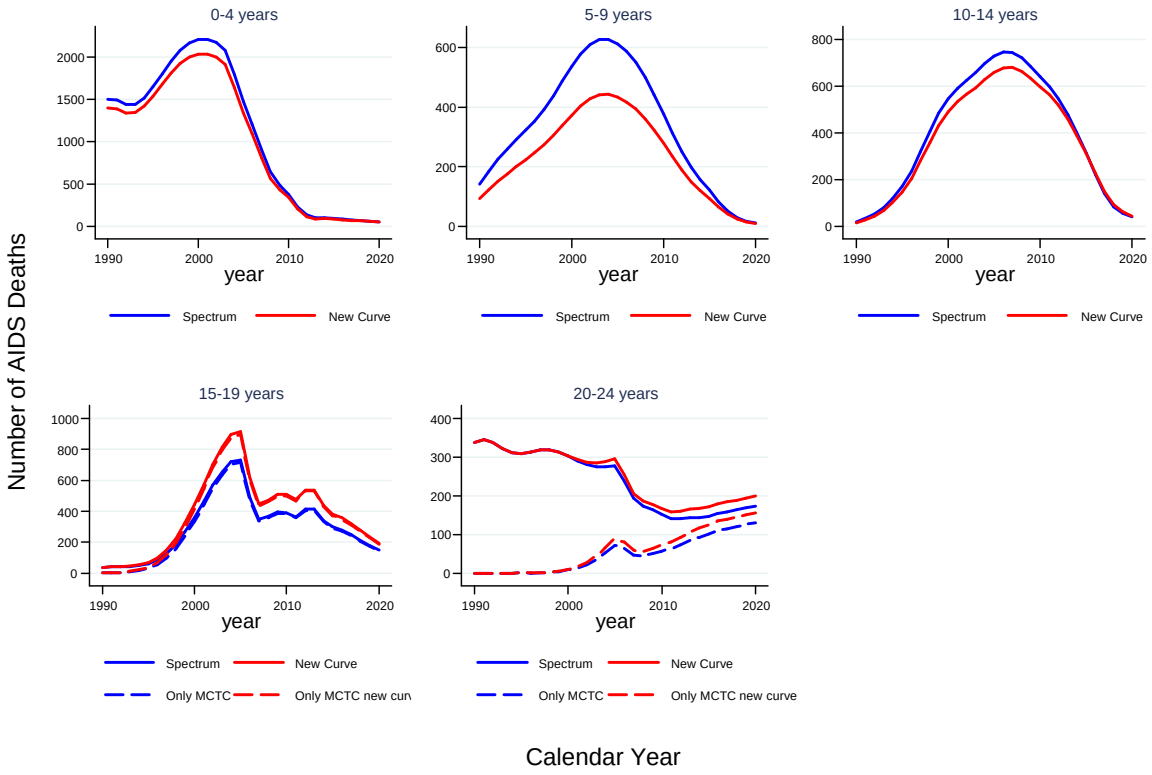


Figure 3.25: AIDS Deaths between 1990 and 2020 by age group from Spectrum using current paediatric survival curve and the new curve. – South Africa

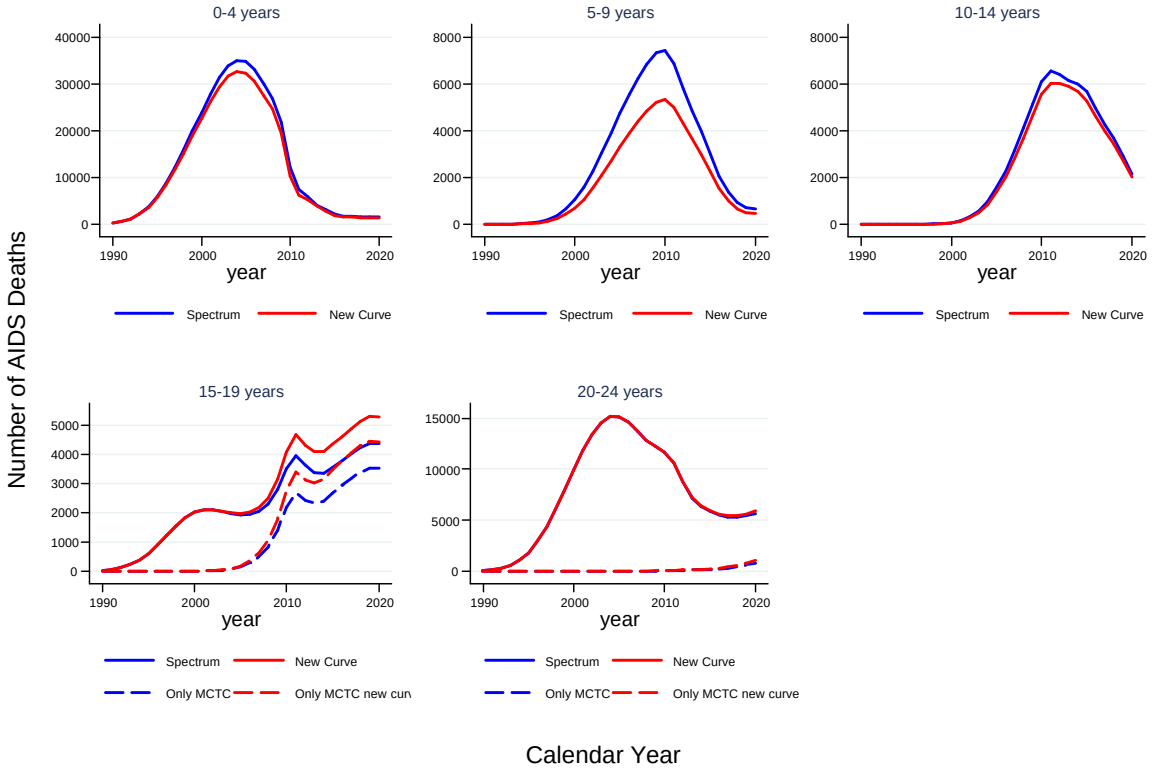


Figure 3.26: AIDS Deaths between 1990 and 2020 by age group from Spectrum using current paediatric survival curve and the new curve. - Swaziland

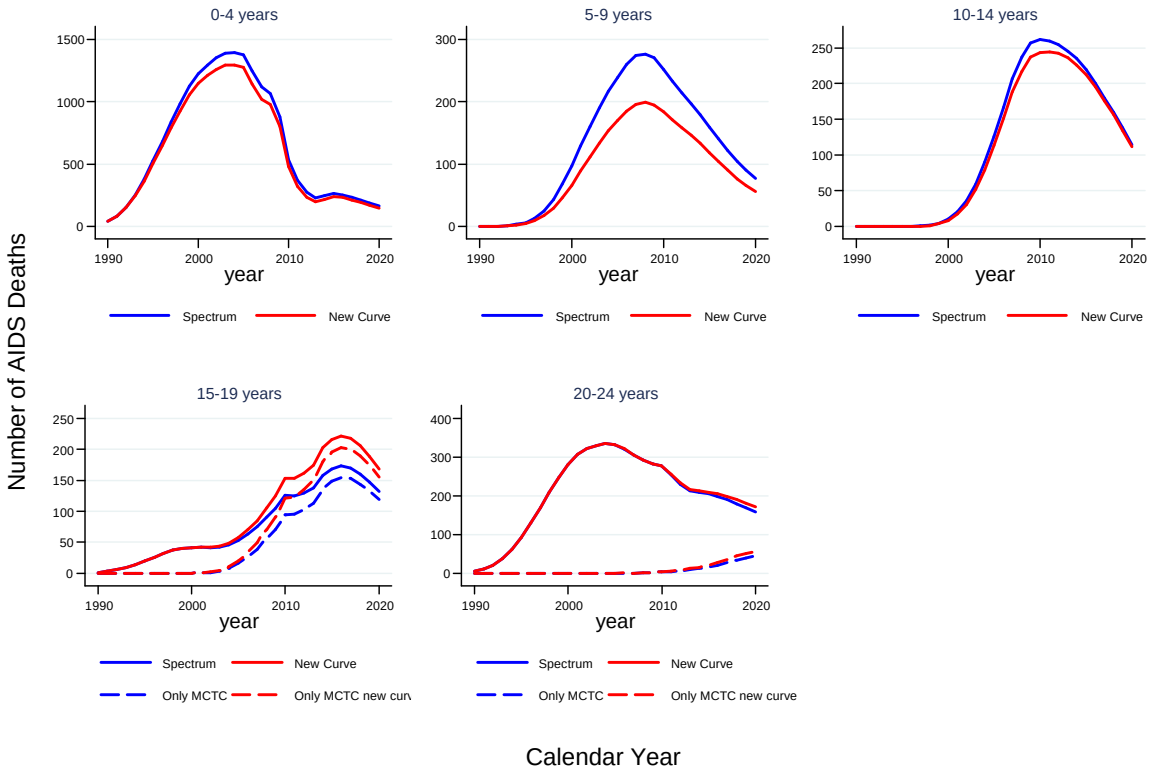


Figure 3.27: AIDS Deaths between 1990 and 2020 by age group from Spectrum using current paediatric survival curve and the new curve. - Tanzania

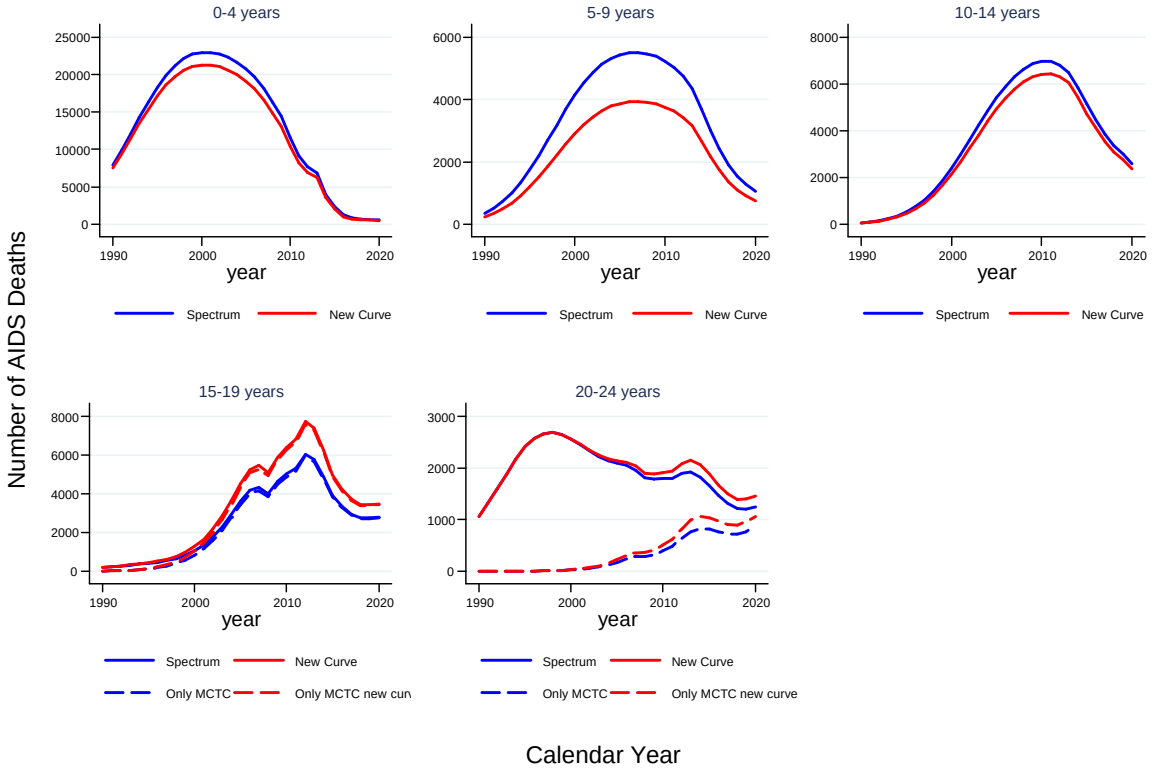


Figure 3.28: AIDS Deaths between 1990 and 2020 by age group from Spectrum using current paediatric survival curve and the new curve. - Uganda

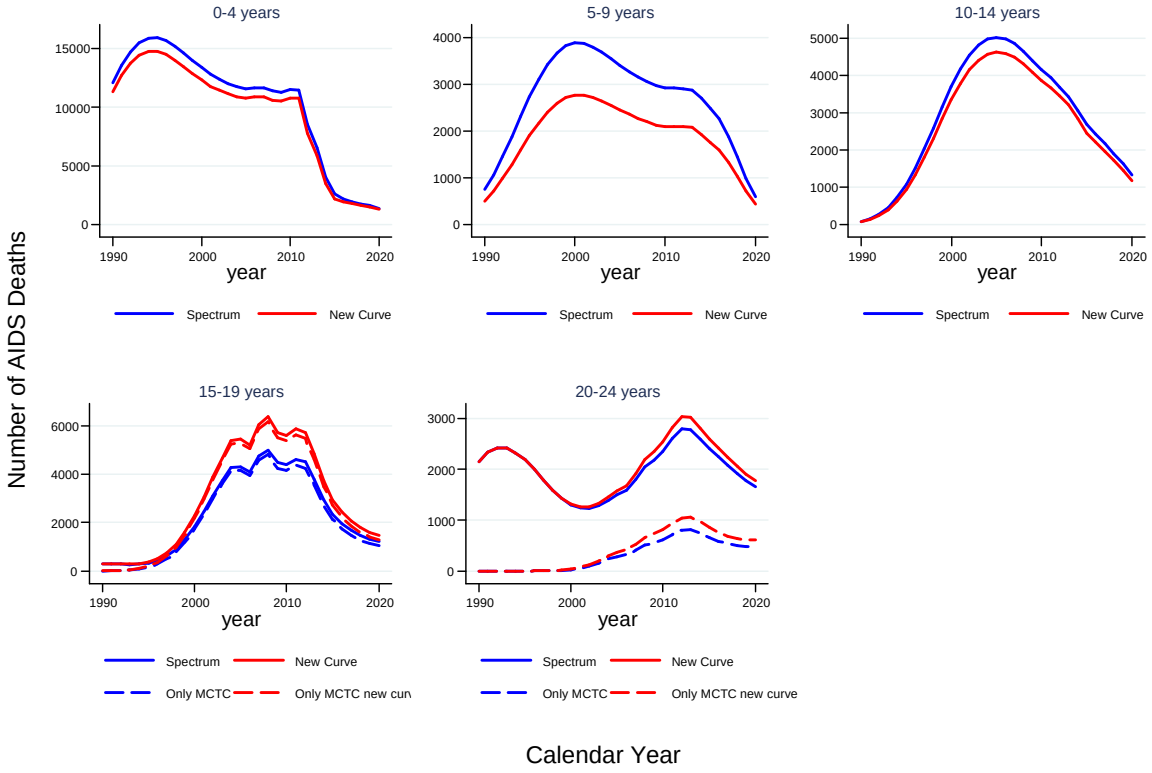


Figure 3.29: AIDS Deaths between 1990 and 2020 by age group from Spectrum using current paediatric survival curve and the new curve. - Zambia

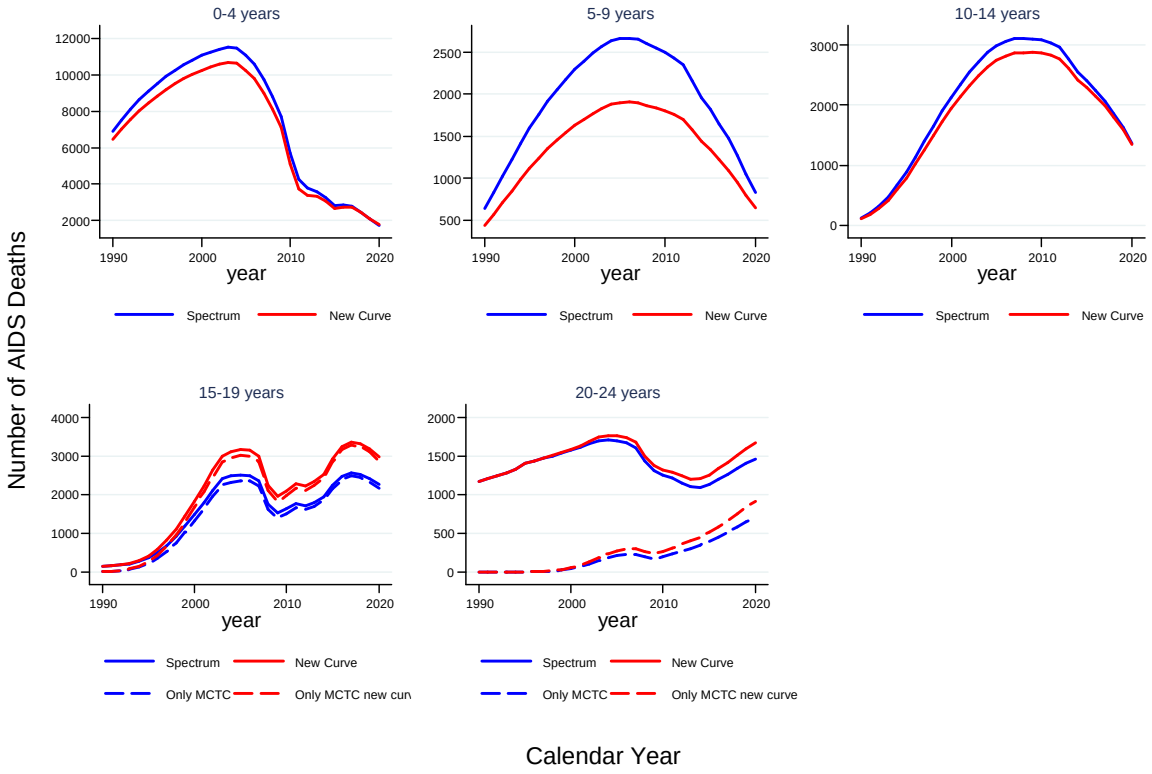
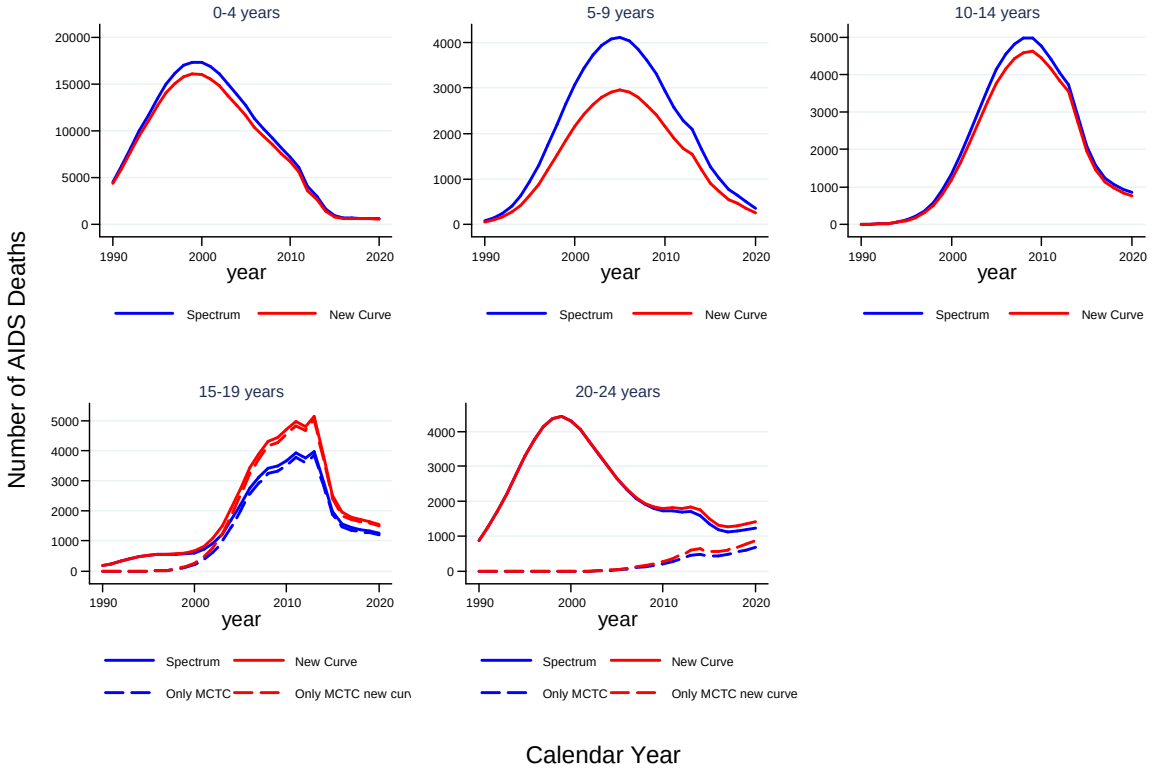


Figure 3.30: AIDS Deaths between 1990 and 2020 by age group from Spectrum using current paediatric survival curve and the new curve. - Zimbabwe



Prevalence

Figure 3.31: HIV prevalence between 1990 and 2020 by age group from Spectrum using current paediatric survival curve and the new curve (using 2014 country files from UNAIDS with no EPP adjustment), note difference y scales. - Botswana

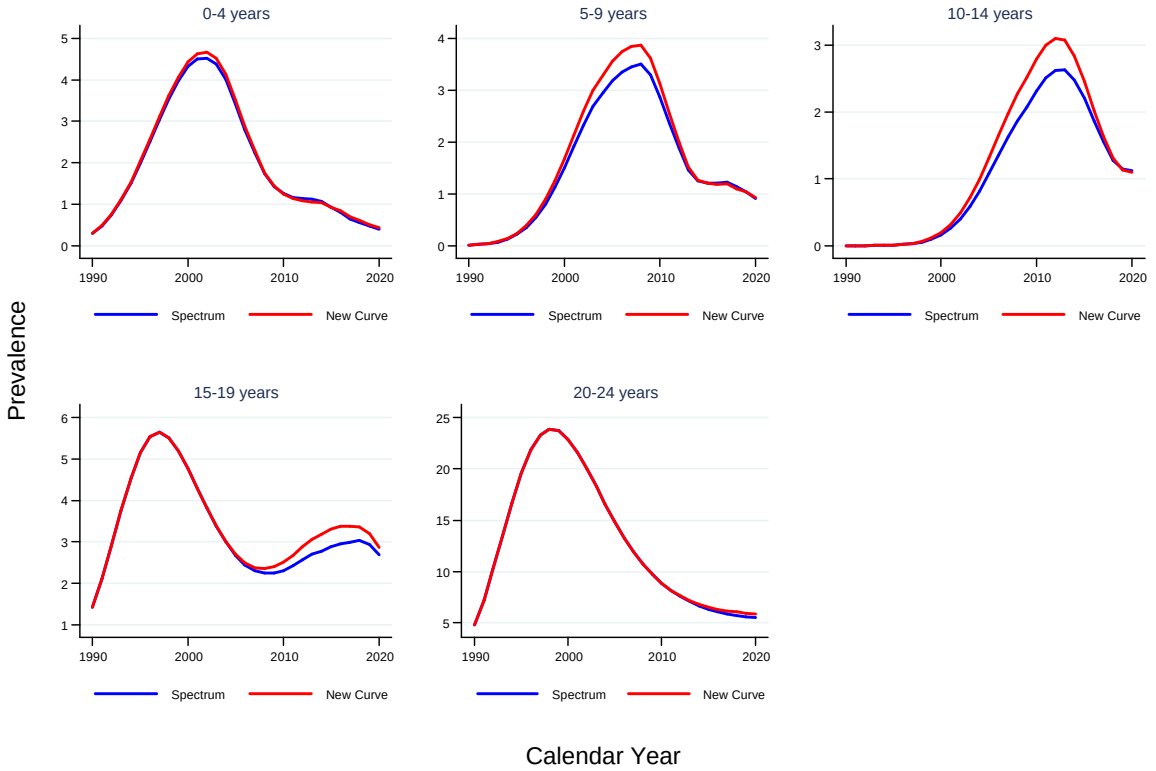


Figure 3.32: HIV prevalence between 1990 and 2020 by age group from Spectrum using current paediatric survival curve and the new curve (using 2014 country files from UNAIDS with no EPP adjustment), note difference y scales. - Lesotho

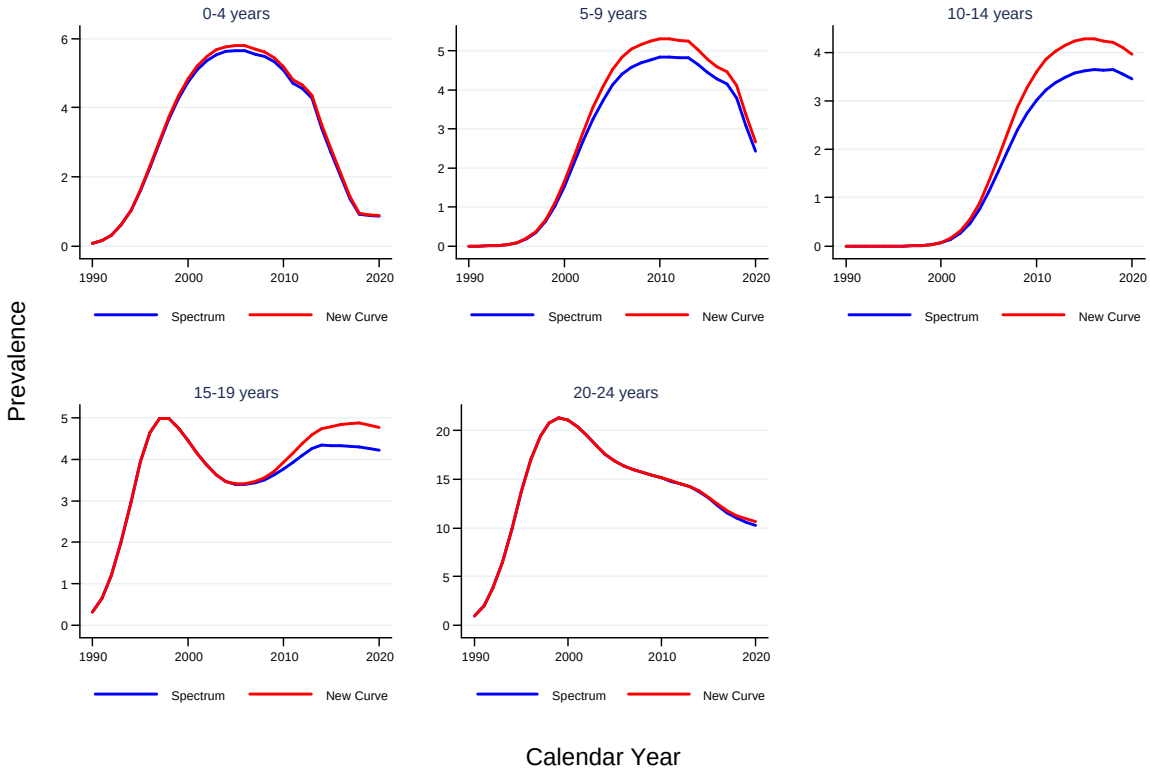


Figure 3.33: HIV prevalence between 1990 and 2020 by age group from Spectrum using current paediatric survival curve and the new curve (using 2014 country files from UNAIDS with no EPP adjustment), note difference y scales. -Malawi

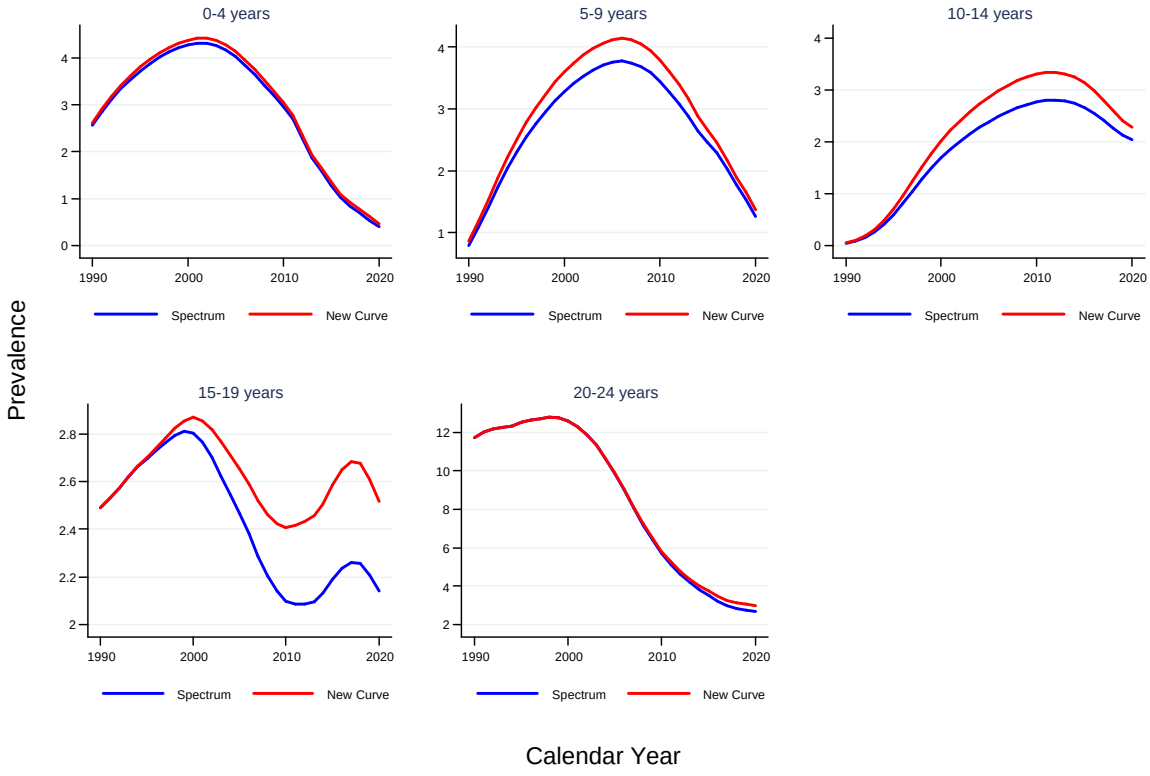


Figure 3.34: HIV prevalence between 1990 and 2020 by age group from Spectrum using current paediatric survival curve and the new curve (using 2014 country files from UNAIDS with no EPP adjustment), note difference y scales. - Mozambique

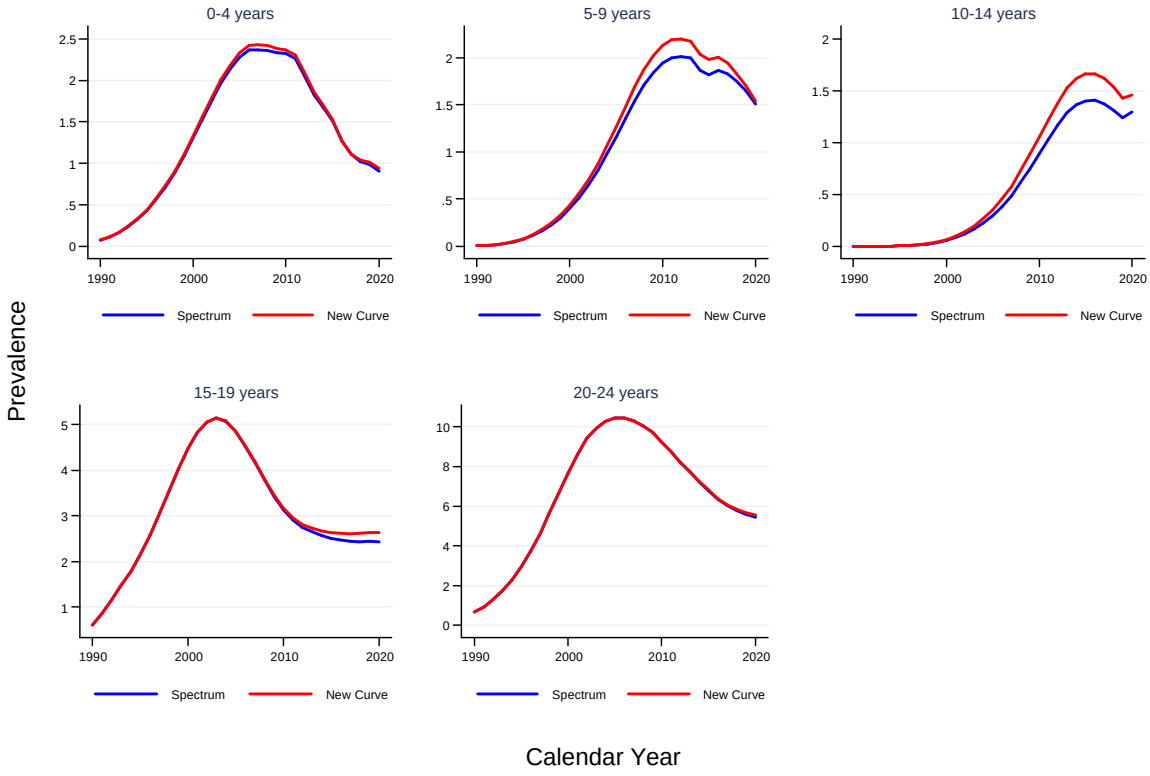


Figure 3.35: HIV prevalence between 1990 and 2020 by age group from Spectrum using current paediatric survival curve and the new curve (using 2014 country files from UNAIDS with no EPP adjustment), note difference y scales. -Rwanda

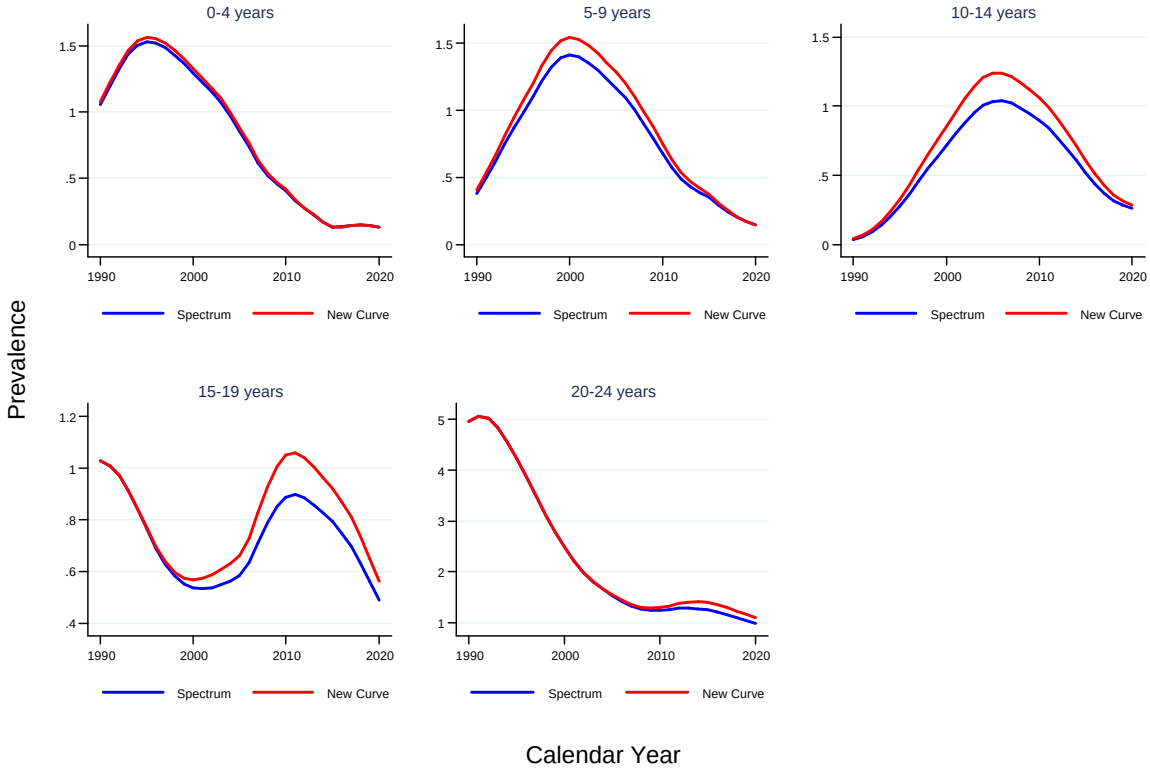


Figure 3.36: HIV prevalence between 1990 and 2020 by age group from Spectrum using current paediatric survival curve and the new curve (using 2014 country files from UNAIDS with no EPP adjustment), note difference y scales. – South Africa

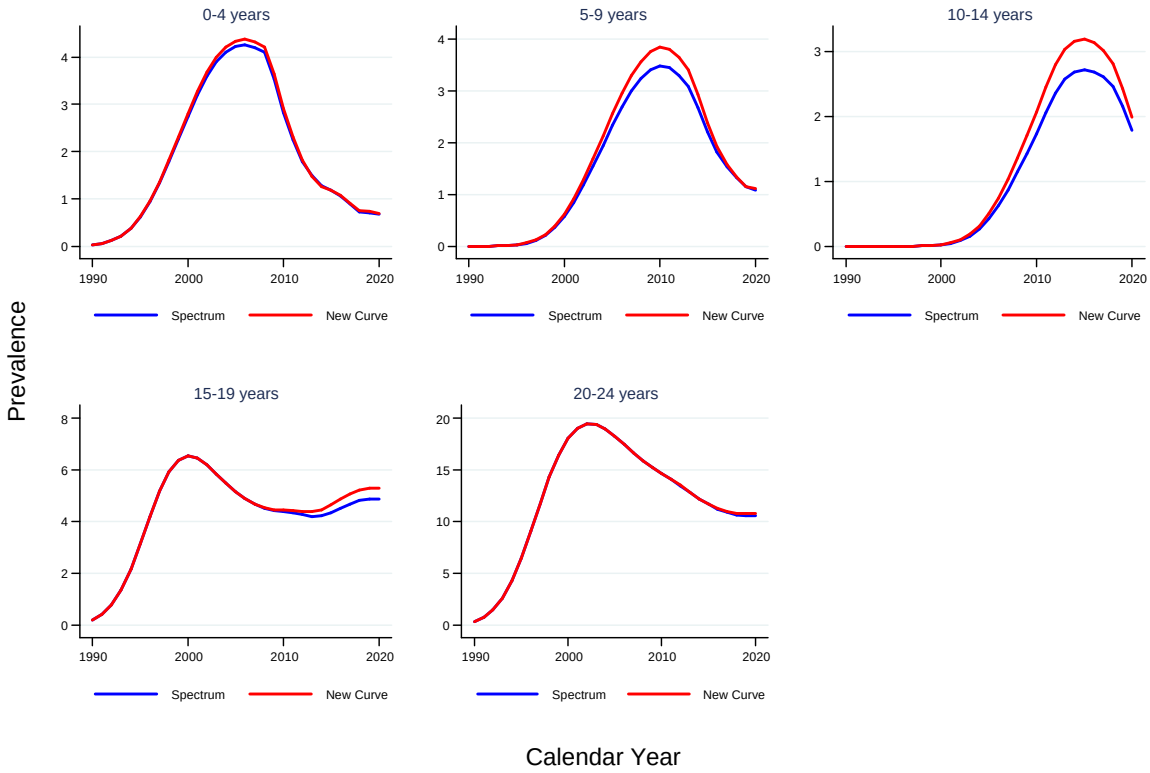


Figure 3.37: HIV prevalence between 1990 and 2020 by age group from Spectrum using current paediatric survival curve and the new curve (using 2014 country files from UNAIDS with no EPP adjustment), note difference y scales. - Swaziland

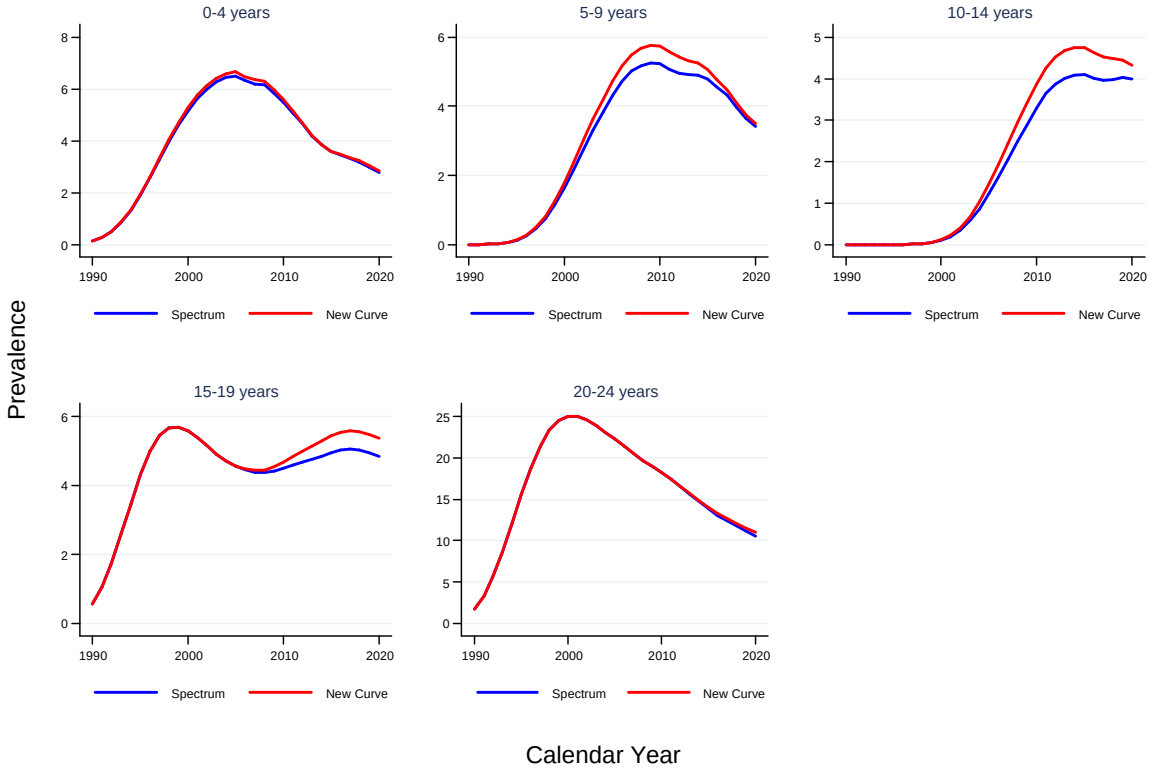


Figure 3.38: HIV prevalence between 1990 and 2020 by age group from Spectrum using current paediatric survival curve and the new curve (using 2014 country files from UNAIDS with no EPP adjustment), note difference y scales. - Tanzania

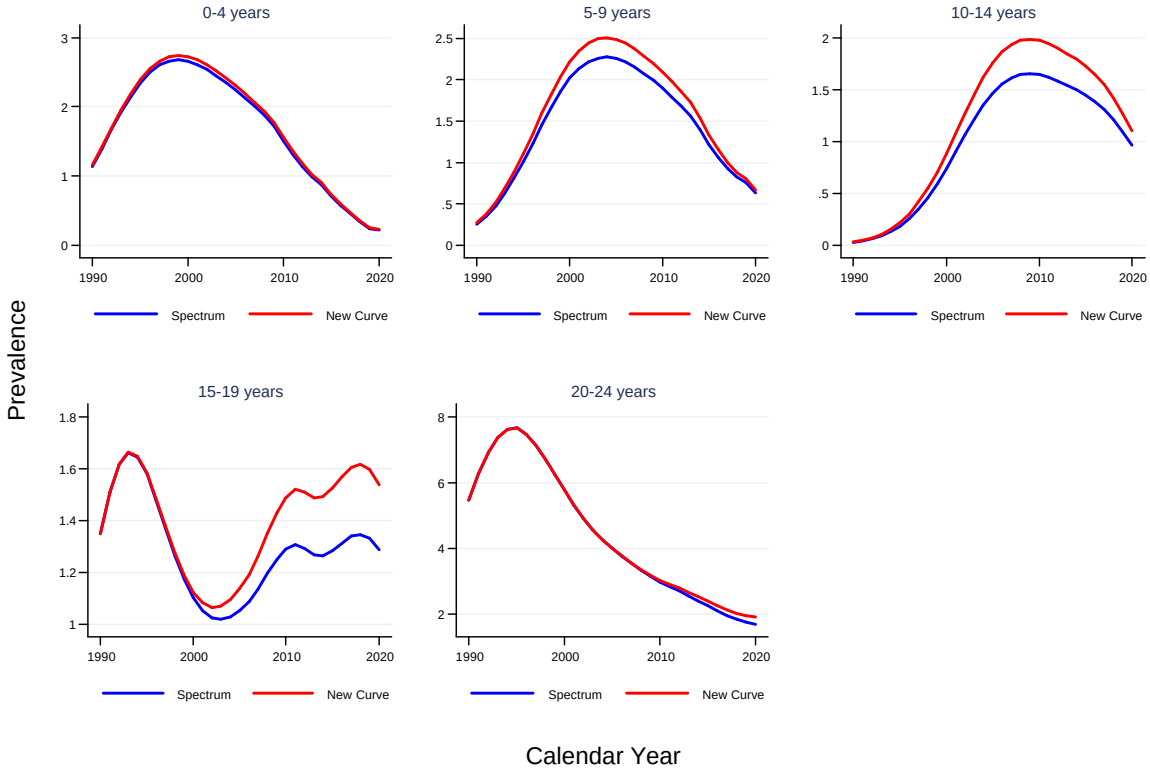


Figure 3.39: HIV prevalence between 1990 and 2020 by age group from Spectrum using current paediatric survival curve and the new curve (using 2014 country files from UNAIDS with no EPP adjustment), note difference y scales. - Uganda

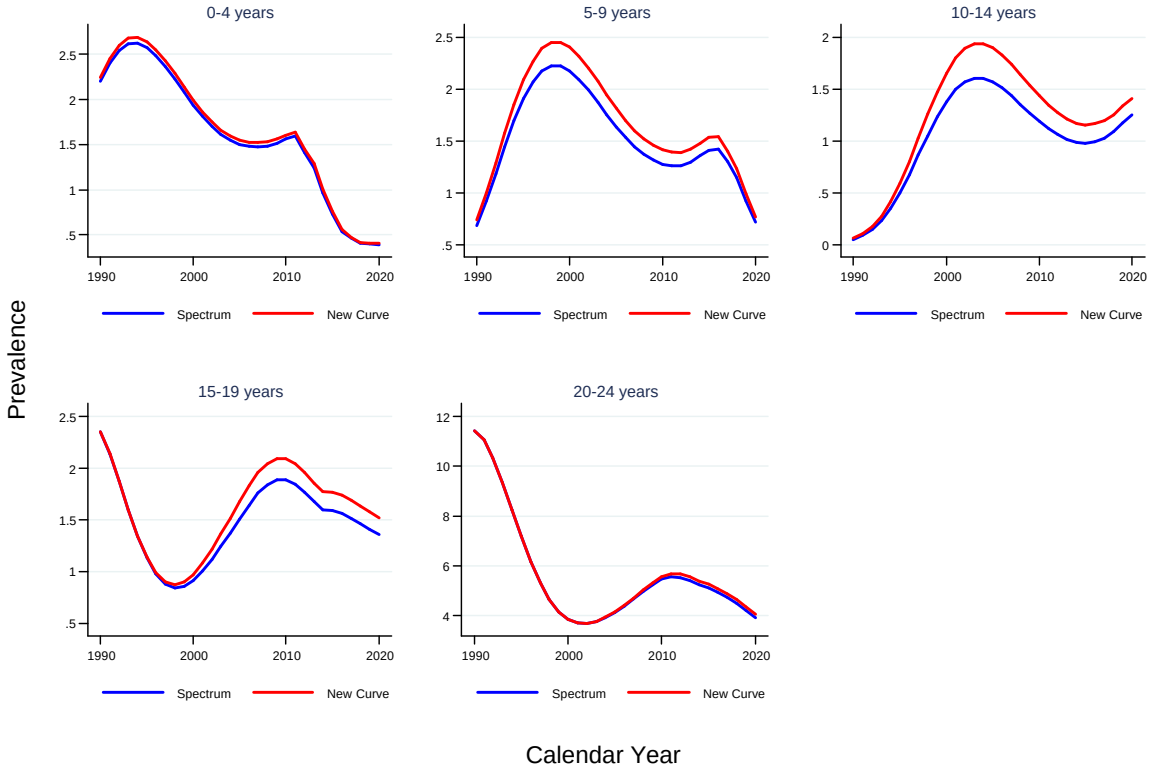


Figure 3.40: HIV prevalence between 1990 and 2020 by age group from Spectrum using current paediatric survival curve and the new curve (using 2014 country files from UNAIDS with no EPP adjustment), note difference y scales. - Zambia

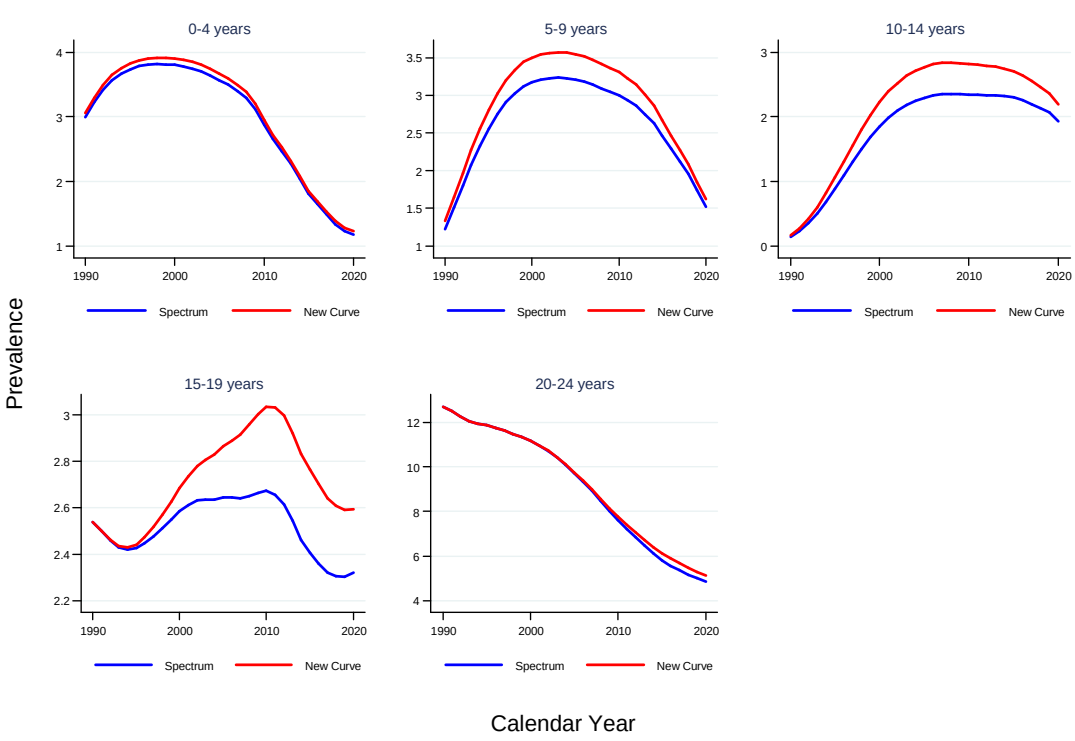


Figure 3.41: HIV prevalence between 1990 and 2020 by age group from Spectrum using current paediatric survival curve and the new curve (using 2014 country files from UNAIDS with no EPP adjustment), note difference y scales. - Zimbabwe

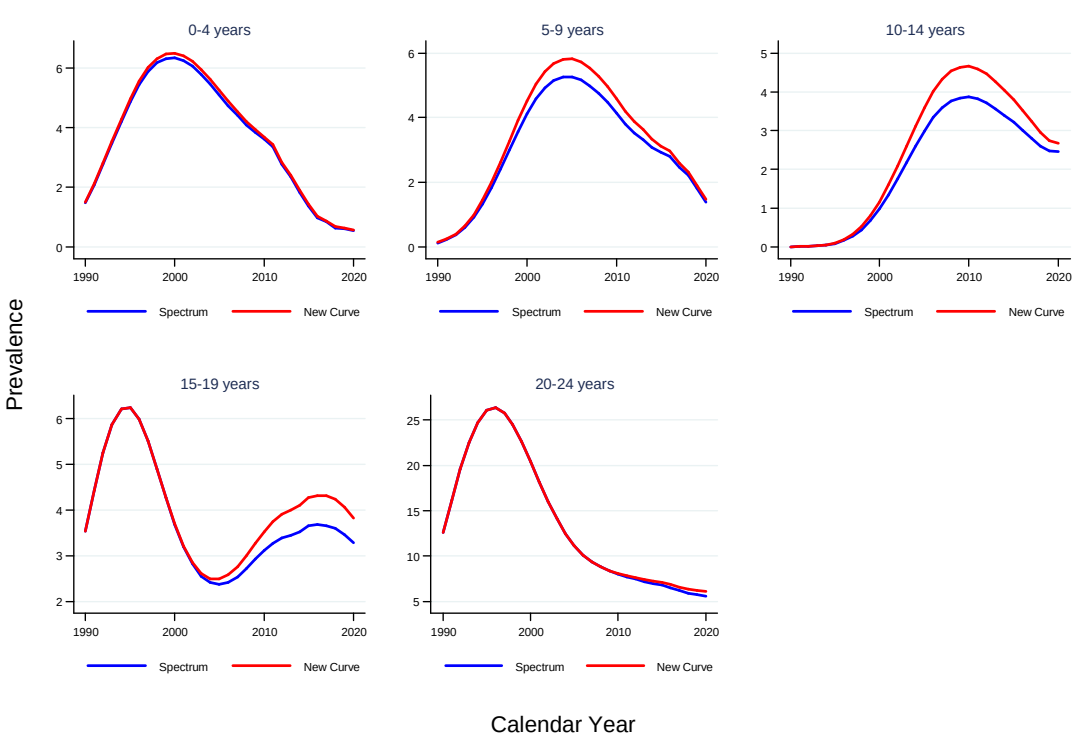


Table 3.11: Estimated HIV prevalence for 15-19 year olds in the DHS , Proportion of HIV positives reporting never having sex and the prevalence of HIV positive 15-19 year olds who report never having sex in the population.

Survey	HIV Prevalence (%)	Percentage of HIV positives who report never having sex	Prevalence of HIV +ve 15-19 year olds who have never had sex
Burkina2003	0.8 (0.4-1.5)	59.0 (28.6-83.9)	0.5 (0.2-1.1)
Burkina2010	0.3 (0.1-0.9)	72.1 (42.8-89.9)	0.2 (0.1-0.5)
Burundi2010	0.3 (0.1-0.6)	67.7 (30.2-91.1)	0.2 (0.1-0.5)
Cameroon2004	1.4 (1.0-2.0)	26.6 (14.4-43.8)	0.4 (0.2-0.7)
Cameroon2011	1.2 (0.9-1.7)	31.6 (17.0-50.9)	0.4 (0.2-0.8)
Congo2009	1.4 (0.8-2.5)	50.3 (26.9-73.7)	0.7 (0.3-1.7)
CoteIvoire2005	0.3 (0.1-0.8)	12.4 (2.8-40.7)	0.0 (0.0-0.1)
DRC2007	1.2 (0.6-2.5)	34.8 (12.4-66.8)	0.4 (0.2-0.9)
DRC2014	0.5 (0.2-1.3)	37.8 (8.5-80.0)	0.2 (0.1-0.6)
Ethiopia2005	0.4 (0.2-0.9)	23.9 (6.4-59.1)	0.1 (0.0-0.3)
Ethiopia2011	0.1 (0.1-0.2)	78.9 (49.6-93.4)	0.1 (0.0-0.2)
Gabon2012	1.0 (0.4-2.2)	23.1 (3.7-70.3)	0.2 (0.0-1.4)
Ghana2003	0.3 (0.2-0.7)	26.1 (6.4-64.8)	0.1 (0.0-0.4)
Guinea2005	0.7 (0.4-1.4)	21.2 (5.1-57.5)	0.2 (0.0-0.6)
Guinea2012	0.9 (0.5-1.7)	50.7 (23.7-77.3)	0.5 (0.2-1.2)
Kenya2003	1.6 (1.1-2.4)	42.8 (23.6-64.4)	0.7 (0.3-1.3)
Kenya2009	1.7 (1.1-2.6)	26.8 (11.9-49.9)	0.5 (0.2-1.1)
Lesotho2004	5.3 (4.1-6.9)	37.9 (26.2-51.1)	2.1 (1.4-3.2)
Lesotho2009	3.5 (2.6-4.7)	36.7 (24.3-51.2)	1.3 (0.8-2.1)
Liberia2007	0.9 (0.5-1.5)	10.2 (2.4-34.6)	0.1 (0.0-0.4)
Liberia2013	0.6 (0.2-1.4)	4.6 (0.9-20.8)	0.0 (0.0-0.1)
Malawi2004	2.1 (1.3-3.3)	32.1 (14.2-57.5)	0.7 (0.3-1.6)
Malawi2010	2.7 (2.0-3.6)	38.5 (25.2-53.7)	1.0 (0.6-1.7)
Mali2006	0.6 (0.4-1.2)	47.3 (21.0-75.2)	0.3 (0.1-0.8)
Mali2013	0.6 (0.3-1.2)	54.5 (19.1-85.8)	0.3 (0.1-0.9)
Mozambique2009	5.0 (3.7-6.6)	14.5 (7.1-27.1)	0.8 (0.4-1.6)
Rwanda2005	0.5 (0.3-0.9)	53.4 (26.0-78.9)	0.3 (0.1-0.6)
Rwanda2010	0.5 (0.3-0.8)	69.9 (44.4-87.1)	0.4 (0.2-0.7)
SaoTome2009	0.7 (0.3-1.6)	70.6 (32.1-92.4)	0.5 (0.2-1.4)
Senegal2005	0.1 (0.0-0.3)	28.5 (3.3-82.3)	0.0 (0.0-0.2)
Senegal2011	0.1 (0.0-0.2)	16.5 (2.0-65.1)	0.0 (0.0-0.1)
SierraLeone2008	0.7 (0.3-1.4)	17.7 (3.7-54.7)	0.1 (0.0-0.5)
SierraLeone2013	1.1 (0.7-1.7)	33.4 (18.8-52.2)	0.4 (0.2-0.7)
Swaziland2007	5.8 (4.8-7.0)	34.8 (27.2-43.3)	2.1 (1.5-2.8)
Tanzania2004	2.1 (1.5-3.0)	41.4 (26.1-58.7)	0.9 (0.5-1.4)
Tanzania2008	1.0 (0.7-1.5)	46.3 (26.9-66.9)	0.5 (0.2-0.9)
Tanzania2012	1.0 (0.7-1.5)	57.2 (37.7-74.8)	0.6 (0.3-1.1)
Uganda2011	2.4 (1.8-3.0)	45.7 (36.3-55.4)	1.1 (0.8-1.5)
Zambia2007	4.7 (3.7-5.9)	40.7 (31.9-50.2)	2.0 (1.4-2.7)
Zimbabwe2006	4.6 (3.8-5.6)	45.3 (35.7-55.2)	2.2 (1.6-2.8)
Zimbabwe2011	3.8 (3.1-4.6)	62.8 (52.8-71.8)	2.4 (1.9-3.1)

4 PAPER B: Is the risk of HIV acquisition increased during and immediately after pregnancy? A secondary analysis of pooled HIV community-based studies from the ALPHA network.

For objective 2 of the PhD: to investigate population level risk of acquisition of HIV in pregnant women; an analysis was conducted using data from the ALPHA network and published in:

Marston, M; Newell, ML; Crampin, A; Lutalo, T; Musoke, R; Gregson, S; Nyamukapa, C; Nakiyingi-Miiro, J; Urassa, M; Isingo, R; Zaba, B. (2013) *Is the Risk of HIV Acquisition Increased during and Immediately after Pregnancy? A Secondary Analysis of Pooled HIV Community-Based Studies from the ALPHA Network.* PLoS One, 8 (12).

4.1 Introduction to paper

Differences in the rate of acquisition of HIV in pregnancy or in the postpartum period compared to non-pregnant non-postpartum time are important to consider when estimating mother to child transmission, as the increased viral load in recent infection would expose the foetus to higher risk of in utero mother-to-child transmission, or a breastfeeding infant to a higher risk of postpartum transmission. Apart from one, all of the previous studies on HIV acquisition in pregnancy were not from a general population, which is an important limitation, as in the general population HIV acquisition in pregnancy depends not only on biological mechanisms for the transmission of HIV and sexual behaviour but also on the level of HIV discordance amongst partners.

Therefore for estimates of paediatric HIV incidence at a population level, an analysis of population level data is required. Population-based HIV cohort studies are ideally placed to provide generalisable estimates of the risk of HIV acquisition during pregnancy in the community; this paper uses data from six such cohorts from eastern and southern Africa which are part of the ALPHA network. The paper assesses the population-level HIV incidence during pregnancy and the post-partum period, adjusting for age.

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

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Student	Camilla Marston
Principal Supervisor	Basia Zaba
Thesis Title	Demographic Determinants of Paediatric HIV in Generalised HIV epidemics

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When was the work published?	December 2013		
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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)	Study sites provided the data which I pooled and checked. I conceived the idea, designed the analysis, carried out the analysis and wrote the paper with co authors commenting and editing drafts

Student Signature: [redacted] **Date:** 27/03/18

Supervisor Signature: [redacted] **Date:** 27.03.2018

Is the risk of HIV acquisition increased during and immediately after pregnancy? A secondary analysis of pooled HIV community-based studies from the ALPHA network.

Milly Marston[1], Marie Louise Newell[2,3], Amelia Crampin[4,1], Tom Lutalo[5], Richard Musoke[5], Simon Gregson[6,7], Constance Nyamukapa[6,7], Jessica Nakiyingi-Miiro[8], Mark Urassa[9,] Raphael Isingo[9], Basia Zaba[1].

1. London School of Hygiene and Tropical Medicine, London, United Kingdom
2. Africa Centre for Health and Population Studies, University of KwaZulu-Natal, Somkhele, South Africa
3. Faculty of Medicine, Faculty of Social and Human Sciences, University of Southampton, Southampton, United Kingdom
4. Karonga Prevention Study, Chilumba, Malawi
5. Rakai Health Sciences program, Kalisizo, Rakai, Uganda
6. Imperial College London, London, United Kingdom
7. Biomedical Research and Training Institute, Harare Zimbabwe.
8. Medical Research Council, Entebbe, Uganda.
9. TAZAMA project, National Institute of Medical research, Mwanza, Tanzania

Corresponding Author: Milly Marston – milly.marston@lshtm.ac.uk

4.2 Abstract

Background

Previous studies of HIV acquisition in pregnancy have been in specific population groups, such as sero-discordant couples which have shown an increased risk of HIV acquisition during pregnancy and studies of sexually active women where the results have been ambiguous. However these studies are unable to tell us what the overall impact of pregnancy is on HIV acquisition in the general population.

Methods

Data from six community-based HIV cohorts were pooled to give 2,628 sero-conversions and a total of 178,000 person years of observation. Multiple imputation was used to allow for the uncertainty of exact sero-conversion date in surveillance intervals greater than the length of a pregnancy. Results were combined using Rubin's rules to give appropriate error bounds. The analysis was stratified into two periods: pre- and post- widespread availability of prevention of mother-to-child HIV transmission services. This allows us to assess whether there is reporting bias relating to a person's knowledge of their own HIV status which would become more widespread in the latter time period.

Results

Results suggest that women while pregnant have a lower risk of acquiring HIV infection over all periods (HRR 0.79, 95%CI 0.70-0.89) than women who were not pregnant. There is no evidence for a difference in the rate of HIV acquisition between postpartum and non-pregnant women (HRR 0.92 95%CI 0.84-1.03).

Discussion

Although there may be immunological reasons for increased risk of HIV acquisition during pregnancy, at a population level this study indicates a lower risk of HIV acquisition for pregnant women. Pregnant women may be more likely to be concordant with their current sexual partner than non-pregnant women, i.e. either already HIV positive prior to the pregnancy or if negative at the time of becoming pregnant more likely to have a negative partner.

4.3 Introduction

Fertility rates are high in many sub-Saharan African countries and, thus, a significant proportion of woman-years are spent pregnant [53]. Evidence regarding the risk of acquisition of HIV infection at and shortly after the time of pregnancy is conflicting [54-60]. An increased risk of HIV acquisition in pregnant women has implications for health services as the increased viral load in acute infection would expose the fetus to higher risk of in utero mother-to-child transmission[61]. This would also have implications for HIV epidemic modelling as estimates for paediatric HIV would need to be revised upwards.

A number of prospective studies from Eastern and Southern Africa have assessed the risk of HIV incidence during pregnancy. A multisite study of sero-discordant couples found that HIV incidence was, in univariate analysis, two-fold higher in pregnant than in not-pregnant women; however, after adjusting for age, any unprotected sex in last month, and contraceptive use, the risk difference was reduced and no longer statistically significant [57]. A similar study in Uganda restricted to married sero-discordant couples reported a non-significant increase in the HIV acquisition rate in pregnant women [54]. Other studies included women regardless of the partners' HIV status; in a Ugandan study of sexually-active women the risk of HIV-1 acquisition was doubled during pregnancy [54]. However, in an HIV prevention trial enrolling women from a number of health services and community venues in southern Africa there was no increased risk of HIV-1 in pregnant women [59]. A study in Uganda and Zimbabwe, in which women from family planning sites were enrolled, found no increased risk of HIV acquisition in pregnant women in the pooled analysis overall, and actually showed some evidence of a protective pregnancy effect in one of the sites in the study after adjusting for covariates [56]. Further studies have shown a possible increased HIV incidence during pregnancy [62-64], others showed a risk comparable to the general population of a similar age [65, 66].

A number of studies have investigated HIV incidence in the postpartum period, again with somewhat conflicting results. In Malawi, a prospective study of women enrolled after delivery found HIV acquisition was increased in the first year postpartum decreasing subsequently [60]; this was also the case in Zimbabwe [58] and Rwanda [55]. The authors of the latter study suggested that the decrease could be partly due to a cohort selection bias with those remaining uninfected for longer having a lower risk of infection . Other studies have not reported an increased risk in the postpartum period [54, 67].

The rate of HIV acquisition and differences between pregnant, postpartum and non-pregnant women at a population level will depend not only on the risk of infection per sexual act with an HIV positive partner, but also on the level of discordance in pregnant and non-pregnant couples and the differences in sexual behaviour between these groups. Therefore results from the studies outlined above cannot be generalised to the general population.

Population-based HIV cohort studies are ideally placed to provide generalisable estimates of the risk of HIV during pregnancy in the community; this paper uses data from six such cohorts from eastern and southern Africa. We aim to assess the population-level HIV incidence during pregnancy and the post-partum period, adjusting for age. The results will inform organisations that provide estimates to health services providers.

4.4 Methods

4.4.1 Data

Data come from six sites: Karonga (Karonga prevention study), Kisesa (TAZAMA), Masaka (UK Medical Research Council and Uganda Virus Research Institute), Rakai (Rakai Health Sciences), Manicaland (Imperial College London and the Biomedical Research and Training Institute) and uMkhanyukude (Africa Centre). Data collection was sufficiently similar to allow pooled analyses, with allowance for unobserved heterogeneity between sites.

The Karonga Demographic Surveillance Study (DSS) is located in rural northern Malawi; it was established in 2002 and has a total population of around 35,000, population-based HIV testing in the DSS was undertaken in four annual rounds from 2007-2011 [25] and average adult HIV prevalence between these dates was 8% [26]. The Kisesa cohort study is situated in rural north-west Tanzania, it was established in 1994 and has a population of around 30,000 it contains a small trading centre located on the main road from Mwanza town to the border of Kenya which runs through the centre of the study area, average HIV prevalence between 1994 and 2010 was 6% [27, 133]. The Masaka DSS is located in rural south west Uganda and was established in 1989. Its initial population was around 10,000 which then increased to 18,000 when 10 villages were added to the census area [31]. Average HIV prevalence between 1989 and 2011 was 8% [32]. The Rakai Health Sciences Program runs the Rakai Community Cohort Study (RCCS), with an adult population of between 12,000-16,000. For this analysis, data were collected from 1999 with 2002/03 adult HIV prevalence reported to be 11.4 % [33]. The Manicaland study was established in 1993. A

prospective household census (population size approximately 37,000) and general population cohort survey (10,000-12,000) were initiated in 12 locations spread across three districts in 1998, with follow-ups being conducted every 2 or 3 years. They comprise two small towns, four agricultural estates, two roadside settlements and four subsistence farming areas. Overall adult HIV prevalence has fallen in these areas from 24% in the late 1990s to 14% at the end of the 2010s [134]. The Africa Centre Surveillance study was established in 2000 in uMkhanyakude, in rural KwaZulu-Natal, South Africa; each round covers approximately 90,000 resident and non-resident household members in approximately 12,000 households, with a key-household respondent [34], an individual HIV surveillance for resident adults (≥15 years) was added in 2003 and adult HIV prevalence in 2012 was around 28% and annual incidence in the 15-50 year age group for women was about 5% [35].

4.4.2 Ethics statement

Each of the six sites contributing data to the pooled analysis has received ethical clearance from the appropriate local ethics review bodies, and from the corresponding Institutional Review Boards for studies which had collaborating partnerships with Northern Universities. **uMkhanyakude**: Annually re-certified ethics permission for the Africa Centre DSS and nested individual HIV surveillance among consenting adults obtained from the Biomedical Research Ethics Committee at the Nelson Mandela School of Medicine, University of KwaZulu-Natal. Detailed written informed consent obtained for participation in the HIV surveillance. **Karonga**: Ethical approval granted by the National Health Sciences Research Committee of Malawi and the ethics Committee of the London School of Hygiene and Tropical Medicine. Written informed consent obtained for HIV testing. **Kisesa**: Ethical approval for each survey round of the Kisesa cohort study granted by the Tanzanian Medical Research Coordinating Committee and the Ethics Committee of the London School of Hygiene and Tropical Medicine. Prior to 2006, verbal consent obtained directly from all study participants (aged 15 and over), due to low literacy rates among the study population. Consent witnessed and documented for each study participant by a member of the sero-survey team. From 2006 onward, consent was again obtained directly from all study participants, however written consent option introduced, for those able to provide this. **Manicaland**: All respondents (all aged 15 years and older) provided written informed consent at each survey round prior to completing survey and providing a blood sample for HIV testing. For respondents under age 18 years, written informed consent was also provided by parent/guardian. Ethical approval for Manicaland HIV/STD Prevention Project

provided by Medical Research Council of Zimbabwe and St. Mary's Research Ethics Committee, London. **Masaka**: The MRC DSS approved by the Uganda Virus Research Institute (UVRI) Science and Ethics Committee (SEC) and the Uganda National Council of Science and Technology (UNCST). Study participants provided written consent to participate in any part of the study. **Rakai**: The Rakai Community Cohort Survey approved by the UVRI SEC andUNCST. Literate participants provided written consent while those unable to read or write had a witness sign on their behalf.

4.4.3 Identifying pregnancy periods

For all the sites, in the absence of active pregnancy reporting, pregnancy periods can be identified from the date of birth of a child. This information either comes from a mother-child data link or from a women reporting that she gave birth. All studies apart from Karonga and Africa Centre also collect routine data on current pregnancy status, giving limited information on pregnancy periods that do not result in a live birth. Such pregnancies are harder to identify for a number of reasons: firstly women rarely report a pregnancy in the first trimester; secondly many DSS use proxy respondents so it is possible that they will not know the women in their household is pregnant until sometime past the first trimester. Pregnancies ending in early miscarriage are thus rarely captured. Rakai is a partial exception as they have done routine hCG (*human chorionic gonadotropin)* testing if the last menstrual period was delayed or the woman was unsure of her pregnancy status [54]. Pregnancies ending in stillbirth may be captured either by asking direct questions about stillbirths since the last DSS round, or by noting reported pregnancies that did not result in a live birth in a later round. However only those DSS which have consistently maintained a short time gap between survey rounds (ideally ≤4 months) can be reasonably certain of interviewing women after the first trimester but before the stillbirth occurs. Early miscarriage and abortion are estimated to make up a fairly small proportion of total time pregnant therefore missing a large fraction of these would be unlikely to affect the results.

4.4.4 Analysis methods

Women of reproductive age (15- 49 years old) were eligible for inclusion in the analysis. Person-years of observation for each woman were split into time not-pregnant, pregnant and one year postpartum. For a woman to be included in the analysis she must have had at least two HIV tests, the first of which must have been negative to allow observation of any

sero-conversion. Follow-up time started from the date of the first negative test and lasted until exit at the date of their last test or at the date of sero- conversion, if earlier.

Time between HIV surveillance tests varies across the different sites ranging from annual to three year inter-test intervals; further, a person might miss a surveillance round thus extending the period between tests. For all study sites, the interval between HIV tests is longer than a full gestation pregnancy, and we cannot be sure whether the sero-conversion occurred before, during or after the pregnancy period. To allow for this uncertainty, the analysis was repeated 100 times, each time with the estimated sero-conversion date assigned at a random point between the last negative and first positive dates, rates and crude and adjusted hazard rate ratios (HRR) were calculated using piecewise exponential regression, so that age (grouped into conventional five year age groups), pregnancy status and calendar time could be treated as time-varying factors. Rates and the log of the hazard rate ratios from the imputations were combined using Rubin's rules [39] to give confidence intervals that reflect the uncertainty about the exact date of sero-conversion. The crude hazard rate ratios converged at around 20 imputations with the adjusted rate ratios taking 30 to 40 imputations to converge to stable values.

Since the introduction of widespread voluntary counselling and testing and the roll-out of antiretroviral treatment (ART) in sub-Saharan Africa, it is possible that the composition of those who do not consent to test/participate in surveillance has changed, potentially biasing results. For example, people who know they are HIV-positive may be less likely to consent to participate in an HIV surveillance round [26, 135, 136], this would be especially pertinent for women who are HIV tested in antenatal care (ANC) clinics in the context of prevention of mother-to-child transmission (PMTCT) services. Women who are not pregnant may have less exposure to HIV testing, although community-based HIV testing is becoming more widespread. The possibility of bias after PMTCT programmes were introduced (post-PMTCT period) is addressed by stratifying the data by the pre- and post-PMTCT periods. Post-PMTCT is defined from the point when PMTCT became available and accessible to the populations. In some studies, this time preceded introduction of HIV treatment programmes (Masaka, Rakai and uMkhanyakude).

Surveillance data from the Kisesa, Masaka, Manicaland and Rakai studies all include a period before PMTCT was widely available at ANC. For Karonga and uMkhanyakude HIV

surveillance data are only available after introduction of widespread PMTCT services (Table 4.1).

Table 4.1: Data available from sites by periods in which availability of PMTCT was low medium and high

Site	Availability of data by level of PMTCT services	
	None/Very low	**Some/Widespread**
Karonga	No data available	2007-2011
Kisesa	1994-May2007	June 2007-2010
Manicaland	1998-2008	No data available
Masaka	1989-Mar2002	April 2002-2010
Rakai	1999-May2004	June 2004-2011
uMkhanyakude	No data available	2001-2011

This paper investigates the risk of HIV acquisition during pregnancy and in the postpartum period in both the pre- and post-PMTCT period. For the pre-PMTCT period person years are censored at date of last test prior to widespread PMTCT. The post-PMTCT period includes all the person years from the date PMTCT began to be more widely available in each site.

4.5 Results

Table 4.2 and Table 4.3 show site specific and pooled rates before and after introduction of PMTCT. Overall there were 2628 sero-conversions and a total of 178 thousand person years contributing to the analysis. The number of person years and sero-conversions in the pre-PMTCT period is lower than in the post-period, partly due to fewer study sites contributing and partly due to the strict censoring at last test prior to PMTCT beginning in each site. uMkhanyakude contributes around two-thirds of the sero-conversions in the post-PMTCT period, but only a sixth of the person-years due to its relatively high incidence and low fertility setting. Karonga only provides a small number of sero-conversions and few person-years due to a shorter follow-up time. Using the mean of the imputation runs 304 sero-conversions occurred in the 25,000 person years spent pregnant.

Table 4.2: Sero-conversion and person years contributing to the analysis for each period (mean of imputation runs). Note that the uMkhanyakude and Karonga site only contributes to the post PMTCT period.

Pregnancy and Maternity Status	All* (Six Sites)			Pre PMTCT (Four sites)			Post PMTCT (Five sites)		
	SC	1000 PY	Rate /1000 PY	SC	1000 PY	Rate /1000 PY	SC	1000 PY	Rate /1000 PY
Maternity Status									
Not pregnant	1861	121.10	15.37	271	28.33	9.57	1245	68.43	18.20
Pregnant	304	24.75	12.28	62	6.65	10.32	169	12.52	13.46
<1 year post partum	463	31.49	14.70	81	8.30	8.87	262	16.52	15.86
Pregnancy Status									
Not pregnant	2324	152.57	15.23	345	36.63	9.41	1507	84.95	17.74
Pregnant	304	24.75	12.28	69	6.65	10.32	169	12.52	13.46

*Note that all is not the sum of pre and post- PMTCT due to the nature of censoring for the pre-PMTCT group

Table 4.3: : Number of Sero-conversions (SC) and person years (PY) contributing to the analysis for each site by period (mean of imputation runs). Note that each site covers a different period of calendar time.

Pregnancy and Maternity Status	Karonga			Kisesa			Manicaland			Masaka			Rakai			uMkhanyakude		
	SC	1000 PY	Rate per 1000 PY	SC	1000 PY	Rate per 1000 PY	SC	1000 PY	Rate per 1000 PY	SC	1000 PY	Rate per 1000 PY	SC	1000 PY	Rate per 1000 PY	SC	1000 PY	Rate per 1000 PY
Pre PMTCT																		
Not pregnant	-	-	-	57	6.30	9.06	84	6.08	13.80	65	9.16	7.05	65	6.80	9.57	-	-	-
Pregnant	-	-	-	12	2.06	5.85	10	0.55	18.31	11	1.88	5.84	36	2.18	16.55	-	-	-
<1 year post partum	-	-	-	17	2.64	6.50	7	0.74	9.99	13	2.30	5.54	36	2.63	13.88	-	-	-
Post PMTCT																		
Not pregnant	34	8.15	4.22	19	3.13	5.93	41	3.70	11.10	83	13.43	6.16	230	20.43	11.26	841	19.70	42.69
Pregnant	9	1.73	4.99	3	0.65	3.99	1	0.34	1.75	16	2.42	6.44	36	5.31	6.80	105	2.04	51.43
<1 year post partum	9	2.46	3.55	6	0.94	6.77	2	0.44	4.24	20	3.22	6.19	80	6.64	11.98	146	2.75	52.88
All Years																		
Not pregnant	34	8.15	4.22	170	17.33	9.78	241	16.95	14.20	175	25.51	6.88	401	33.44	11.99	841	19.70	42.69
Pregnant	9	1.73	4.99	36	5.19	6.84	23	1.55	14.65	31	4.84	6.40	100	9.40	10.64	105	2.04	51.43
<1 year post partum	9	2.46	3.55	53	6.52	8.10	39	2.11	18.46	38	6.17	6.20	178	11.47	15.55	146	2.75	52.88

In the pooled data, the crude analysis showed no evidence of different risks of HIV acquisition between pregnant or postpartum women and non-pregnant women in the pre-PMTCT era (Table 4.4). After adjusting for age, the rate ratios showed a protective effect for pregnant and postpartum women compared to those who were not pregnant, although this did not reach statistical significance for pregnant women (HRR 0.85, 95%CI 0.63-1.13 and HHR 0.75 95%CI 0.57-0.98, respectively). In the post-PMTCT period, there was evidence of a protective effect against HIV acquisition in both pregnant and postpartum women when adjusted for age (HHR 0.60, 95%CI 0.50-0.71 and HHR 0.71 95%CI 0.62-0.82 respectively (Table 4.5)). After adjusting for study site the evidence became of borderline statistical significance for postpartum women.

Table 4.4: Incident rate ratio comparing pregnancy status for pre PMTCT period

Pregnancy and Maternity Status	Crude		Adjusted Age		Adjusted Age and Site	
	HRR	95% CI	HRR	95% CI	HRR	95% CI
Maternity Status						
Not pregnant	1		1		1	
Pregnant	1.08	(0.82-1.42)	0.85	(0.64-1.13)	0.89	(0.67-1.19)
<1 year postpartum	0.93	(0.71-1.21)	0.75	(0.57-0.98)	0.78	(0.59-1.03)
Pregnancy Status						
Not pregnant	1		1		1	
Pregnant	1.10	(0.84-1.43)	0.93	(0.71-1.22)	0.96	(0.73-1.26)

Table 4.5: Incident rate ratio comparing pregnancy status for the period post widespread PMTCT

Pregnancy and Maternity Status	Crude		Adjusted Age		Adjusted Age and Site	
	HRR	95% CI	HRR	95% CI	HRR	95% CI
Maternity Status						
Not pregnant	1		1		1	
Pregnant	0.74	(0.63-0.87)	0.60	(0.50-0.71)	0.75	(0.64-0.89)
<1 year postpartum	0.87	(0.76-1.00)	0.71	(0.62-0.82)	0.89	(0.77-1.02)
Pregnancy Status						
Not pregnant	1		1		1	
Pregnant	0.76	(0.64-0.89)	0.65	(0.55-0.76)	0.77	(0.65-0.91)

Combining all data from all periods gave results very similar to those in the post-PMTCT period: with a rate ratio comparing pregnant to non-pregnant women adjusted by age of 0.69 (95%CI 0.61-0.78), indicating a lower HIV acquisition risk during pregnancy (Table 4.6). This effect remained when adjusting by study site.

Table 4.6: Incident rate ratio comparing pregnancy status for all periods

Pregnancy and Maternity Status	Crude		Adjusted Age		Adjusted Age and Site	
	HRR	95% CI	HRR	95% CI	HRR	95% CI
Maternity Status						
Not pregnant	1		1		1	
Pregnant	0.80	(0.71-0.90)	0.64	(0.57-0.73)	0.77	(0.68-0.88)
<1 year postpartum	0.96	(0.86-1.06)	0.78	(0.70-0.87)	0.92	(0.84-1. 03)
Pregnancy Status						
Not pregnant	1		1		1	
Pregnant	0.81	(0.71-0.91)	0.69	(0.61-0.78)	0.79	(0.70-0.89)

There was evidence of an interaction between age and pregnancy status indicating that the protective effect did not apply to the 15-24 year old age group (all periods pooled HRR 0.84 95%CI 0.50-1.41), this effect remained significant excluding the uMkhayakude which contributes the most data. There was no evidence of interaction between pregnancy status and study site. The analysis was repeated on individual site data combining the pre- and post-PMTCT periods (Table 4.7); both the Kisesa and Rakai studies individually showed a significant decrease in HIV acquisition rates comparing pregnant to non-pregnant women when adjusted for age (HRR 0.57, 95%CI 0.37-0.87 and HRR 0.71 , 95%CI 0.57-0.89 respectively). Masaka and Manicaland showed a non-significant decrease in HIV acquisition, Karonga and Africa Centre showed no evidence for any difference between HIV acquisitions in pregnant women compared to non-pregnant women; however, the confidence intervals in Karonga are very wide due to the small sample. Kisesa showed a significant decrease and Masaka a borderline significant decrease in HIV acquisition in postpartum compared to non-pregnant women; the other sites showed no evidence for any difference between the two groups.

Table 4.7: Incident rate ratio adjusted for age comparing pregnancy status for all periods by study site

Pregnancy and Maternity Status	Karonga		Kisesa		Manicaland		Masaka		Rakai		uMkhanyakude	
	HRR	95% CI	HRR	95% CI	HRR	95% CI	HRR	95% CI	HRR	95% CI	HRR	95% CI
Maternity Status												
Not pregnant	1		1		1		1				1	
Pregnant	1.17	(0.49-2.79)	0.70	(0.47-1.03)	1.02	(0.62-1.68)	0.93	(0.62-1.39)	0.89	(0.71-1.11)	1.20	(0.97-1.48)
<1 year postpartum	0.82	(0.33-2.04)	0.83	(0.60-1.14)	1.29	(0.90-1.86)	0.90	(0.63-1.29)	1.30	(1.08-1.55)	1.24	(1.03-1.48)
Pregnancy Status												
Not pregnant	1		1		1		1		1		1	
Pregnant	1.21	(0.51-2.86)	0.66	(0.43-0.99)	0.98	(0.60-1.62)	0.95	(0.64-1.40)	0.82	(0.66-1.03)	1.17	(0.95-1.44)

Adjusted

Pregnancy and Maternity Status	Karonga		Kisesa		Manicaland		Masaka		Rakai		uMkhanyakude	
	HRR	95% CI	HRR	95% CI	HRR	95% CI	HRR	95% CI	HRR	95% CI	HRR	95% CI
Maternity Status												
Not pregnant	1		1		1		1				1	
Pregnant	0.97	(0.40-2.40)	0.56	(0.38-0.84)	0.81	(0.49-1.34)	0.76	(0.50-1.15)	0.73	(0.58-0.92)	0.91	(0.73-1.12)
<1 year postpartum	0.67	(0.26-1.72)	0.68	(0.48-0.95)	1.04	(0.72-1.50)	0.74	(0.51-1.09)	1.08	(0.89-1.30)	0.94	(0.78-1.13)
Pregnancy Status												
Not pregnant	1		1		1		1		1		1	
Pregnant	1.08	(0.45-2.60)	0.57	(0.37-0.87)	0.80	(0.48-1.33)	0.82	(0.55-1.23)	0.71	(0.57-0.89)	0.92	(0.74-1.13)

4.6 Discussion

This study is the first to look at risk of HIV acquisition during pregnancy at a population level, without restricting the analysis to sexually active women or to sero-discordant couples. These data show some evidence that, in the whole population, pregnant women have a lower risk of HIV acquisition during pregnancy than women who are not pregnant and no evidence that postpartum women have a different risk of HIV acquisition in the first year post-pregnancy compared to non-pregnant women.

A study by Mugo et al. found an unadjusted rate ratio of 2.34 (95% CI 1.33-4.09) comparing pregnant to non-pregnant women [57], however, this study enrolled sero-discordant couples with at least three reported episodes of vaginal intercourse during the three months prior to screening and who intended to remain a couple and thus were a selected population. In the population overall, pregnancy is more likely to be desired in a stable partnership such as marriage. Being in a stable partnership would imply that the couple have had sex on a frequent basis, and, therefore by the time of a pregnancy, will be more likely to be sero-concordant with their partner. The higher the parity of the birth, the more likely the couple are to be HIV concordant (if the births have occurred within the same partnership) as they will have had a longer period of sexual partnership. Assuming that a higher proportion of pregnant women are in stable partnerships than non-pregnant women, it is likely that a higher proportion of pregnant women have sero-negative partners compared to the non-pregnant women. This is because those already concordant-positive will not be at risk of infection and therefore will be excluded from the analysis. The interaction evidence that the slight protective effect is not seen in the youngest age group might go further to support this theory as they have had less time to become concordant with their partner. Also those who have never had a sexual partner, a relatively large fraction of the under-20 age group, will not be at risk of infection and will not be pregnant.

Studies of sexually active women are less selective than sero-discordant couple studies but could still be different to those based on the whole population. The definition of sexually active women varies across studies, some exclude all women who report no sexual activity in the intervals between survey rounds, which may cause the exclusion of women who report no sexual activity during or immediately after pregnancy [54], some exclude only women who did not have a partner in the last 12 months [59], and some exclude those who were not sexually active at enrolment [56] with the time reference period left unspecified. If all sexually inactive women in both the non-pregnant and pregnant groups were excluded, differences in the age-specific proportion sexually inactive in the two groups could give rise to spurious results. Pregnant women or those who had recently given birth might be less sexually active due to the pregnancy, especially in

cultures where prolonged post-partum abstinence is the cultural norm [137]. Non-pregnant women may be excluded because they have never had a sexual partner – in these two cases the excluded women are at lower risk of infection. But in other cases, exclusion of women retrospectively reporting no recent sexual activity may lead to excluding high risk groups: e.g. women whose marriages have recently broken up due to widowhood and separation (these events occur more frequently among women with HIV positive partners [106]); or women who live apart from their partners because of the nature of their employment [138]. The prospective behaviour of women who have recently experienced a period without sexual activity may also place them at high risk in the near future e.g. at the time of first sex or when acquiring a new partner [139].

Using sexually active women from sites in Uganda and Zimbabwe Morrison et al [56] overall found no difference between the pregnant and not pregnant women (HRR 0.56 95% CI 0.30-1.05); however, they did find evidence for an interaction with site; the Zimbabwean site showed a lower risk of HIV acquisition in pregnant women (HR 0.26; 95% CI 0.10-0.68). As with this study they also found some evidence of interaction with age, with no difference in HIV acquisition for younger women (HRR 1.14; 95% CI 0.47-2.80) but a lower risk during pregnancy for older women (HRR 0.37 95% CI 0.13-1.09); however, this was not statistically significant. A further prospective study found no increased risk [59]. Only one prospective study of sexually active women in Uganda found a significant increased risk in HIV transmission during pregnancy (HRR 2.03 95% CI% 1.33-3.11) unadjusted and a similar result after adjusting for covariates [54]. The study shows that when stratifying by age the rate ratio only remains statistically significant for those 15-19 years old, showing a similar age effect to this study and to the study by Morrison et al [56]. The Ugandan study sample of sexually active women [54] came from the same population as the Rakai study in this analysis at an earlier time period but gives an increased risk of HIV acquisition in pregnant women rather than the decreased risk we see in this analysis when using the whole population.

In this analysis overall, we find no evidence of increased HIV incidence in the post-partum period when compared to non-pregnant and non-postpartum periods. There was some evidence of a decreased risk in this period once adjusted for age; however, statistical significance was lost when also adjusting for site indicating heterogeneity between study sites. To be consistent with studies that found a higher incidence immediately postpartum followed by a decrease over time, we would expect to see a significantly higher incidence in women in the post-partum period than in women who were neither pregnant nor post-partum. There are a number of differences in the studies cited above: those noting an increase in risk are not from the general population but from

antenatal clinics or hospital delivery wards, therefore restricting the analysis to women who have given birth, whereas in this study the non-pregnant non-postpartum women may never have given birth or last gave birth a long time ago. Also it is possible, as Leroy et al suggest [55], that studies noting a decrease in incidence over time could be affected by a cohort selection effect whereby high risk sub-groups sero-convert early on, leaving the cohort survivors composed mainly of low risk sub-groups. Finally, the incident rate confidence intervals in these studies either overlapped between groups [55] or are not shown [60]; therefore, the results give weak but inconclusive evidence. Our results here are consistent with a study of sexually active women in Uganda [54] which showed no significant difference in those women breastfeeding compared to those not pregnant and non-lactating.

The major strength of this study is that it is population-based rather than selected from clinics or hospitals, therefore we are able to assess the population risk of HIV transmission during pregnancy. Also we have pooled data from six different study sites that contribute 178,000 person years of data which makes this study much larger than previous studies on this topic.

Four sites were able to contribute to the pre-PMTCT period, where there is less possibility of bias due to those who know they are infected being less likely to agree to testing, however the results from the pre- and post-analysis were consistent although the pre-PMTCT period did not reach statistical significance because of the limited sample size available. If there was a bias in the post-PMTCT period it would have to be very large to overturn the protective effect of pregnancy shown in this study (HRR 0.65; 95%CI 0.61-0.78) and generate an increased risk of around two as seen in the sero-discordant couple studies. Kisesa, one of the study sites that, on its own, showed a lower risk of HIV acquisition during pregnancy, actually had one of the shortest periods where PMTCT was available, therefore it is less likely to be biased due to differences between pregnant and non-pregnant women knowing their HIV status and their subsequent participation in the surveillance study.

The major limitation of this analysis is the source of HIV test data from surveillance rounds that may be two or three years apart giving long sero-conversion intervals. Thus, we only know that a woman was pregnant at some point during the interval but do not know if the sero-conversion occurred before, during, or immediately after, the pregnancy. The imputation method used enables us to allow for this uncertainty and to generate confidence intervals to reflect this. When restricting the analysis to shorter sero-conversion intervals, the results did not change. The identification of a pregnancy

interval may also lead to uncertainty, pregnancies that end in miscarriage are rarely reported in these studies, stillbirths are also often not captured, therefore some of the pregnancy person years will be miscategorised as not pregnant. However these person-years will be small in comparison with all the pregnancies identified by live births and those pregnancies that are captured with a pregnancy report. HIV infected women suffer more miscarriages and stillbirths than their uninfected counterparts [86] however this decrease in viability of pregnancy is associated with longer duration of infection [119], there are no studies that suggest an association of sero-conversion with pregnancy loss.

Although there might be immunological reasons for increased risk of HIV acquisition during pregnancy, at a population level this study indicates a lower risk of HIV acquisition in pregnant women. This is probably due to a range of socio-behavioural characteristics of women and their partners that determine which women are most likely to become pregnant and which women will become infected, and these factors could be investigated in further analyses.

This study furthers understanding of the population risk of HIV acquisition during pregnancy and in the first year postpartum. The results can inform modellers and help health care providers with decisions on the kinds of interventions that would do most to help prevent the spread of HIV.

4.7 Acknowledgments

All the sites thank all the community members for their continued participation in the surveillance, and the staff for their dedication to research.

5 Paper C: Measuring the Impact of antiretroviral therapy roll-out on population level fertility in three African countries

For objective 3 of the PhD: to investigate whether there is an impact of ART on fertility at the population level; an analysis was conducted using longitudinal data from the ALPHA network and published in:

Marston, M; Nakiyingi-Miiro, J; Hosegood, V; Lutalo, T; Mtenga, B; Zaba, B; ALPHA network; (2016) *Measuring the Impact of Antiretroviral Therapy Roll-Out on Population Level Fertility in Three African Countries.* PLoS One, 11 (3).

5.1 Introduction to paper

Fertility of HIV positive women compared to HIV negative women is a key input into estimates of the number of children born to HIV positive women, therefore it is essential to understand what impact ART will have. The majority of the work comparing differences in fertility between HIV positive and negative women was carried out before ART was available. In the presence and increased coverage of ART, it has been speculated that the fertility of HIV positive women on ART will become the same as fertility of HIV negative women, due to improved health and changes in the desire for children. Many of the studies in the ALPHA network have fertility data that span the pre- and post-ART era. If ART influences fertility we would expect to see a narrowing of the gap in fertility levels between HIV positive and negative women once ART had been rolled out.

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

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Thesis Title	Demographic Determinants of Paediatric HIV in Generalised HIV epidemics

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Student Signature: [redacted] **Date:** 27/03/18

Supervisor Signature: [redacted] **Date:** 27.03.2018

Measuring the Impact of antiretroviral therapy roll-out on population level fertility in three African countries

Milly Marston[1*], Jessica Nakiyingi-Miiro[2], Victoria Hosegood[3,4] , Tom Lutalo[5], Baltazar Mtenga[6], Basia Zaba[1], on behalf of the ALPHA network[^].

1. London School of Hygiene and Tropical Medicine, London, United Kingdom
2. Medical Research Council, Entebbe, Uganda.
3. Africa Centre for Health and Population Studies, University of KwaZulu-Natal, Somkhele, South Africa.
4. Faculty of Medicine, Faculty of Social and Human Sciences, University of Southampton, Southampton, United Kingdom
5. TAZAMA Project, National Institute of Medical Research, Mwanza, Tanzania.
6. Rakai Health Sciences Program, Kalisizo, Rakai, Uganda

*Corresponding Author

e-mail: milly.marston@lshtm.ac.uk

^Complete membership of the author group can be found in the acknowledgements. Details of the ALPHA Network are found at alpha.lshtm.ac.uk

5.2 Abstract

Background

UNAIDS official estimates of national HIV prevalence are based on trends observed in antenatal clinic surveillance, after adjustment for the reduced fertility of HIV positive women. Uptake of ART may impact on the fertility of HIV positive women, implying a need to re-estimate the adjustment factors used in these calculations. We analyse the effect of antiretroviral therapy (ART) provision on population-level fertility in Southern and East Africa, comparing trends in HIV infected women against the secular trends observed in uninfected women.

Methods

We used fertility data from four community-based demographic and HIV surveillance sites: Kisesa (Tanzania), Masaka and Rakai (Uganda) and uMkhanyakude (South Africa). All births to women aged 15–44 years old were included in the analysis, classified by mother's age and HIV status at time of birth, and ART availability in the community. Calendar time period of data availability relative to ART introduction varied across the sites, from 5 years prior to ART roll-out, to 9 years after. Calendar time was classified according to ART availability, grouped into pre ART, ART introduction (available in at least one health facility serving study site) and ART available (available in all designated health facilities serving study site). We used Poisson regression to calculate age adjusted fertility rate ratios over time by HIV status, and investigated the interaction between ART period and HIV status to ascertain whether trends over time were different for HIV positive and negative women.

Results

Age-adjusted fertility rates declined significantly over time for HIV negative women in all four studies. However HIV positives either had no change in fertility (Masaka, Rakai) or experienced a significant increase over the same period (Kisesa, uMkhanyakude). HIV positive fertility was significantly lower than negative in both the pre ART period (age adjusted fertility rate ratio (FRR) range 0.51 95%CI 0.42-0.61 to 0.73 95%CI 0.64-0.83) and when ART was widely available (FRR range 0.57 95%CI 0.52-0.62 to 0.83 95%CI 0.78-0.87), but the difference has narrowed. The interaction terms describing the difference in trends between HIV positives and negatives are generally significant.

Conclusions

Differences in fertility between HIV positive and HIV negative women are narrowing over time as ART becomes more widely available in these communities. Routine adjustment of ANC data for estimating national HIV prevalence will need to allow for the impact of treatment.

5.3 Background

There has been a rapid scale up in the provision of Antiretroviral therapy (ART) in Sub Saharan Africa in the last decade with more than 7.5 million people receiving treatment by the end of 2012[140] this comes hand in hand with increased access to HIV testing and therefore knowledge of HIV status. A large proportion of those with HIV in sub Saharan Africa are women of reproductive age who are routinely tested for HIV at antenatal care clinics (ANC) in order to try to prevent mother to child transmission and those testing positive are referred to clinics for treatment[141].

Official estimates of national HIV prevalence by UNAIDS are currently based on trends observed in antenatal clinic surveillance[142] and far more ANC data are becoming available due to routine reports from PMTCT programs. ANC prevalence trends are then adjusted to match prevalence levels estimated from national population surveys [143]. Part of this adjustment accounts for the reduced fertility of HIV positive women [72, 144] , however increased access to care and treatment services and uptake of antiretroviral therapy may impact on the fertility of HIV positive women for biological and behavioural reasons, implying a need to re-estimate the adjustment factors used in these calculations.

There have been no longitudinal studies in Sub-Saharan Africa that have looked at the population level impact of ART on fertility. A few studies have measured fertility or incidence of pregnancy in women on ART[116, 119, 121, 145] but these lack suitable comparators (HIV negative women in the same community) and may not be representative of all HIV positive women. A cross sectional comparison using Malawian Demographic and Health Survey data (DHS) found an increased probability of giving birth for HIV positive women relative to HIV negative women between 2004 and 2010 [79] which is attributed to the increase in access to mother to child transmission and ART services in Malawi. We analyse the effect of antiretroviral therapy provision on population-level fertility in four cohort studies in Southern and East Africa, comparing trends in HIV infected women against the secular trends observed in uninfected women.

5.4 Methods

5.4.1 Sites and setting

Fertility data that span the pre-ART era and the time of introduction and widespread use of ART are available from four community-based demographic and HIV surveillance sites: Kisesa (managed by the National Institute of Medical Research Mwanza in Northern Tanzania), Masaka (MRC/UVRI Uganda Research Unit on AIDS), Rakai (Rakai Health Sciences) – both in South-west Uganda, and uMkhanyukude (Africa Centre, in KwaZulu-Natal, South Africa). These sites belong to the network for analysing

longitudinal population based data on HIV in Africa (ALPHA)[9, 146] and have been described in detail elsewhere [27, 31, 32, 35, 147-149].

5.4.2 Data, HIV and ART provision

The ALPHA network standardises site-specific data to a common format to enable joint analysis. In brief, each study records demographic data including dates of birth (of mothers and infants). The studies also collect data on HIV status and provide dates of testing and test results for their populations. In Kisesa, Rakai, and uMkhanyakude, the HIV surveys were done separately to the demographic surveillance rounds, and data were linked afterwards using unique identifiers. In Masaka, HIV testing was done immediately after demographic surveillance rounds which were used to list those eligible for HIV testing. HIV testing took place in the home for all sites apart from Kisesa where temporary village clinics are used to which people are transported from their homes. Prior to the availability of antiretroviral therapy, testing protocols used informed consent without disclosure, so that participants did not learn the results of the HIV research tests, however with the advent of ART, sites began to offer full pre-test and post-test counselling to the participants during the data collection round. Participants are still not obliged take part in the counselling or to learn their results. In Rakai the samples taken in the home were tested at the field laboratory and then returned by a community based counsellor to those participants requesting the results.

The introduction and level of uptake of ART in the different studies varies. ART was introduced in the study areas between 2004 and 2005, when selected clinics were allowed to administer drugs and people were mobilised to make them aware of the new services. Further details of ART introduction and uptake are described elsewhere[150-153].

5.4.3 Study Population

The population included in this analysis is women of reproductive age (15-44) living in the surveillance areas between the time point corresponding to five years before ART was introduced, to the last date for which data were available for each site up to 2015. Table 5.1 shows prevalence for each site in pre and post ART years for women aged 15-49.

All live births to women aged 15–44 years old while under observation in the study were included in the analysis, classified by mother's age, area of residence and HIV status at time of the birth, and by ART availability in the community. We did not include 45-49

year olds to create the standard fertility analysis grouping of 15-49 years as there were very few births to HIV positive women at this age.

Table 5.1: HIV prevalence of women aged 15-49 in Study sites

Study Site, Round (years)	ART period	N	Prevalence	(95% CI)
Kisesa 4 (2003-2004)	Pre ART	3369	5.11	(4.36 - 5.85)
Kisesa 6 (2010-2010)	Post ART	2445	7.08	(6.06 - 8.09)
Manicaland 3 (2003-2005)	Pre ART	8273	20.45	(19.58 - 21.32)
Manicaland 5 (2009-2011)	Post ART	6150	17.54	(16.59 - 18.50)
Masaka 14 (2002-2003)	Pre ART	2361	14.06	(12.66 - 15.46)
Masaka 16 (2004-2005)	Post ART	2485	17.99	(16.48 - 19.50)
Rakai 9 (2002-2003)	Pre ART	3708	13.65	(12.54 - 14.75)
Rakai 12 (2006-2008)	Post ART	4507	14.98	(13.93 - 16.02)
uMkhanyakude 1 (2002-2005)	Pre ART	6533	27.2	(26.12 - 28.28)
uMkhanyakude 4 (2007-2008)	Post ART	3604	27.58	(26.12 - 29.04)

All sites are predominately rural, though most contain areas with local markets, health and education facilities. Area of residence is classified differently for each site. The Masaka DSS is divided into two areas: old villages where surveillance began in 1989; and new villages where surveillance began in November 1999. In Kisesa sub-villages are classified according to their distance from the small trading centre on the main road. In Rakai the peri urban group comprises trading towns, villages along secondary roads and fishing communities and the rural category are communities beyond those located along secondary roads. uMkhanyakude is predominantly rural but also includes an small town and peri-urban densely populated areas.

5.4.4 Measures

HIV Status was classified as negative, positive and unknown. Negative person time was defined as the time between first testing negative and last testing negative, also included in negative time was a site specific time following the last negative test, this was allocated according to the HIV incidence rates in the sites, the cut off for post negative time was taken as the time at which the cumulated probability of becoming infected following the last test reached 5%. This cut-off point was five years in Kisesa, Masaka and Rakai and two years in uMkhanyakude. HIV positive time was all the person time after the first positive test. The sero conversion interval was calculated as the mid point between first positive and last negative test and positive and negative time was assigned accordingly. Interval censoring was invoked if the midpoint of the sero conversion interval was longer than the site specific post negative time – in that case only the post negative time was assigned to negative and one year pre positive time was assigned to positive, the

remainder of the interval was designated unknown. The composition of the unknown group over time changes due to the different ways HIV positive and HIV negative time is allocated and is also affected by participation changes in testing[26, 136] therefore we do not present results from this group. No pressure was put on participants to receive their HIV status as part of research survey procedures, therefore we would not expect a link between participation in testing and fertility.

Calendar time period of data availability relative to ART introduction varied across the sites (Figure 5.1), from 5 years prior to ART roll-out, to 9 years after. Calendar time was classified according to ART availability, grouped into pre ART, ART Introduction (introduced in at least one of the health facilities serving the community) and ART available (available in all the health facilities serving the community that were designated as ART providers according to national guidelines). We limit results presented for the short ART roll out period to just the age specific rates, as this time period is relatively short and is different in each site depending on the speed and nature of the roll out therefore tells us little about general patterns and trends.

5.4.5 Analysis

We used Poisson regression to calculate age adjusted fertility rate ratios over time by HIV status, and investigated the interaction between ART period and HIV status to ascertain whether trends over time were different for HIV positive and negative women. We adjust for age and area of residence in this analysis to control for any changes in the composition of the study site that may have occurred between the pre and post ART periods. The analysis was performed separately for each site and pooled across sites where appropriate, the pooled results were adjusted by study site.

At ages under 20, HIV infection and fertility are highly correlated as many teenagers will not yet have had sex, and only those who have had sex are at risk of becoming pregnant or acquiring HIV. Therefore fertility in the 15-19 year old age group is almost always higher in HIV positive women[144]. We therefore stratify our analysis to look at 15-19 year olds and 20-44 year olds separately.

5.5 Ethics statements

Each of the six sites contributing data to the pooled analysis has received ethical clearance from the appropriate local ethics review bodies, and from the corresponding Institutional Review Boards for studies which had collaborating partnerships with Northern Universities.

uMkhanyakude

Annually re-certified ethics permission for the Africa Centre DSS and nested individual HIV surveillance among consenting adults is obtained from the Biomedical Research Ethics Committee at the Nelson Mandela School of Medicine, University of KwaZulu-Natal. Detailed written informed consent obtained for participation in the HIV surveillance.

Kisesa

Ethical approval for each survey round of the Kisesa cohort study granted by the Tanzanian Medical Research Coordinating Committee and the Ethics Committee of the London School of Hygiene and Tropical Medicine. Prior to 2006, verbal consent was obtained directly from all study participants (aged 15 and over), due to low literacy rates among the study population. Consent was witnessed and documented for each study participant by a member of the sero-survey team or senior person from the community. From 2006 onward, consent was again obtained directly from all study participants, however a written consent option was introduced, for those able to provide this and written parental consent for those under 18 years was also obtained.

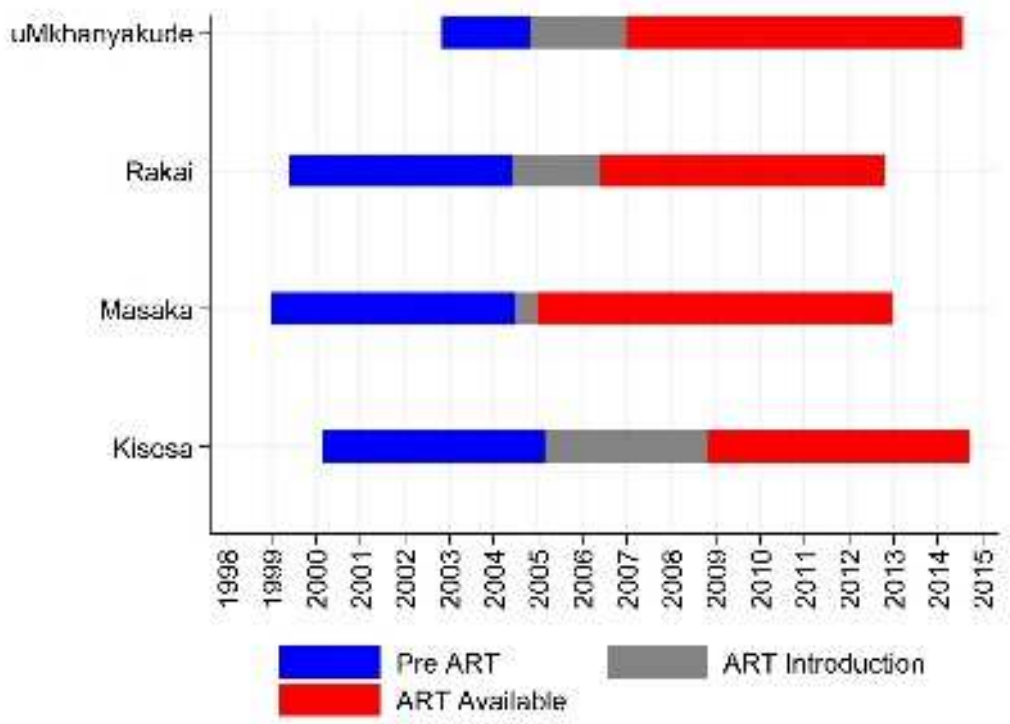
Masaka

The MRC DSS is approved by the Uganda Virus Research Institute (UVRI) Science and Ethics Committee (SEC) and the Uganda National Council of Science and Technology (UNCST). Study participants provided written consent to participate in all parts of the study.

Rakai

The Rakai Community Cohort Survey is approved by the UVRI SEC and UNCST. Literate participants provided written consent while those unable to read or write had a witness sign on their behalf. Those unable to read or write used a thumbprint to document consent and a witness would also sign as evidence that the consent had been read to the participant who had understood and consented to participate.

Figure 5.1. Dates of ART Periods included in the analysis



5.6 Results

Overall crude and age specific fertility rates fell or remained the same between the pre and post ART periods for all sites (Table 5.2-Table 5.5). Classifying the crude fertility rates by HIV status shows that overall fertility declined in the HIV negative but remained more or less the same or increased slightly for the HIV positive (For the HIV positive in Rakai this is true if we exclude 15-19 year olds). Age specific rates by HIV status follow this general trend for all sites apart from slight increases in HIV negative 25-34 year olds in Masaka, 35-39 year olds in Rakai and 15-19 year olds in uMkhanyakude. Overall fertility is higher in the rural areas for all sites.

Table 5.2: Fertility of women aged 15-44 years old, by calendar time period and stratified by individual HIV status for Kisesa.

	All			HIV-Negative			HIV-Positive		
	Births	Person Years	Rate /1000	Births	Person Years	Rate /1000	Births	Person Years	Rate /1000
Kisesa									
ART Period									
Pre ART	5253	26.2	200.1	4108	17.6	233.1	132	1.0	126.9
ART Introduction	3715	19.5	190.6	2763	12.6	218.4	106	0.8	132.0
ART available	5895	37.2	158.3	2924	15.4	190.3	195	1.4	144.2
Age									
15-19									
Pre ART	846	6.2	136.6	584	3.6	160.2	12	0.1	197.6
ART Introduction	518	4.8	108.3	308	2.9	107.3	8	0.0	232.3
ART available	792	9.5	83.6	335	3.6	93.3	4	0.0	81.5
20-24									
Pre ART	1461	5.4	270.8	1117	3.4	325.8	23	0.2	144.7
ART Introduction	952	3.8	250.7	714	2.3	309.2	9	0.1	97.5
ART available	1475	7.2	205.1	637	2.7	237.1	24	0.1	193.6
25-29									
Pre ART	1294	4.9	264.1	1002	3.2	311.7	44	0.3	157.6
ART Introduction	897	3.3	270.1	676	2.1	315.3	34	0.2	202.7
ART available	1402	6.3	223.9	693	2.4	285.1	40	0.2	185.5
30-34									
Pre ART	877	4.0	221.3	705	2.8	254.3	38	0.3	143.7
ART Introduction	746	3.1	237.7	563	2.1	272.0	32	0.2	133.3
ART available	1131	5.6	200.5	621	2.4	254.7	66	0.3	197.1
35-39									

Pre ART	569	3.3	173.6	510	2.6	198.8	13	0.2	80.4
ART Introduction	426	2.4	180.9	356	1.7	212.8	16	0.2	102.2
ART available	805	5.0	162.5	454	2.3	201.2	55	0.4	131.9
40-44									
Pre ART	206	2.5	81.8	190	2.0	95.0	2	0.1	17.3
ART Introduction	176	2.1	83.9	146	1.6	92.3	7	0.1	62.6
ART available	290	3.7	78.1	184	2.0	93.7	6	0.2	28.3
Residence									
Rural									
Pre ART	3125	13.4	233.2	2564	10.1	254.2	71	0.4	171.0
ART Introduction	2295	9.9	232.0	1805	7.2	252.4	54	0.3	162.7
ART available	3453	17.9	193.0	1932	8.9	215.9	103	0.6	164.3
Peri Urban/Urban									
Pre ART	2128	12.8	165.7	1544	7.5	204.8	61	0.6	97.6
ART Introduction	1420	9.6	147.9	958	5.5	174.2	52	0.5	110.4
ART available	2442	19.3	126.3	992	6.4	154.6	92	0.7	126.8

Table 5.3: Fertility of women aged 15-44 years old, by calendar time period and stratified by individual HIV status for Masaka.

	All			HIV-Negative			HIV-Positive		
	Births	Person Years	Rate /1000	Births	Person Years	Rate /1000	Births	Person Years	Rate /1000
Masaka									
ART Period									
Pre ART	2524	14.8	170.1	2285	12.8	179.2	117	1.0	115.2
ART Introduction	510	3.3	153.6	466	2.8	164.0	21	0.3	83.8
ART available	4185	28.0	149.7	3672	23.3	157.4	281	2.3	119.7
Age									
15-19									
Pre ART	490	4.6	107.0	448	4.2	106.9	14	0.1	205.3
ART Introduction	101	1.0	105.3	91	0.9	102.3	2	0.0	112.2
ART available	665	8.5	78.5	593	7.6	77.6	25	0.2	159.4
20-24									
Pre ART	766	2.9	261.3	701	2.5	277.6	32	0.2	185.3
ART Introduction	155	0.6	245.1	145	0.5	266.8	3	0.0	77.3
ART available	1115	4.9	226.6	1005	4.1	242.6	58	0.3	186.8
25-29									
Pre ART	562	2.4	231.9	497	2.0	252.0	38	0.3	136.5
ART Introduction	126	0.5	229.9	115	0.4	260.9	6	0.1	101.3
ART available	1012	4.3	237.1	884	3.5	256.1	71	0.4	163.7
30-34									
Pre ART	357	1.9	192.4	316	1.5	211.9	20	0.2	88.8
ART Introduction	69	0.4	154.4	63	0.4	175.6	4	0.1	69.3
ART available	786	4.0	195.3	680	3.2	215.4	71	0.5	133.5
35-39									
Pre ART	263	1.7	152.8	241	1.4	168.4	11	0.2	62.7

ART Introduction	38	0.4	98.4	32	0.3	100.4	5	0.0	117.7
ART available	466	3.3	139.6	387	2.6	149.6	47	0.5	92.1
40-44									
Pre ART	86	1.3	64.9	82	1.1	71.7	2	0.1	20.9
ART Introduction	21	0.3	60.4	20	0.3	68.9	1	0.0	29.0
ART available	141	2.9	48.1	123	2.3	52.6	9	0.4	22.2
Residence									
Original Study Villages									
Pre ART	1989	11.3	175.5	1820	9.9	183.6	81	0.7	116.5
ART Introduction	382	2.4	158.1	347	2.1	164.8	16	0.2	97.8
ART available	3003	19.5	153.7	2675	16.6	161.4	182	1.5	121.4
New villages									
Pre ART	535	3.5	152.7	465	2.8	163.8	36	0.3	112.4
ART Introduction	128	0.9	141.6	119	0.7	161.6	5	0.1	57.4
ART available	1182	8.4	140.5	997	6.8	147.6	99	0.8	116.7

Table 5.4: Fertility of women aged 15-44 years old, by calendar time period and stratified by individual HIV status for Rakai.

	All			HIV-Negative			HIV-Positive		
	Births	Person Years	Rate /1000	Births	Person Years	Rate /1000	Births	Person Years	Rate /1000
Rakai									
ART Period									
Pre ART	6598	51.8	127.3	5805	35.9	161.8	495	5.5	90.2
ART Introduction	2598	23.1	112.5	2304	15.5	148.5	201	2.3	88.6
ART available	6634	68.7	96.6	5736	42.8	134.0	547	6.9	79.3
Age									
15-19									
Pre ART	1220	13.4	91.3	1119	8.1	137.3	38	0.3	131.0
ART Introduction	310	5.7	54.8	273	3.0	90.7	7	0.1	83.9
ART available	674	17.4	38.8	601	9.2	65.2	17	0.2	90.8
20-24									
Pre ART	2320	12.8	181.4	2090	9.6	217.9	137	1.1	127.4
ART Introduction	872	5.4	161.6	799	3.8	208.7	50	0.4	129.5
ART available	1953	14.8	131.8	1651	9.0	183.0	125	0.9	139.0
25-29									
Pre ART	1713	10.3	166.7	1460	7.3	199.5	183	1.6	116.7
ART Introduction	791	4.8	165.2	693	3.5	199.0	80	0.6	133.4
ART available	1992	13.7	145.9	1641	8.6	190.0	178	1.6	112.6
30-34									
Pre ART	830	6.4	128.8	684	4.4	156.5	96	1.3	74.6
ART Introduction	425	3.4	124.9	369	2.4	155.8	40	0.6	65.0
ART available	1309	10.9	119.7	1077	6.8	158.5	131	1.7	75.4
35-39									

Pre ART	382	4.8	79.0	331	3.4	96.4	36	0.8	45.4
ART Introduction	155	2.0	76.0	130	1.5	88.9	19	0.3	55.1
ART available	572	7.1	80.3	458	4.3	106.1	65	1.3	50.8
40-44									
Pre ART	133	4.1	32.4	121	3.0	40.2	5	0.5	10.5
ART Introduction	45	1.8	24.9	40	1.4	29.3	5	0.2	21.0
ART available	134	4.8	28.1	116	2.9	40.3	7	0.8	8.4
Residence									
Rural									
Pre ART	5483	41.2	133.2	4872	29.3	166.4	390	4.2	91.9
ART Introduction	2200	18.2	121.1	1979	12.6	157.3	157	1.7	91.7
ART available	5156	49.7	103.7	4459	31.7	140.8	400	4.7	85.9
Peri Urban/Urban									
Pre ART	1115	10.7	104.5	933	6.6	141.4	105	1.2	84.3
ART Introduction	398	4.9	80.7	325	2.9	110.7	44	0.6	79.1
ART available	1401	18.5	75.7	1019	8.9	114.7	118	1.8	65.1

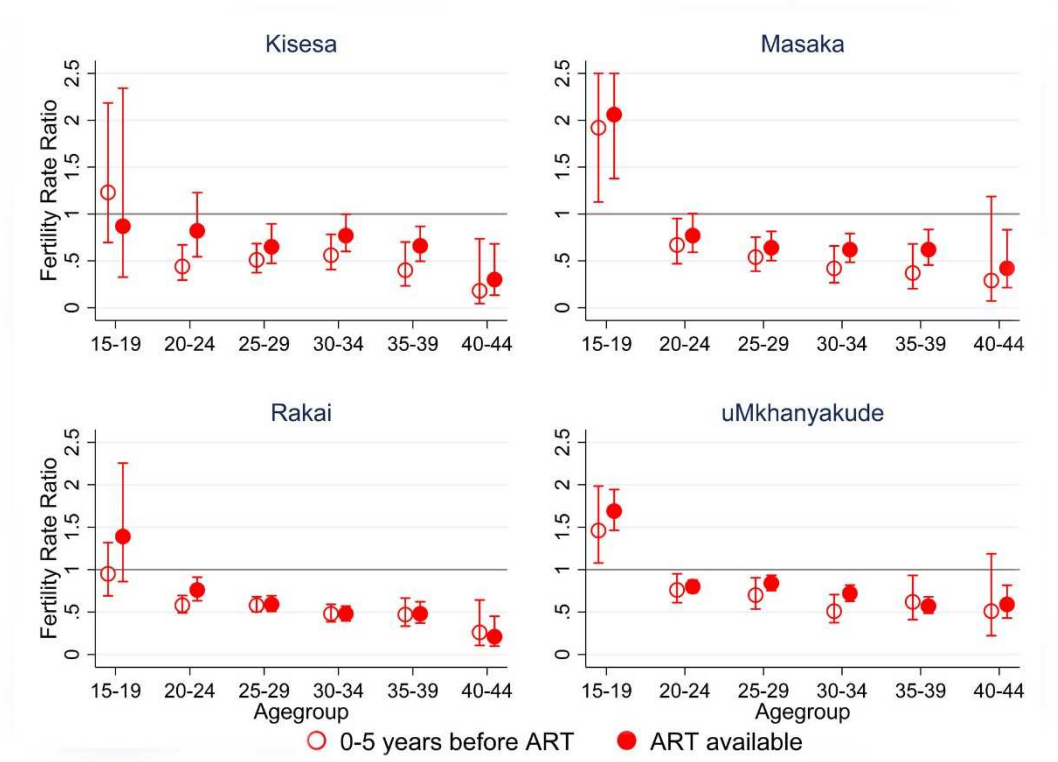
Table 5.5: Fertility of women aged 15-44 years old, by calendar time period and stratified by individual HIV status for uMkhanyakude.

	All			HIV-Negative			HIV-Positive		
	Births	Person Years	Rate /1000	Births	Person Years	Rate /1000	Births	Person Years	Rate /1000
uMkhanyakude									
ART Period									
Pre ART	3337	31.8	104.8	1550	14.0	110.7	297	3.0	98.3
ART Introduction	3899	33.7	115.7	1887	15.3	123.6	581	4.9	119.1
ART available	11601	119.5	97.0	4741	41.0	115.7	2264	23.7	95.4
Age									
15-19									
Pre ART	794	9.3	85.2	485	5.9	82.6	45	0.4	120.7
ART Introduction	1019	9.8	104.2	664	6.4	103.4	85	0.4	196.8
ART available	2836	32.8	86.4	1639	17.3	94.5	217	1.4	159.3
20-24									
Pre ART	1014	6.6	154.5	435	2.4	182.2	95	0.7	138.7
ART Introduction	1262	7.4	169.6	589	3.2	182.4	211	1.1	184.9
ART available	3749	25.2	149.0	1631	9.3	175.4	587	4.2	140.2
25-29									
Pre ART	653	4.8	135.3	209	1.3	167.0	77	0.7	116.3
ART Introduction	689	4.9	139.5	228	1.3	170.4	133	1.0	129.4
ART available	2398	20.3	118.2	661	4.5	145.5	680	5.6	122.0
30-34									
Pre ART	491	4.1	121.0	206	1.2	168.9	47	0.5	86.7
ART Introduction	505	4.2	119.5	184	1.2	158.3	95	0.9	103.1
ART available	1487	15.9	93.8	397	3.0	132.4	483	5.1	94.7
35-39									

Pre ART	284	3.6	79.9	154	1.5	104.6	27	0.4	64.8
ART Introduction	301	3.7	80.6	148	1.4	106.0	43	0.8	57.0
ART available	880	13.5	65.2	305	3.1	99.0	240	4.2	56.8
40-44									
Pre ART	101	3.5	28.7	61	1.8	34.0	6	0.3	17.4
ART Introduction	123	3.6	34.3	74	1.7	42.9	14	0.6	23.3
ART available	251	11.9	21.1	108	3.7	29.2	57	3.3	17.3
Residence									
Rural									
Pre ART	2069	18.9	109.8	1076	9.6	112.2	165	1.6	100.3
ART Introduction	2382	19.8	120.2	1288	10.3	124.9	335	2.7	123.9
ART available	6955	66.2	105.1	3220	26.8	120.4	1190	12.2	97.7
Peri Urban/Urban									
Pre ART	1192	12.2	97.5	452	4.2	107.1	126	1.3	95.0
ART Introduction	1387	12.6	110.0	548	4.6	118.9	234	2.0	114.8
ART available	4476	48.4	92.5	1486	13.7	108.3	1048	10.8	97.1

Fertility rates in HIV positive women are consistently lower than those of HIV negative women apart from the youngest age group of 15-19 years olds (Figure 5.2). For all sites apart from uMkhanyakude fertility rates in HIV positive women aged over 20 are around half those of the negatives in the pre ART period and 0.73 (95%CI 0.64-0.83) times the negative rates in uMkhanyakude. In the post ART period overall the differences between positive and negative are smaller, with rate ratios ranging from 0.57 (95%CI 0.52-0.62) in Rakai to 0.83 (95%CI 0.78-0.87) in uMkhanyakude. In both periods fertility differences between positive and negative women become greater as age increases.

Figure 5.2. Unadjusted fertility rate ratios by age and ART period comparing positives to negatives



For all women aged 15-44 years old, age and residence adjusted fertility rates declined significantly over time, driven by the significant decline in fertility among HIV negative women in all four studies (Table 5.6). For HIV positive women in Kisesa and Masaka there is a fertility increase of borderline significance of 1.21(95%CI 0.99-1.49) and 1.16(95%CI 0.96-1.41) respectively, and no change in uMkhanyakude and Rakai. The interaction between HIV Status and ART period was significant for all sites apart from uMkhanyakude showing that the changes in fertility over the two ART periods are significantly different for HIV positive and HIV negative women. Excluding 15-19 year olds (Table 5.7) whose fertility rates are determined largely by patterns of sexual debut, yields an overall reduction in fertility in HIV negative women in all sites and increases among HIV positive women in Kisesa and Masaka with rate ratios of 1.29 (95%CI 1.04-1.59) and 1.21 (95%CI 0.99-1.47) respectively, and no change in uMkhanyakude and

Rakai. In this narrower age range the interaction terms between HIV Status and ART period were significant for all sites apart from Rakai.

Table 5.6: Fertility Rate Ratio (FRR) for 15-44 year olds comparing ART period with pre ART adjusted for by age and residence

ART Period	HIV Negative		HIV Positive		Interaction p-value*
	FRR	(95% CI)	FRR	(95% CI)	
Kisesa					
Pre-ART	1		1		
ART Available	0.84	(0.81- 0.88)	1.21	(0.99- 1.49)	0.001
Masaka					
Pre-ART	1		1		
ART Available	0.90	(0.86- 0.94)	1.16	(0.96- 1.41)	0.010
uMkhanyakude					
Pre-ART	1		1		
ART Available	0.98	(0.93- 1.03)	1.04	(0.92- 1.16)	0.363
Rakai					
Pre-ART	1		1		
ART Available	0.84	(0.81- 0.86)	0.96	(0.86- 1.08)	0.020

**Interaction between ART period and HIV status*

Table 5.7: Fertility Rate Ratio (FRR) for 20-44 year olds comparing ART period with pre ART adjusted for by age and residence

ART Period	HIV Negative		HIV Positive		Interaction p-value*
	FRR	(95% CI)	FRR	(95% CI)	
Kisesa					
Pre-ART	1		1		
ART Available	0.89	(0.86- 0.93)	1.29	(1.04- 1.59)	0.001
Masaka					
Pre-ART	1		1.00		
ART Available	0.94	(0.90- 0.99)	1.21	(0.99- 1.47)	0.016
uMkhanyakude					
Pre-ART	1		1		
ART Available	0.90	(0.84- 0.95)	1.04	(0.92- 1.17)	0.033
Rakai					
Pre-ART	1		1		
ART Available	0.93	(0.90- 0.96)	1.00	(0.89- 1.12)	0.252

**Interaction between ART period and HIV status*

The data for 20-44 year olds were pooled for the comparison of the period when ART was available with the pre ART period, giving overall rate ratios of 0.9 (95%CI 0.89-0.92) for HIV negative women and 1.08 (95%CI 1.01-1.16) for HIV positive women adjusted for age, residence and study site, with a significant interaction (p<0.001) between HIV status and ART period. Focussing on 15-19 year olds (Table 5.8), there has been a significant reduction in fertility for HIV negative women in all sites apart from uMkhanyakude where the relative increase was 1.11 (95%CI 1.01-1.22). The confidence intervals for the rate ratios for the HIV positive are very large, so no real pattern can be determined.

Table 5.8: Fertility Rate Ratio (FRR) for 15-19 year olds comparing ART period with pre ART adjusted for by age and residence

ART Period	HIV Negative		HIV Positive		Interaction
	FRR	(95% CI)	FRR	(95% CI)	p-value*
Kisesa					
Pre-ART	1		1		
ART Available	0.56	(0.49- 0.64)	0.40	(0.14- 1.12)	0.524
Masaka					
Pre-ART	1		1		
ART Available	0.75	(0.67- 0.85)	0.73	(0.41- 1.32)	0.936
uMkhanyakude					
Pre-ART	1		1		
ART Available	1.11	(1.01- 1.22)	1.32	(0.97- 1.79)	0.278
Rakai					
Pre-ART	1		1		
ART Available	0.49	(0.44- 0.53)	0.66	(0.38- 1.13)	0.277

**Interaction between ART period and HIV stat*

For the two sites with data available (Kisesa and Masaka) in the 5-10 years prior to ART there was no evidence of any interaction between HIV status and period when comparing the periods 0-5 years and 5-10 years prior to ART (Not shown).

Person years with unknown HIV status were lowest in Masaka at 7.2% in the pre ART period and 8.2% in the post ART period, in Rakai they were 20.2% and 27.7%, Kisesa 28.9% and 52.0%, uMkhanyakude 46.5% and 38.3% respectively. The HIV status unknown category includes the unclassified post negative time intervals and time before the first HIV test.

5.7 Discussion

This analysis uses community based cohort studies to look at the population impact of ART on fertility. We have shown that changes in fertility have been different in HIV positive women compared to the HIV negative over the pre and post ART Period - representing a discontinuity since the pre ART era. This would indicate that the introduction of ART is narrowing the gap in fertility rates between the HIV positive and negative. These results are similar to those found in the cross sectional study using the Malawi DHS [79] which showed a decrease over two surveys in the relative difference in fertility comparing the HIV positive and HIV negative at the time of the survey. Since our longitudinal data can accurately measure HIV status at the time of birth these results are a strong affirmation of the cross-sectional findings.

Fertility dynamics, HIV and changes due to ART are complex and can be both biological and behavioural. Earlier studies showed that HIV positive women with further disease progression have lower fertility than the uninfected and those more recently infected [119, 121, 154]. Women with HIV also have increased risk of spontaneous abortion and still birth [86] which lower their fertility. It is possible that the improved health of women on ART increases their fecundity although one study found an increase in still births for HIV positive women on ART compared to those not on ART[92].

Relationship dynamics may also change: studies from the pre ART era have shown an increased risk of widowhood and marital dissolution for HIV positive women and low rates of remarriage[107, 155], therefore decreasing their chances to bear more children. In the era of ART the risk of widowhood will decrease and marital dissolution rates may change leading to more opportunity for childbearing.

Fertility intentions are likely also to change, HIV positive women are more likely to report desiring fewer births than those uninfected[115] but some studies that compared fertility intentions of HIV positive women on treatment to those not on treatment found an increase in desire for children with increasing duration on ART [116, 117, 145]. It is unclear whether these intentions translate into actual increases in fertility. A cross sectional study from a perinatal HIV Research Unit in Soweto found no difference in fertility intentions between those on ART or not[114] – however all participants were attending the HIV clinic so according to the authors, the intentions of those not yet on treatment may have been shaped by the knowledge that ART was available when needed. A multicounty HIV care and treatment program cohort study in sub-Saharan Africa reported HIV positive women on treatment having 1.74(95%CI 1.19-2.54) higher incidence of pregnancy than those not on treatment[121]. The study was unable to determine the factors underlying the results with both biological and behavioural factors being possible.

This analysis shows the extent of changes in fertility trends at the population level which is important for modellers and policy makers. It does not tell us how much of the change is attributable to biological factors directly associated with improved health of those receiving ART, psychological changes that alter fertility intentions, or social changes in marital dynamics and stigma. It is important to note that in the pre ART era most people in these studies would not have known their HIV status so reasons for low fertility in the HIV positives would not include a conscious desire for fewer children motivated by knowledge of status. These topics need further analysis with individual linkage to clinic data to classify time on treatment, to investigate biological factors, and more detailed demographic and behavioural background characteristics.

Differences in fertility between HIV positive and HIV negative women are narrowing over time as ART becomes more widely available in these communities. Routine adjustment of ANC data for estimating national HIV prevalence will need to allow for the impact of treatment. Given the profound differences between fertility rate ratios and trends in infected and uninfected women under 20 with those aged 20 and over, it would be useful to classify ANC data on HIV prevalence by age, reporting separately on those under 20.

5.8 Acknowledgements

This paper is written on behalf of the ALPHA network:
Principle investigators:
Steve Tollman (Agincourt), Agincourt, School of Public Health, University of the Witwatersrand, Johannesburg, South Africa. Honorati Masanja (Ifakara), Ifakara Health Institute, Dar-Es-Salaam, Tanzania. Amelia Crampin (Karonga), Malawi Epidemiology and Intervention Research Unit, London School of Hygiene and Tropical Medicine, Lilongwe, Malawi. Mark Urassa, (Kisesa) Tazama Project, Tanzania National Institute for Medical Research, Mwanza, Tanzania. Daniel Kwaro (Kisumu), Kisumu, Kenya Medical Research Institute and the Centers for Disease Control, Kisumu, Kenya. Simon Gregson (Manicaland), Manicaland HIV/STD prevention project, Biomedical Research and Training Institute, Harara, Zimbabwe and School of Public Health, Imperial College, London, UK. Pontiano Kaleebu (Masaka), MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda. Alex Ezeh (Nairobi), African Population and Health Research Center, Nairobi, Kenya. Tom Lutalo (Rakai), Rakai Health Sciences Program, Uganda Virus Research Institute, Rakai, Uganda. Deenan Pillay (uMkhanyakude), Univ KwaZulu Natal, Wellcome Trust Africa Ctr Hlth & Population Studies, Durban, South Africa.

Grant Holders:
Basia Zaba, Jim Todd, Department of Population Health, London School of Hygiene and Tropical Medicine, London, UK. Samuel J Clark, Department of Sociology, University of Washington, Seattle WA, USA. Victoria Hosegood, Department of Social Statistics and Demography, Southampton University, Southampton, UK.

Pooled Analysis Group:

Basia Zaba, Milly Marston, Emma Slaymaker, Georges Reniers, Alison Wringe, Department of Population Health, London School of Hygiene and Tropical Medicine, London, UK. Victoria Hosegood, Department of Social Statistics and Demography, Southampton University, Southampton, UK. Samuel J Clark, Department of Sociology, University of Washington, Seattle WA, USA. Kobus Herbst Africa Centre for Health and Population Studies, University of KwaZulu Natal, Somkhele, South Africa.

Lead Author on behalf of the ALPHA network:

Milly Marston, Department of Population Health, London School of Hygiene and Tropical Medicine, London, UK. Email: milly.marston@lshtm.ac.uk

6 Paper D: The effects of HIV on fertility by infection duration: evidence from African population cohorts before ART availability

For objective 4 of the PhD: to estimate the population impact of HIV on fertility and to examine the effect of duration of infection on fertility and whether this is independent of age using longitudinal data from the ALPHA network; was published in:

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6.1 Introduction to paper

The age specific differences in the effects of HIV on fertility have been well documented, showing increasing subfertility amongst HIV positive women compared to negative women as age increases. An exception is seen in the youngest women 15-19 where selection effects cause the fertility to be higher in HIV positive women than negative women. However there are no estimates of the independent effect of duration of infection. This could be important in estimates of changes due to HIV epidemic duration, because increased HIV subfertility at older ages may be due to longer duration of infection, so subfertility may change over different epidemic stages. Earlier in the epidemic women are more likely to be more recently infected than later in the epidemic. Longer survival of infected women on ART further increases the mean duration since infection.

Previous estimates of age specific HIV subfertility have mainly relied on retrospective data that may be subject to a number of biases. Survivorship bias arises because women who have died in the period before the survey are not included. These women are more likely to have had longer duration of infection and lower fertility, therefore their exclusion causes over estimates of HIV positive fertility. Measurement bias arises because HIV status is measured at the time of the survey, therefore those who sero converted in the reference period before the survey analysis contribute some HIV negative exposure time which is wrongly allocated to the HIV positive group. Longitudinal community-based studies are well placed to assess the level of these possible biases in the analysis of the impact of HIV on fertility.

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

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Student	Camilla Marston
Principal Supervisor	Basia Zaba
Thesis Title	Demographic Determinants of Paediatric HIV in Generalised HIV epidemics

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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 conceived the study with co author Jeffrey Eaton. I carried out the analysis and wrote the paper, Jeffrey Eaton wrote the first draft of the introduction. Co-authors commented and edited drafts.

Student Signature: [redacted] **Date:** 27/03/18

Supervisor Signature: [redacted] **Date:** 27.03.2018

The effects of HIV on fertility by infection duration: evidence from African population cohorts before ART availability

Milly Marston[1], Jessica Nakiyingi-Miiro[3], Sylvia Kusemererwa[3], Mark Urassa[2], Denna Michael[2], Constance Nyamukapa[4], Simon Gregson[4,5], Basia Zaba[1], Jeffrey W. Eaton[5], on behalf of the ALPHA network^.

7. London School of Hygiene and Tropical Medicine, London, United Kingdom
8. TAZAMA Project, National Institute of Medical Research, Mwanza, Tanzania.
9. Medical Research Council, Entebbe, Uganda.
10. Biomedical Research and Training Institute, Harare, Zimbabwe,
11. Department of Infectious Disease Epidemiology, Imperial College London, London, United Kingdom

*Corresponding Author

e-mail: milly.marston@lshtm.ac.uk

^Details of the ALPHA Network are found at alpha.lshtm.ac.uk

6.2 Abstract

Objectives: To estimate the relationship between HIV natural history and fertility by duration of infection in East and Southern Africa before the availability of antiretroviral therapy, and assess potential biases in estimates of age-specific sub-fertility when using retrospective birth histories in cross-sectional studies.

Design: Pooled analysis of prospective population-based HIV cohort studies in Masaka (Uganda) Kisesa (Tanzania), and Manicaland (Zimbabwe).

Methods: Women aged 15-49 who had ever tested for HIV were included. Analyses were censored at antiretroviral treatment roll out. Fertility rate ratios were calculated to see the relationship of duration of HIV infection on fertility, adjusting for background characteristics. Survivorship and misclassification biases on age-specific subfertility estimates from cross-sectional surveys were estimated by reclassifying person time from the cohort data to simulate cross-sectional surveys and comparing fertility rate ratios to true cohort results.

Results: HIV negative and positive women contributed 15,440 births and 86320 person years; and 1,236 births and 11240 thousand person years respectively to the final dataset. Adjusting for age, study site and calendar year, each additional year since HIV sero conversion was associated with a 0.02 (95%CI 0.01-0.03) relative decrease infertility for HIV-positive women. Survivorship and misclassification biases in simulated retrospective birth histories resulted in modest underestimates of sub-fertility by 2-5% for age groups 20-39y.

Conclusion: Longer duration of infection is associated with greater relative fertility reduction for HIV-positive women. This should be considered when creating estimates for HIV prevalence among pregnant women and PMTCT need over the course of the HIV epidemic and ART scale-up.

6.3 Introduction

The effects of HIV infection on fertility have been extensively studied in generalized HIV epidemic settings in sub-Saharan Africa [41, 72, 107, 119, 156, 157]. This was of interest for two reasons: firstly, to forecast the demographic impacts of hyper-endemic HIV [158, 159] and, secondly, because HIV prevalence among pregnant women was widely used for estimating general population HIV prevalence levels and trends[142, 143, 160]. More recently, the need to plan and evaluate prevention of mother-to-child transmission (PMTCT) programmes has further increased the importance of accurate predictions of fertility of HIV-positive women and changes therein.

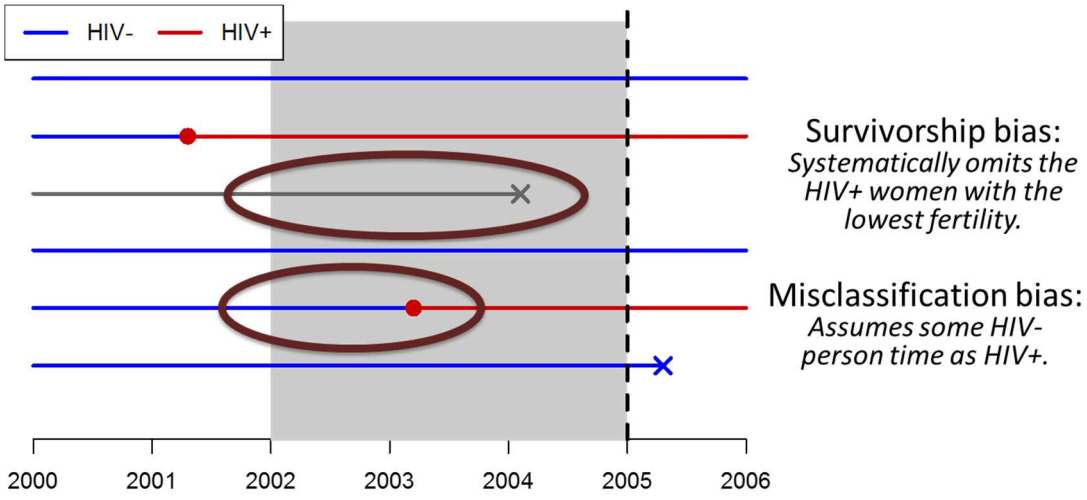
Existing literature, largely based on analysis of cross-sectional data, has demonstrated that the relationship between HIV infection and fertility depends strongly on age. Among young women (age 15–19 years) ANC prevalence is higher than general population prevalence because both pregnancy and HIV risk occur among the subset of women who are sexually active, but among older age groups the fertility rate ratio among HIV-positive women becomes increasingly lower relative to HIV-negative women [41, 144, 161].

Presently, the Spectrum model uses estimates of the fertility rate ratio (FRR) for HIV-positive to HIV-negative women by age-group estimated by Chen and Walker [41] to generate estimates of HIV prevalence among pregnant women and need for PMTCT. However, rather than a direct effect of age, the lower prevalence among older pregnant women may primarily be associated with reduced fertility during later stages of HIV infection[108, 119-121, 154]. This distinction is potentially important because of its interaction with the stages of the HIV epidemic—during the early exponential growth period of the epidemic, many more women are recently infected, and so HIV-related subfertility will be lower than later in the epidemic, even among older women. Moreover, antiretroviral treatment (ART) is disproportionately provided to those infected the longest and experiencing the most serious clinical symptoms—those who are expected to experience the greatest fertility reductions. If the effects of HIV on fertility are strongly related to the duration of infection, then these two effects may contribute to biased predictions about need for PMTCT services as ART programmes scale-up.

Finally, the hypothesised relationship between duration of HIV infection and fertility may influence our ability to estimate the relationship between HIV and fertility. Widely used estimates of age-specific fertility rate ratios (FRR) by HIV status rely on cross-sectional Demographic and Health Survey data to compare fertility over the previous three years among HIV-positive and HIV-negative women [41]. This poses two potential biases (Figure 6.1). First, it excludes women who do not survive the three-year period preceding the survey. If duration of infection influences fertility, then this survivorship bias would

exclude women with the lowest fertility, resulting in an underestimate of subfertility based on cross sectional surveys. Second, retrospective analyses assume the HIV status at the time of the survey is unchanged over the previous three years. For women who seroconverted during the three years prior to the survey, this misclassifies some HIV-negative person-time as HIV-positive, again potentially overestimating the true fertility of HIV-positive women.

Figure 6.1: Survivorship and misclassification bias



In this analysis, we estimate the relationship between the imputed duration of HIV infection and fertility using data from three prospective general-population open cohorts in Uganda, Tanzania and Zimbabwe – all members of the ALPHA network[9]. The objective of this analysis is to estimate the relationship of HIV natural history and fertility in the absence of treatment, and as such we censor the cohort data at the time when ART became available in the population (population-wide fertility trends in these cohorts since ART scale-up have been described elsewhere[78]). We use the prospective demographic and HIV surveillance data to empirically quantify the expected magnitude of survivorship and misclassification biases on age specific subfertility from cross sectional surveys.

6.4 Methods

6.4.1 Sites and setting

Data come from three community-based demographic and HIV open cohort studies. Kisesa (managed by the National Institute for Medical Research Mwanza) located in north western Tanzania, was established in 1994 and has a population of around 34,000. It is predominately rural with a small trading centre on the main road. The average HIV prevalence between 1994 and 2010 was 6% [27]. The Manicaland study (managed by the

Biomedical Research and Training Institute and Imperial College London) in Zimbabwe was established in 1998. A prospective household census (population size approximately 37,000) and general population cohort survey (10,000-12,000) were initiated in 12 geographically distinct study sites spread across three districts, with follow-up rounds conducted every 2 or 3 years. The Manicaland study sites comprise two small towns, four agricultural estates, two roadside settlements and four subsistence farming areas. Overall adult HIV prevalence was around 25% in the late 1990s and has declined steadily to around 15% in 2012-13 [28]. Masaka (managed by MRC/UVRI Uganda Research Unit on AIDS) is situated in rural south west Uganda and was established in 1989. Its initial population was around 10,000 which then increased to 18,000 when 10 villages were added to the census area in 2000. Average HIV prevalence between 1989 and 2011 was 8%[32].

6.4.2 Fertility data

In Kisesa there are two sources of data that are used to estimate fertility. At each demographic surveillance round conducted one to two times per year a proxy respondent is asked whether each woman in the household gave birth since the previous round and the birth outcome. Also all new members of the household, including newborns are linked to their mother if she lives in the household. These two pieces of information are reconciled to give the date of delivery of each birth observed in the DSS.

In Masaka there are four sources of data for estimating fertility. At each annual census, women of child bearing age are asked whether they were pregnant in the previous 12 months and the birth outcome. The names and identification number of the child are recorded on the mother's record. Secondly, each new member of the household is enumerated during the annual census and the reasons for joining obtained. If the reason is new born, the mother's identification number is recorded on the child's census record. Thirdly, village leaders are asked to report all births in their village on a monthly basis to the study clerks. This information is entered and any child reported by these recorders but not on census is added to the census file. Fourth, every 3 years, all children aged <18 years are asked about their parents to establish/confirm who they are and their vital status.

In the Manicaland study, survey rounds are conducted every two to three years. At each survey round, eligible women are enumerated in a household census and invited to participate in an open cohort study. Participants report all births since the previous survey round through a structured questionnaire. For women who die between survey rounds, any births occurring since the previous survey round are recorded in a verbal autopsy interview with the next of kin.

6.4.3 HIV data

In Kisesa, the HIV surveys were carried out separately to the demographic surveillance rounds every two to three years, and data were linked afterwards using unique personal identifiers. In Masaka, HIV testing was done immediately after demographic surveillance rounds which were used to list those eligible for HIV testing. HIV testing took place in the home for all sites apart from Kisesa where temporary village clinics are used, to which people are transported from their homes. Prior to the availability of antiretroviral therapy, testing protocols used informed consent without disclosure, so that participants did not learn the results of the HIV research tests. In Manicaland, following household census enumeration, research assistants interview eligible individual participants to collect dried blood spot samples, which are transported to and analysed in an offsite laboratory.

6.5 Statistical Analysis

6.5.1 Imputation of date of seroconversion

Calculating the fertility rate by duration of HIV infection requires data about when a woman seroconverted, which is not exactly observed. We generated 100 imputations for the date of seroconversion for each HIV-positive woman. For women who are observed HIV-negative in one survey round and HIV-positive in a subsequent round ('seroconverters'), we imputed dates of seroconversion from a uniform distribution between the dates of the last negative and first HIV positive test.

For women who were already HIV positive the first time they were tested in the cohort ('prevalent cases'), we imputed 100 seroconversion dates from a distribution determined by the convolution of the age-specific HIV incidence rates and the probability of surviving from seroconversion until the woman's latest age at interview.

6.5.2 Fertility rate ratio by duration of infection

Person time and live births of women of reproductive age (15- 49 years old) who had ever tested for HIV in the studies were eligible for inclusion in the analysis. HIV negative person-time for women with no subsequent positive test was assumed to last for up to five years past their last negative test, the exact cut-off point was determined by the HIV incidence rates in the sites, defined as the time at which the cumulated probability of becoming infected following the last negative test reached 5%. Data for each cohort were censored at the start of ART introduction (Kisesa March 2005, Masaka January 2004, Manicaland June 2005), in order to estimate the intrinsic relationship between HIV and fertility before the availability of antiretroviral therapy. For women ever testing HIV positive imputed seroconversion dates were used to assign person-time by HIV status.

The imputed duration of infection is defined as 0 for HIV-negative, and is treated as a continuous variable in years following sero-conversion. Fertility rate ratios (FRR) by HIV status and duration of infection are calculated using piecewise exponential regression allowing for clustering of births in each women, adjusting for age-specific fertility in each site and a log-linear trend in fertility over calendar time centred on the year 2001. The analysis was repeated 100 times using independently imputed sero conversion dates. The log of the hazard rate ratios from the imputations were combined using Rubin's rules [39] to give confidence intervals that reflect the uncertainty about the exact date of sero-conversion. Older age at infection pre ART is associated with a shorter survival time [7] independent of current age [5]. We investigated whether this could also have an effect on subfertility classified by duration of infection (model not shown)

6.5.3 The effects of survivorship and misclassification bias in retrospective survey analysis

We quantified the potential magnitude of survivorship and misclassification biases when estimating age specific subfertility from cross sectional surveys by using the population cohort data to simulate the three-year retrospective fertility history analysis and compared the resulting age-specific FRRs to the true FRRs observed in the cohorts. Person time was classified in three year intervals 2000-2002 and 2003-2005 then aggregated over the six-year period. We calculated actual sub-fertility by age (adjusted for study site, residence and calendar time), then calculated sub-fertility by age as assumed in cross-sectional studies by allocating all the person time of women who were positive at the end of the time period to HIV positive for the whole period (simulating misclassification) and removing any person time and births to women who died in the period (simulating survivorship bias).

All analysis was done using Stata 14.1.

6.6 Ethics statement

Each of the three sites contributing data to the pooled analysis received ethical clearance from the appropriate local ethics review bodies, and from the corresponding Institutional Review Boards at relevant collaborating partner universities.

6.7 Results

6.7.1 Estimates of HIV subfertility by duration of infection

The dataset compiled for women aged 15-49 years contained 15,451 births and 86280 person years to HIV negative women; 993 births and 9580 person years to HIV positive

women; and 315 births and 2510 person years with HIV status unknown. Prior to imputation the latter group comprised the time before a first positive test and person time in the sero conversion interval (Table 6.1). Kisesa contributed the most births (54%) and person years (42%) (Table 1). Manicaland contributed the highest number of births and person years to HIV positive women (477 births 5750 person years) due to the higher HIV prevalence in Zimbabwe. After imputation of sero conversion dates HIV negative and positive women contributed 15,440 births and 86320 person years; and 1,236 births and 11240 person years respectively. The total fertility rate over the pre ART time period used was highest in Kisesa at 6.2 followed by Masaka at 5.2 and lowest in Manicaland at 3.1.

Table 6.1: Births and person years by HIV status and study site for women aged 15-49 who ever tested for HIV

	Kisesa		Manicaland		Masaka		All sites	
HIV Status	Births	Person Years per 1000	Births	Person Years per 1000	Births	Person Years per 1000	Births	Person Years per 1000
Negative	8581	38.11	2003	19.87	4867	28.30	15451	86.28
Positive	284	2.17	381	4.93	328	2.48	993	9.58
Unknown	162	1.12	96	0.85	57	0.54	315	2.51

Note for those HIV negative women were included up to 5 years post last negative test

Crude fertility rates patterns were broadly similar in the observed prevalent positive person time compared to the imputed positive person time with the rates slightly higher in the imputed positive person time, consistent with imputed positive being biased towards earlier duration after sero conversion (not shown). Crude rates show a decrease in fertility by duration of infection (Table 6.2).

Compared to HIV-negative women, the relative fertility of HIV-positive 20-24 year-olds was 0.72 (95%CI 0.66-0.79), and relative fertility further reduced with age (Table 6.3, Model 1). The 15-19 year old HIV-positive women have higher fertility compared to those who are uninfected due to the fact that many women in this age-group are not sexually active and therefore are not exposed to HIV.

Including duration of infection in the model showed that each additional year since seroconversion was associated with a 0.979 (95%CI 0.965-0.995) times reduction in fertility for HIV-positive women, adjusted for age, the effect of age at sero-conversion, study site and calendar year (Model 2, Table 6.3). Accounting for duration attenuated the relative fertility of positive women compared to negative women to 0.78 (95%CI 0.70-0.88) and similarly for other age groups (Model 2, Table 6.3).

Restricting the model to HIV positive women (Not shown) shows that with increasing year of age at sero conversion there is an increase in the effect of duration on subfertility (FFR 0.997 95%CI 0.994-0.999).

Table 6.2: Crude rates with imputed data by HIV status .

	HIV Negative			Imputed Positive			All imputed data		
	Births	Person Years per 1000	Fertility Rate per 1000	Births	Person Years per 1000	Fertility Rate per 1000	Births	Person Years per 1000	Fertility Rate per 1000
Age Group									
15-19	2683.47	21.98	122.07	122	0.70	173.47	2806	22.69	123.66
20-24	4445.68	15.40	288.66	381	1.97	193.19	4826	17.37	277.83
25-29	3505.11	12.83	273.12	393	2.69	146.36	3898	15.52	251.18
30-34	2485.16	11.03	225.41	209	2.29	91.31	2694	13.31	202.35
35-39	1592	9.72	163.76	106	1.66	63.72	1698	11.39	149.14
40-44	621.26	8.53	72.87	21	1.25	16.53	642	9.78	65.66
45-49	106.89	6.83	15.66	4	0.67	6.11	111	7.50	14.80
HIV status									
Negative	15440	86.32	178.87				15440	86.32	178.87
Positive				1236	11.24	109.98	1236	11.24	109.98
Duration of infection									
1 year				130	0.81	160.13	130	0.81	160.13
1-2 years				265	1.87	142.15	265	1.87	142.15
3-4 years				252	1.87	135.13	252	1.87	135.13
5-6 years				205	1.68	121.66	205	1.68	121.66
7-8 years				145	1.39	104.62	145	1.39	104.62
9+ years				226	3.56	63.52	226	3.56	63.52
Study Site									
Kisesa	8582.09	38.16	224.89	389	2.78	139.75	8971	40.94	219.10
Manicaland	2002.82	19.89	100.67	477	5.75	82.97	2480	25.65	96.70

Masaka	4854.66	28.26	171.78	370	2.70	136.78	5224	30.96	168.73
Calendar Year									
1990	185.89	1.08	171.57	20	0.13	148.61	206	1.22	169.06
1991	335.79	1.61	209.15	34	0.19	179.94	370	1.80	206.05
1992	322.34	1.66	193.84	34	0.18	184.99	356	1.85	192.97
1993	232.02	1.68	138.42	36	0.18	197.64	268	1.86	144.22
1994	587.16	2.98	197.17	44	0.27	164.69	631	3.25	194.48
1995	1109.32	4.93	225.06	60	0.40	151.54	1170	5.33	219.56
1996	1079.8	5.02	214.92	61	0.41	149.27	1141	5.43	210.00
1997	1111.19	5.11	217.29	65	0.43	152.19	1176	5.54	212.30
1998	919.17	5.16	178.27	37	0.42	88.61	956	5.57	171.58
1999	1369.48	7.02	195.03	104	0.96	107.58	1473	7.98	184.49
2000	1562.19	9.17	170.37	155	1.48	104.97	1718	10.65	161.28
2001	1684.16	9.72	173.25	145	1.46	99.67	1829	11.18	163.65
2002	1711.85	10.23	167.27	169	1.49	113.05	1881	11.73	160.37
2003	1750.11	10.97	159.58	130	1.56	82.92	1880	12.53	150.02
2004	1242.34	7.92	156.90	108	1.26	86.04	1351	9.18	147.16
2005	236.76	2.06	115.13	34	0.42	81.86	271	2.48	109.51

Births and person years are averaged over 100 datasets

Table 6.3: Effects of HIV on fertility by age and duration of infection

	Model 1 - No duration		Model 2 - With duration	
	FRR	95%CI	FRR	95%CI
Duration of infection			0.979	(0.964-0.995)
HIV status				
HIV Negative	1		1	
HIV Positive	0.72	(0.66-0.79)	0.78	(0.70-0.88)
Effects of HIV by age				
15-19,HIV Positive	2.02	(1.67-2.45)	1.95	(1.60-2.38)
20-24,HIV Positive	1		1	
25-29,HIV Positive	0.86	(0.75-0.98)	0.90	(0.78-1.03)
30-34,HIV Positive	0.69	(0.58-0.81)	0.74	(0.62-0.89)
35-39,HIV Positive	0.73	(0.58-0.92)	0.81	(0.63-1.03)
40-44,HIV Positive	0.46	(0.28-0.76)	0.52	(0.32-0.87)
45-49,HIV Positive	0.90	(0.27-2.99)	1.01	(0.30-3.39)
Age Group				
15-19	0.50	(0.47-0.54)	0.50	(0.47-0.54)
20-24	1		1	
25-29	0.96	(0.92-1.01)	0.96	(0.92-1.01)
30-34	0.81	(0.77-0.85)	0.81	(0.77-0.85)
35-39	0.63	(0.59-0.67)	0.63	(0.59-0.67)
40-44	0.31	(0.28-0.35)	0.31	(0.28-0.35)
45-49	0.09	(0.07-0.12)	0.09	(0.07-0.12)
Study Site				
Kisesa	1		1	
Manicaland	0.66	(0.62-0.71)	0.67	(0.62-0.71)
Masaka	0.87	(0.82-0.92)	0.87	(0.82-0.92)
Calendar Year	0.99	(0.99-1.00)	0.99	(0.99-1.00)

Results from exponential regression of fertility rates as a function of HIV status, age and duration of infection controlling for interaction between study site and age (not shown), study site and calendar year (not shown). Calendar year is centred at 2001, age at sero conversion is centred at age 25. .Pooled results based on 100 datasets for imputed date of sero conversion.

6.7.3 Estimates of survivorship bias in retrospective surveys

Age specific subfertility was larger in the ALPHA sites compared to that found by Chen and Walker[41] apart from the 15-19 year age group (Figure 6.2a). The reduction in fertility was 3-12% greater in the age groups 20-34 years, and somewhat larger at the oldest age groups, for example 41% lower in the 40-44 year age group. However, confidence intervals encompassed Chen and Walker estimates apart from the 40-44 year old age group. Figure 6.2 b compares the observed subfertility by age in the cohorts (red dots) to the subfertility estimates when analysed using the assumptions of a retrospective cross-sectional survey (blue triangles). Estimates with simulated misclassification and survivorship bias attenuated the subfertility by age by between 2-5% in the age groups between 20 and 39 years old and 22% in the 40-44 year age group.

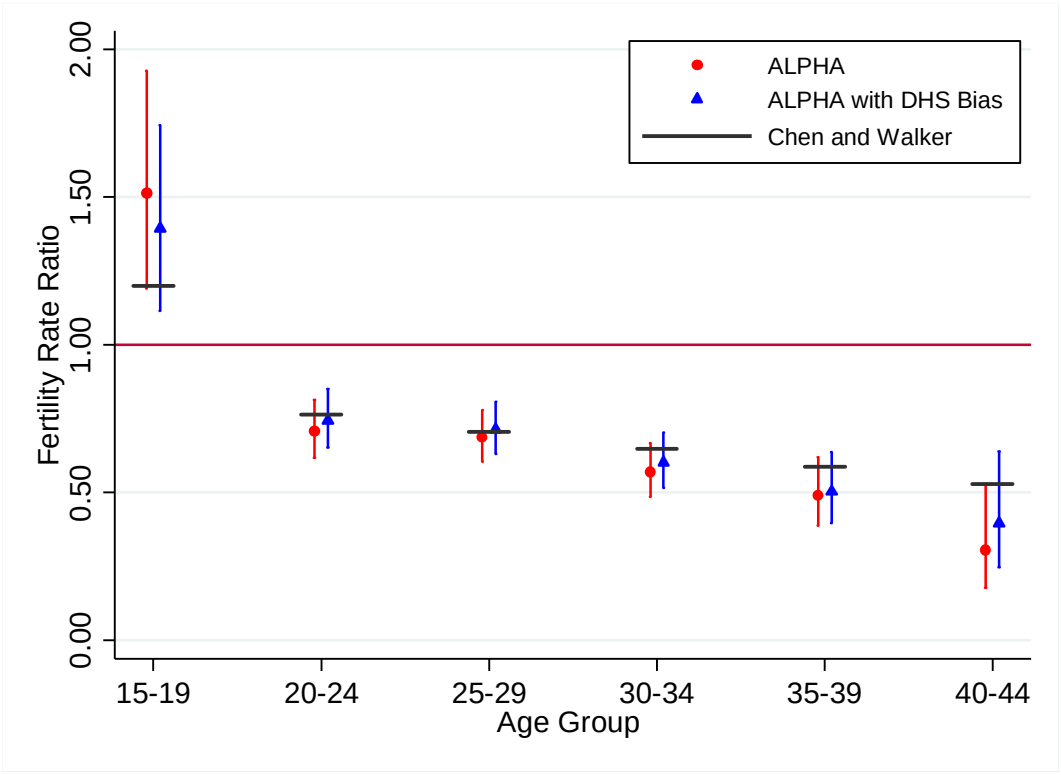
There was some evidence for variation of age specific subfertility by study site with subfertility in Manicaland lower than in Masaka and Kisesa

6.8 Discussion

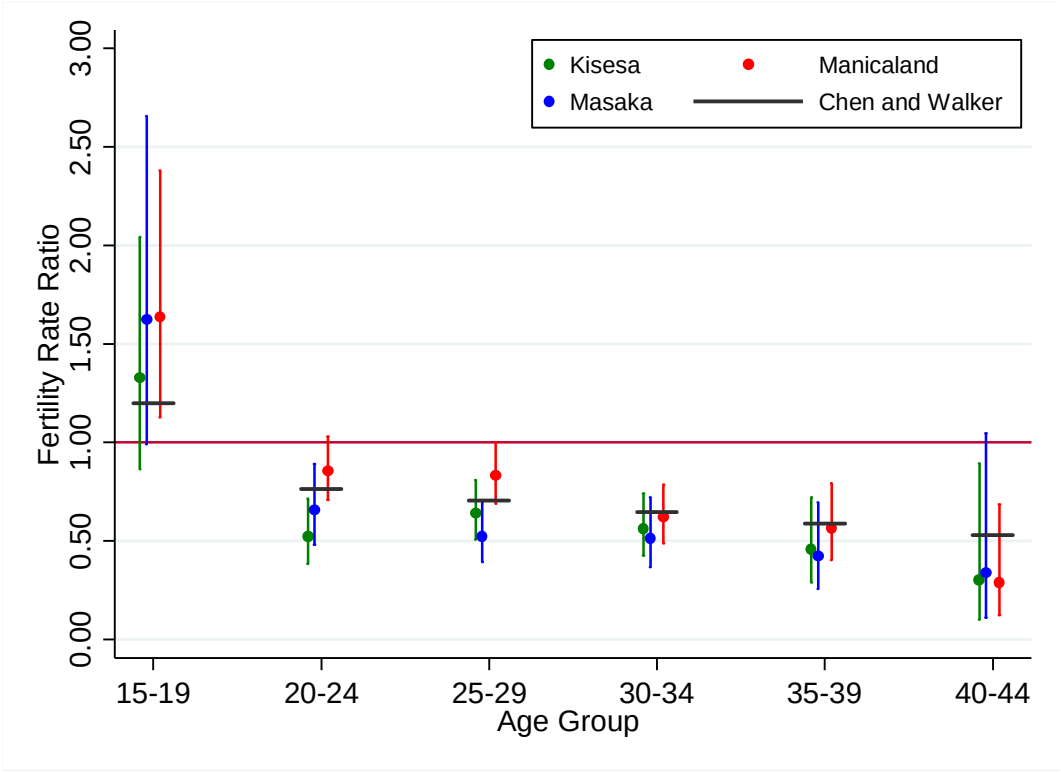
These data show that longer duration of HIV infection is associated with increased subfertility. Estimating age specific HIV subfertility using retrospective cross sectional surveys underestimates subfertility, particularly for older ages, due to survivorship bias being more important at longer duration of infection which corresponds to greater fertility reducing effects of HIV infection.

Many studies have documented the effect of HIV on fertility and on age-specific subfertility[41, 72, 144, 161] at the population level during the pre-ART period. A number of studies in sub-Saharan Africa have looked at disease progression in relation to fertility, a case control study in Uganda found that high viral load was associated with reduced rates of pregnancy and a reduction in live births[119], despite being sexually active and not using contraception. Also a clinical cohort found that fertility is reduced from the earliest stage of HIV infection with a large reduction in fertility following the progression to AIDS [108] – this finding was adjusted for sexual activity but not for contraceptive use. A clinical cohort study in Tanzania also found reduced fertility related to clinical stage of HIV [120] adjusting for social and demographic characteristics. A multi-site HIV care and treatment programme analysis showed a strong association between disease progression and a reduction in the incidence of pregnancy[121].

Figure 6.2: a) Fertility rate ratio from Chen and Walker – Survivorship bias b) Age specific Fertility rate ratio (HIV positive/HIV negative) by study site compared to Chen and Walker



b)



Increased subfertility by duration of infection at the population level could have both biological and behavioural factors. Biologically, as well as increases in viral load or decreases in CD4 count as explanatory factors, the semen quality of HIV positive partners could be reduced over the time of their infection [95, 96, 101] or their increased illness could impact on their sexual activity. In terms of behaviour, HIV positive women are more likely to be widowed[107, 122, 155] due to having had an HIV positive partner. Although voluntary testing and counselling was rare in these sites prior to ART introduction, suspicion of HIV status or illness in a partner with HIV may reduce the desire for more pregnancies [115] which may be more obvious at longer durations of infection and it may also increase divorce or separation [107, 155]

Increased age at seroconversion accelerated the effects of infection duration on subfertility. Older age at infection leads to shorter survival post infection[5, 7], so a shorter duration to low CD4 count and higher viral load which have been shown to reduce fertility. Also at older ages of sero conversion it is more likely the partner (who is more likely to be older) has been infected for a longer duration therefore there is a higher chance of widowhood early on in the women's HIV infection lowering her changes of pregnancy. Finally, older women are likely to have higher parity and therefore may have lower desires for more children than a younger woman who has none or few children.

Compared to the DHS analysis by Chen and Walker [41], ALPHA cohorts showed greater fertility reductions among HIV-positive women by five year age group, particularly in the older age groups. Around half of this discrepancy was explained by biases inherent in estimating subfertility from cross sectional data due to not including the person years and births of those who died prior to interview and classifying all person years according to the HIV status at time of interview.

Residual differences between our findings and those of Chen and Walker [41] could have a number of causes. This DHS analysis uses countries across South, East and Western Africa, whereas our analysis uses study sites from East and Southern Africa where Manicaland, Zimbabwe showed lower subfertility than the two east Africa sites (although confidence intervals overlapped) which may indicate some differences in subfertility and duration of infection in different settings as found in previous studies [107, 157]. Modern contraceptive use by all women is much higher in Zimbabwe at 40.1% in 2005-06 compared to Tanzania and Uganda, 22.5% in 2004-05 and 19.6% in 2006 respectively [162] which may contribute to these differences [107]. Deliveries and the deaths of children dying in early infancy (particularly in the neonatal period) could be underreported in the ALPHA studies due to recall bias or lack of knowledge on the part of a proxy respondent,

which would affect HIV positive women disproportionally due to the high infant mortality of children infected through vertical transmission [13]. This could artificially increase subfertility estimates in the cohort studies. The DHS will be prone to more recall bias than the cohort studies, however, if analysis is limited to the first few years prior to the interview, and the respondent is the women rather than a proxy it is possible this will lead to less bias in reporting of births to infants who have died in DHS compared to ALPHA studies. We find that subfertility increases with duration of HIV infection in the absence of ART. This has two important implications that should be considered in future HIV epidemic estimates and the estimates of need for PMTCT. Firstly, over the course of the epidemic the distribution of duration of infection changes. During the exponential growth phase a higher proportion of women will be recently infected, and as incidence declines average duration of infection will become longer. This means that the population-level effects of HIV on fertility, and hence the relationship between HIV prevalence measured among pregnant women and general population prevalence, will change.

Second, initiation of anti-retroviral treatment has been disproportionately among women in later stages of infection who might be expected to have the lowest fertility rates. Thus, following ART scale-up, not only might women on ART have increased fertility [73], but also the fertility of untreated HIV-positive women may be higher because those who would have the lowest fertility are selectively removed into the treatment group. Implementation of Option B+ over the past several years, in which all pregnant women are initiated on lifelong ART, will further change these dynamics. In light of the demonstrated association between duration of infection and fertility reduction, we recommend that model-based approaches account for not only age but also stage of infection and ART status when estimating HIV prevalence among pregnant women and PMTCT need.

Our results also imply that there are differences in fertility by setting. This underscores that, where possible, locally available data such as prevalence from routine HIV testing of pregnant women should be used in place of default model values to inform appropriate model assumptions about subfertility when generating estimates of PMTCT need.
Finally, it is worth noting that survivorship bias will be less important in the era of ART, as HIV mortality is lower. The assumption that women who are HIV positive at the time of interview have been infected for at least 3 years will also become more realistic as longer durations of infection become more common in the era of ART. These factors should also be considered when interpreting changes over time in the relationship between HIV and fertility from cross-sectional surveys.

6.9 Acknowledgements

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M.M. & J.W.E. conceived the concept and directed the study; M.M. performed the analysis; M.M. J.W.E. contributed to the writing. S.G., J.N. S.K., M.U, D.M, C.N, contributed clean harmonised data and commented on drafts, B.Z is the PI of the ALPHA network who designed the harmonisation and structure of the data used for the analysis and commented on drafts.

7 PAPER E: The relationship between HIV and fertility in the era of antiretroviral therapy in sub Saharan Africa – Evidence from 48 Demographic & Health Surveys

7.1 Introduction to chapter

For objective 5 of the PhD: to estimate the population impact of HIV on fertility and investigate if there are variations by region, urban and rural residence and ART coverage using cross sectional data from demographic and health surveys; an analysis was conducted using data from demographic and health surveys and published in:

Marston, M., B. Zaba, and J.W. Eaton, *The relationship between HIV and fertility in the era of antiretroviral therapy in sub-Saharan Africa: evidence from 49 Demographic and Health Surveys.* Trop Med Int Health, 2017. **22**(12): p. 1542-1550.

Understanding the fertility of HIV positive women has been of central importance to the HIV response in sub-Saharan Africa for planning and evaluating programmes to prevent mother-to-child HIV transmission (PMTCT). Conversely, understanding differences in HIV prevalence in pregnant women and the general female population is vital for the interpretion HIV prevalence trends observed among pregnant women, and extrapolation of these trends to estimate prevalence in the general population.

An earlier systematic review and an updated search showed that there are few population-based studies in the era of ART[73]. One study looked at HIV subfertility using demographic and health surveys (DHS) prior to ART roll out[41]. Another focused on DHS from Malawi pre and post ART roll out[79]. Two studies used community-based cohort studies, one comparing pre and post ART periods[78], the other using only the period before ART roll out[43]. All studies found lower fertility in HIV positive women in general, and both studies looking at the pre and post ART periods found some evidence for a narrowing of the differences in fertility in the period after ART roll out.

This paper uses data from 48 demographic and health surveys (DHS) and AIDS indicator surveys (AIS) from 27 countries in sub-Saharan Africa from 2003 through to 2015. This greatly expands a previous analysis of 16 surveys in Sub Saharan African from 2003

through 2007, and in particular extends the analysis into the ART era. This larger dataset is also used to examine regional, urban/rural and temporal differences.

For the purposes of this PhD, appendix 1 of the paper is presented in an expanded format in section 7.2 and appendix 2 has been incorporated into the main text in section 7.2.

For objective 6 of the PhD: to investigate possible biases affecting the analysis of the impact of HIV on fertility that arise from the use of retrospective data such as DHS or prospective data; an analysis was carried out using DHS and ALPHA network data. Part of this work was published as supplementary material to paper E (Appendix 1)

The work presented here (section 7.2) is broader than that published in the supplementary material to paper E, and not only covered biases when using retrospective data such as DHS but also looks at biases that arise when using longitudinal data from the ALPHA network. It assesses whether we can attribute the higher HIV subfertility at younger ages found in ALPHA network sites (paper D) compared to those using DHS studies (paper E) to biases inherent in the analyses of these two data sources.

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

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Student	Camilla Marston
Principal Supervisor	Basia Zaba
Thesis Title	Demographic Determinants of Paediatric HIV in Generalised HIV epidemics

If the Research Paper has previously been published please complete Section B, If not please complete Section C

SECTION B

Where was the work published?			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	PLoS One
Please list the paper's authors in the intended authorship order:	Milly Marston, Jeffrey W. Eaton, Basia Zaba.
Stage of publication	**Submitted**

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 conceived the analysis, prepared the data and carried out the analysis, co-authors commented on analysis and edited drafts.

Student Signature: [redacted] **Date:** 27/03/18

Supervisor Signature: [redacted] **Date:** 27.03.2018

PAPER E: The relationship between HIV and fertility in the era of antiretroviral therapy in sub Saharan Africa – Evidence from 48 Demographic & Health Surveys"

Milly MARSTON [1],Basia ZABA[1], Jeffrey W EATON[2].

1 London School of Hygiene and Tropical Medicine, London

2 Department of Infectious Disease Epidemiology, Imperial College, London

Corresponding Author: Milly Marston, London School of Hygiene and Tropical Medicine, London, UK, WC1E 7HT. Tel: +44 (0)207 299 4665

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7.1.1 Abstract

Objectives

Describe regional differences in the relative fertility of HIV positive women compared to negative women and changes as antiretroviral treatment (ART) is scaled-up, in order to improve estimates of predicted need for and coverage of prevention of mother-to-child transmission services at national and subnational levels.

Methods

We analysed 48 nationally representative household surveys in sub-Saharan Africa between 2003 and 2015 to estimate fertility rate ratios of HIV positive and HIV negative women by age using exponential regression, and test for regional and urban/rural differences. We estimated the association between national ART coverage and the relationship between HIV and fertility.

Results

Significant regional differences exist in HIV and fertility relationships, with less HIV-associated subfertility in Southern Africa. Age patterns of relative fertility are similar. HIV impact on fertility is weaker in urban than rural areas. For women below age 30, regional and urban/rural differences are largely explained by differences in age at sexual debut. Higher levels of national ART coverage appear to slightly attenuate the relationship between HIV and fertility.

Conclusions

Regional differences in HIV-associated subfertility and urban/rural differences in age patterns of relative fertility should be accounted for when predicting need for and coverage of PMTCT services at national and subnational level. Although HIV impacts on fertility are somewhat reduced at higher levels of national ART coverage, differences in fertility between HIV positive and negative remain, and fertility of women on ART should not be assumed to be the same as HIV-negative women.

7.1.2 Introduction

Elimination of mother-to-child transmission of HIV (MTCT) through provision of antiretroviral treatment (ART) to all HIV positive pregnant women is a major policy objective for national HIV programmes, The Joint United Nations Programme on HIV/AIDS (UNAIDS), and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) [1]. Accurate estimates of the number of HIV-positive pregnant women at the national and sub-national level are essential for planning and allocating resources needed for services to prevent mother-to-child transmission (PMTCT), calculating coverage and unmet need of existing services, and evaluating progress towards elimination targets [2]. Estimates of PMTCT need, coverage, and MTCT rates are key outputs of official annual national HIV programme reports, generated with support from UNAIDS[163]. HIV prevalence in antenatal care and PMTCT settings is the main indicator of national HIV epidemic trends, but in order to interpret it correctly as a guide to prevalence in the general population we need to understand the relative incidence of pregnancy in HIV positive and negative women.

Coverage and unmet need for PMTCT services are estimated by dividing number of pregnant women receiving PMTCT services from routine programmatic data (the numerator) by a modelled estimate of the number of HIV positive pregnant women (the denominator). Estimating the number of HIV positive pregnant women, and hence need for PMTCT services, relies on information about (1) age- and sex-specific HIV prevalence in the population, (2) age-specific fertility rates, and (3) the fertility of HIV-positive women relative to HIV-negative women. Existing literature about the effects of HIV status on fertility emphasises a changing relationship with age[41, 43, 72, 144, 164]. At the youngest ages HIV-positive women, relative to HIV negative women have higher fertility due to selection of sexually active women. The fertility of HIV positive women relative to HIV negative women steadily declines with age, due to both biological effects of HIV on fecundity [108, 144, 165] and differences in exposure to pregnancy including factors such as higher divorce and widowhood in HIV positive women[155]. A few studies have suggested regional differences in HIV-related subfertility [43, 78, 157] although regional variation is not systematically accounted for in current estimates of PMTCT need.

It is widely anticipated that ART scale-up will ameliorate the subfertility of HIV positive women, which would affect the number of HIV positive pregnant women, although evidence of this is limited [73]. In the era of ART most studies of the impact of ART on pregnancy or fertility have been clinic based [73] which have shown some evidence that fertility increases after the first year on ART but still remains lower than HIV negative women. Elul et al [74] have criticised existing evidence from clinical cohorts which do not

account for the effect of pregnancy status at enrolment. Allowing for this in an analysis of 26 clinics in East Africa, they found little evidence that ART initiation is associated with an increased risk of pregnancy in women who enrol in HIV care. A number of population level studies have shown evidence of a narrowing of fertility differences between HIV positive and HIV negative women[78, 79] in the era of ART.

This study aims to improve the characterization of the relative fertility of HIV positive women to HIV negative women by region and place of residence, and update widely used estimates with data from the ART era.

7.1.3 Methods

Data

We used data from 48 Demographic and Health Surveys (DHS) and AIDS indicator surveys (AIS) conducted in 27 sub-Saharan African countries between 2003 and 2016 in which both full birth histories and HIV testing outcomes were available [40]. National ART coverage estimates for adult women were taken from UNAIDS estimates [166] and ranged from none in the earlier years to 72% in Zimbabwe in 2015 (Table 7.1).

DHS and AIS are nationally representative household surveys [40]. All analyses account for the two-stage cluster sampling survey design and use the HIV weights provided by DHS. In pooled analysis, surveys are re-weighted so that each survey contributes equally toward the analysis.

Table 7.1: Demographic and Health Surveys with HIV women testing population samples by September2017

Region	Survey	Year	n	HIV prevalence Women 15-49 (95% CI)*	Estimated female adults 15+ ART coverage(%)†	Median age at first sex 25-29 year olds‡		
						Urban	Rural	All
Southern Africa								
	Lesotho	2004	3030	26.3 (24.5-28.2)	1 (1-1)	19.0	18.6	18.7
	Lesotho	2009	3778	26.7 (25.0-28.6)	27 (25-29)	18.9	18.3	18.5
	Lesotho	2014	3175	29.7 (27.7-31.8)	40 (37-43)]	18.8	18.3	18.5
	Namibia	2013	4051	16.9 (15.4-18.4)	62 (50-70)	19.0	18.3	18.8
	Swaziland	2006-07	4424	31.1 (29.4-32.9)	10 (8-11)	18.6	17.9	18.1
	Zimbabwe	2005-06	6947	21.1 (19.7-22.6)	2 (2-3)	19.7	18.4	18.9
	Zimbabwe	2010-11	7313	17.7 (16.6-18.8)	31 (24-38)	20.5	18.6	19.3
	Zimbabwe	2015	8667	16.7 (15.6-17.8)	72 (57-84)	20.0	17.9	18.6
East and Mid Africa								
	Burundi	2010	4533	1.7 (1.4-2.1)	33 (26-40)	20.7	19.9	19.9
	Kenya	2003	3151	8.7 (7.6-10.0)	0 (0-0)	18.9	17.6	18.0
	Kenya	2008-09	3641	8.0 (6.8-9.3)	16 (15-18)	19.5	17.7	18.3
	Malawi	2004	2686	13.3 (12.0-14.8)	1 (1-2)	18.2	17.4	17.5
	Malawi	2010	7091	12.9 (11.8-14.1)	31 (29-33)	17.9	17.1	17.3
	Malawi	2015-16	7737	10.8 (9.9-11.7)	66 (63-71)	18.1	16.9	17.2
	Rwanda	2005	5641	3.6 (3.1-4.2)	9 (8-11)	20.3	19.9	20.0
	Rwanda	2010	6917	3.7 (3.3-4.2)	45 (39-51)	21.5	21.3	21.3
	Rwanda	2014-15	6752	3.6 (3.2-4.1)	67 (59-76)	21.4	21.5	21.5
	Tanzania	2007-08	8179	6.6 (5.9-7.4)	10 (8-12)	18.2	17.3	17.5
	Tanzania	2011-12	9756	6.2 (5.6-6.8)	24 (18-28)	18.3	17.3	17.9
	Zambia	2007	5502	16.1 (14.7-17.5)	20 (19-22)	17.9	17.0	17.4
	Zambia	2013-14	14719	15.1 (14.2-16.0)	53 (50-56)]	18.3	16.9	17.5
West and Central Africa and Ethiopia								
	Burkina	2003	4086	1.5 (1.2-2.0)	1 (1-1)	18.4	17.3	17.4
	Burkina	2010	8298	1.2 (0.9-1.5)	32 (25-40)	18.6	17.3	17.6
	Cameroon	2004	5128	6.6 (5.9-7.4)	2 (2-3)	17.1	15.8	16.5
	Cameroon	2011	7221	5.6 (5.0-6.3)	18 (15-20)	17.7	16.5	17.3
	Chad	2014-15	5656	1.8 (1.4-2.2)	50 (42-59)	16.7	16.1	16.2
	Cote Ivoire	2005	4413	6.4 (5.5-7.5)	6 (5-7)	16.9	16.1	16.4
	Cote Ivoire	2011-12	4509	4.6 (3.9-5.4)	25 (22-27)	17.6	16.3	16.9

DRC	2007	4492	1.6 (1.2-2.2)	5 (4-6)	17.4	16.4	16.9
DRC	2013-14	9264	1.6 (1.2-2.2)	24 (19-29)	17.4	16.4	16.8
Ethiopia	2005	5736	1.9 (1.4-2.4)	2 (2-3)	20.7	16.1	16.6
Ethiopia	2011	14695	1.9 (1.5-2.3)	41 (32-51)	18.3	17.2	17.4
Gabon	2012	5459	5.8 (4.7-7.1)	32 (26-38)	17.1	16.7	17.1
Gambia	2013	4089	2.1 (1.6-2.8)	24 (18-30)	20.6	18.0	19.3
Ghana	2003	5097	2.3 (1.9-2.8)	0 (0-0)	19.4	17.9	18.3
Guinea	2005	3742	1.9 (1.4-2.6)	2 (1-2)	16.7	15.9	16.0
Guinea	2012	4622	2.1 (1.7-2.6)	28 (21-34)	17.6	15.7	16.3
Liberia	2007	6382	1.8 (1.4-2.1)	3 (2-3)	16.6	16.1	16.3
Liberia	2013	4397	2.0 (1.5-2.8)	19 (15-24)	16.6	16.0	16.4
Mali	2006	4528	1.4 (1.0-2.0)	8 (6-10)	16.8	15.9	16.2
Mali	2012-13	4806	1.3 (1.0-1.8)	32 (24-40)]	18.0	16.5	16.8
Niger	2006	4406	0.6 (0.4-0.9)	3 (2-4)	17.9	15.6	15.8
Niger	2012	5000	0.4 (0.2-0.5)	27 (20-32)	18.7	15.8	16.0
Sao Tome	2009	2378	1.3 (0.8-2.0)	.	17.6	17.3	17.5
Senegal	2005	4229	0.7 (0.4-1.0)	0	21.2	17.5	19.3
Senegal	2010-11	5326	0.6 (0.4-0.8)	33 (25-40)	21.1	17.9	19.4
Sierra Leone	2008	3448	1.7 (1.3-2.3)	4 (3-5)	16.7	15.7	16.0
Sierra Leone	2013	7695	1.7 (1.3-2.0)	21 (13-29)	17.0	16.0	16.4
Togo	2013-14	4737	3.1 (2.6-3.7)	37 (27-49)	18.6	17.4	18.1

* Estimated HIV prevalence, see methods section

† http://aidsinfo.unaids/, accessed 07 September 2017. Note for those surveys running over two years the earlier year is given

‡ICF International, 2015. The DHS Program STATcompiler. http://www.statcompiler.com. September 07 2017

Calculating age specific fertility rates

Each woman respondent was asked birth history questions for up to 20 births, beginning with the most recent. Dates of birth of the women and children are given in months and years, we assigned the day of birth to be the midpoint of the month.

We initially analysed fertility rates by HIV status during the three years prior to the interview. This cut-off was used in previous studies[41, 42] to balance the benefits of maximizing the person-years of observation while seeking to minimize maternal survivorship bias, recall bias and misclassification of HIV status over the three preceding years[43]. However, we report results adjusted for the first year prior to the survey due to evidence of persistence of these biases when using data from longer than a year prior to the survey (see section 7.2, which shows the analysis). We used the standard demographic definition of age-specific fertility rates (ASFR):

$$ASFR_{x-x+4} = \frac{Number\ of\ births\ to\ women\ aged\ x\ to\ x+4}{Number\ of\ person\ years\ contributed\ by\ women\ aged\ x\ to\ x+4}$$

we then estimated the fertility rate ratios in the general population. Subsequently, we restricted the analysis to person years after first sex to assess the extent to which variation in age at first sex explains fertility differences among HIV positive women and HIV negative women in the younger age groups. We assumed sexual debut occurred on the date corresponding to the midyear of the reported age at first sex (which is reported as an integer age). Age at first sex was changed to nine months before the reported date of first birth if this was earlier than the midpoint of reported age at first sex.

Other Variables

Other variables included women's HIV status at the time of the survey, calendar year, ART coverage, region, and place of residence (urban/rural). Those infected with HIV-2 and whose HIV test was indeterminate were excluded from the analysis (0.04%).

Countries were grouped into regions as follows: Southern (Zimbabwe, Lesotho, Swaziland and Namibia), East and mid- Africa (Tanzania, Kenya, Uganda, Rwanda, Burundi, Malawi and Zambia) and West and Central Africa with Ethiopia (Table 7.1). HIV epidemics in the East and Mid African countries occurred earlier than in Southern Africa. West and central Africa along with Ethiopia have lower prevalence and HIV transmission is likely more concentrated.

ART coverage estimates were taken from UNAIDS estimates[167] of national female adult ART coverage at the time of each survey were stratified into categories <20%, 20-49%, and >50% (Table 7.1). For surveys that ran over two different years a midpoint of the estimated coverage in both years was taken.

Analysis

We used exponential regression to investigate the interaction between HIV status and five-year age group, place of residence, region and ART coverage with respect to their impacts on fertility. Each analysis was adjusted for country and survey year. The analysis was repeated excluding person time prior to first sex. The multivariate Wald test was used to assess significance of interaction terms. The first model includes only the interaction between age and HIV status controlled for country and year of survey. Subsequent models include the effect of place of residence, region and national ART coverage and the interactions between them and age and HIV status.

All models included the three-way interaction between year before the survey, five year age group and HIV status. Results are reported for the first year before the interview date.

Analyses were conducted using Stata version 14.1

7.1.4 Results

Pooled analysis of DHS surveys

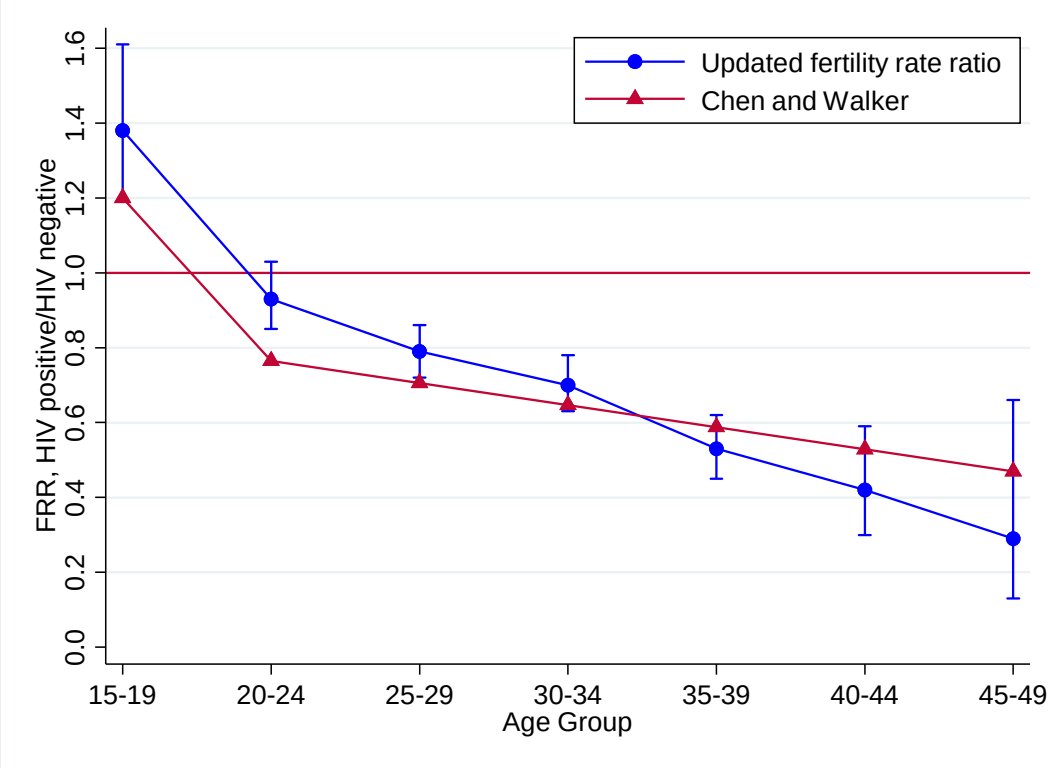
Model 1 (Table 7.2) estimated the crude fertility rate ratio (FRR) for HIV positive women relative to HIV negative women by five-year age group across all countries and surveys, adjusted only for calendar year and country. In the 15-19 year age group, fertility was 1.38 (95% CI 1.19-1.61) times higher in HIV positive women compared to HIV negative women, consistent with the fact that for younger ages many women have not yet been exposed to sex therefore are also not exposed to HIV. Thereafter, fertility of HIV positive relative to HIV negative women decreased with age from a FRR of 0.93 (95%CI 0.85-1.03) in 20 to 24 year olds to 0.29 (95CI 0.13-0.66) in 45-49 year olds (Figure 7.1, show stratum specific ratios derived from Table 7.2, Model 1 along with estimates made by Chen and Walker [41]).

Table 7.2: Adjusted fertility rate ratios for all women aged 15-49

	Model 1		Model 2	
	FRR	95 %CI	FRR	95 %CI
HIV status				
HIV negative	1		1	
HIV Positive	0.70	(0.63-0.78)	0.62	(0.53-0.73)
Effects of HIV by age				
15-19, HIV positive	1.92	(1.59-2.32)	2.39	(1.86-3.08)
20-24, HIV positive	1.32	(1.15-1.52)	1.54	(1.29-1.85)
25-29, HIV positive	1.14	(0.99-1.30)	1.31	(1.08-1.59)
30-34, HIV positive	1		1	
35-39, HIV positive	0.76	(0.63-0.92)	0.80	(0.62-1.04)
40-44, HIV positive	0.62	(0.43-0.87)	0.67	(0.41-1.09)
45-49, HIV positive	0.41	(0.18-0.95)	0.10	(0.01-0.94)
Effects of HIV by Place of residence				
Urban, HIV positive			1	
Rural, HIV positive			1.18	(1.02-1.36)
Effects of Place of residence on age and HIV status interaction				
Rural, HIV positive,15-19			0.71	(0.56-0.89)
Rural, HIV positive,20-24			0.77	(0.65-0.92)
Rural, HIV positive,25-29			0.78	(0.65-0.92)
Rural, HIV positive,30-34			1	
Rural, HIV positive,35-39			0.91	(0.71-1.16)
Rural, HIV positive,40-44			0.91	(0.57-1.44)
Rural, HIV positive,45-49			4.71	(0.60-36.8)
Effects of HIV by Region				
Southern, HIV positive			1.12	(1.05-1.20)
Eastern, HIV positive			1	
Western, HIV positive			0.99	(0.91-1.08)
Effects of HIV by ART Coverage				
<20%, HIV positive			1	
20-49%, HIV positive			1.05	(0.98-1.11)
>50%, HIV positive			1.09	(1.01-1.18)
Age Group				
15-19	0.57	(0.55-0.60)	0.50	(0.47-0.53)
20-24	1.08	(1.04-1.12)	0.98	(0.93-1.03)
25-29	1.13	(1.09-1.17)	1.11	(1.05-1.16)
30-34	1		1	
35-39	0.76	(0.73-0.80)	0.69	(0.65-0.74)
40-44	0.33	(0.31-0.36)	0.26	(0.23-0.29)
45-49	0.09	(0.07-0.10)	0.06	(0.05-0.08)
Place of residence				
Urban			1	
Rural			1.37	(1.32-1.42)
Effects of age by Place of residence				
Rural, 15-19			1.25	(1.18-1.32)
Rural, 20-24			1.18	(1.13-1.23)
Rural, 25-29			1.04	(1.00-1.09)
Rural, 30-34			1	
Rural, 35-39			1.13	(1.06-1.20)
Rural, 40-44			1.36	(1.21-1.53)
Rural, 45-49			1.58	(1.21-2.06)
Region				
Southern			0.67	(0.64-0.70)
Eastern			1	
Western			0.72	(0.68-0.77)
ART Coverage				
<20%			1	
20-49%			0.96	(0.93-1.00)
>50%			0.77	(0.73-0.82)

Results from exponential regression of fertility rates as a function of HIV status, age controlling for Country and calendar year. Also not shown is the additional interaction between years before the survey, HIV status and age group. Model 2 has an additional interaction between place of residence, age group and HIV status, region and HIV status, and ART coverage and HIV status.

Figure 7.1: Age specific fertility rate ratio comparing HIV positive to HIV negative women in the year before the survey, adjusting for country and year and the interaction between years before survey and HIV status, compared to Chen and Walker estimates.



Variation by region and place of residence

There was a significant interaction between HIV status and region (Table 2, Model 2). In Southern Africa, the relative fertility rate of HIV positive compared to HIV negative women was 1.12 (95%CI 1.05-1.20) times higher than in the Eastern region (Table 7.2, Model 2). West and Central countries were similar to East and Mid Africa (RR 0.99, 95% CI 0.91-1.08; Table 7.2, Model 2 and Figure 7.2a). There was no significant interaction between region, five-year age group, and HIV status (Wald test F=1.37, p=0.173), indicating lack of evidence of regional difference in the relative age pattern of HIV subfertility.

For all surveys except two, fertility rates are higher in rural areas than urban areas for 15-49 year old women whilst HIV prevalence is lower in rural areas compared to urban areas (Table 7.3). The statistically significant effect of place of residence on the relationship between HIV and fertility (Table 7.2, Model 2) indicates that these systematic urban/rural differences in fertility and HIV partially explains the overall lower fertility of HIV positive women. In contrast to region, place of residence did significantly affect the age-pattern of relative fertility (Wald test F=2.80, p=0.010), with a steeper gradient in urban areas than in rural areas (Figure 7.2a). Among 30-34 year olds, the relative fertility of women in rural areas was 1.18 (95%CI 1.02-1.36) times greater than

in urban areas, while among 15-19 year olds relative fertility of HIV-positive women was 0.83 (95%CI 0.69-0.995) times lower in rural areas than urban.

Figure 7.2: Adjusted Age specific fertility rate ratios comparing HIV positive women to negative women by region and Urban and Rural residence (Adjusted for Region, place of residence, the effect of five year age group on HIV status and place of residence, ART coverage, Country, Calendar year) using all women person years (a) and excluding person years prior to first sex (b)

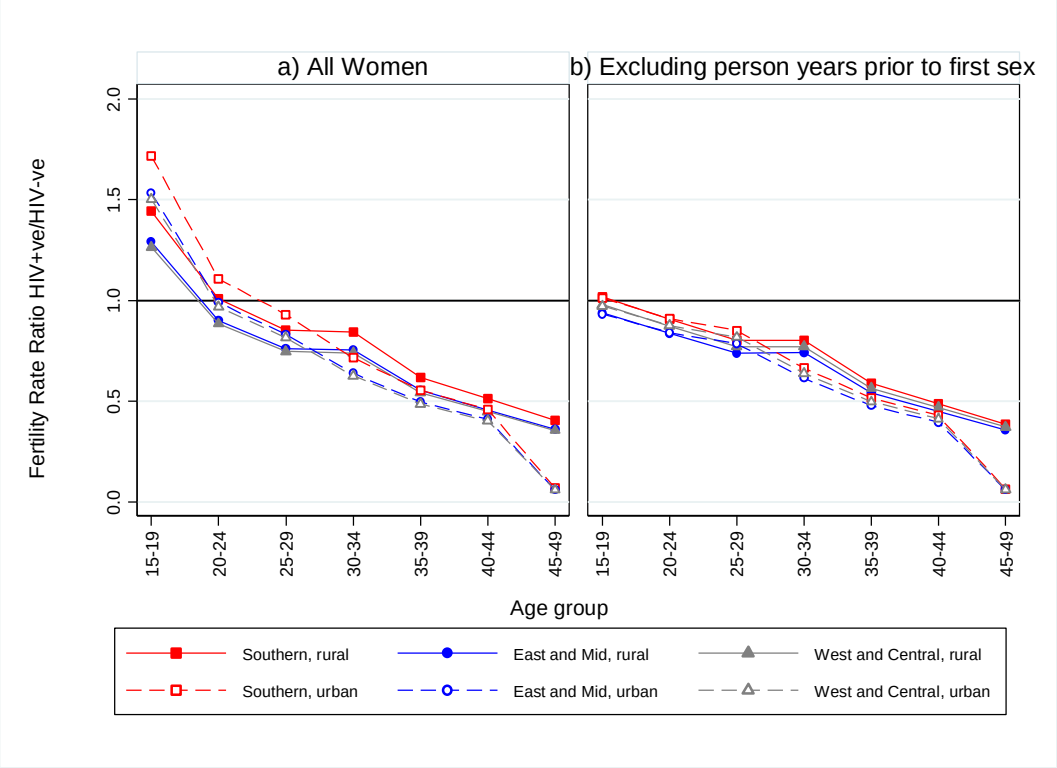
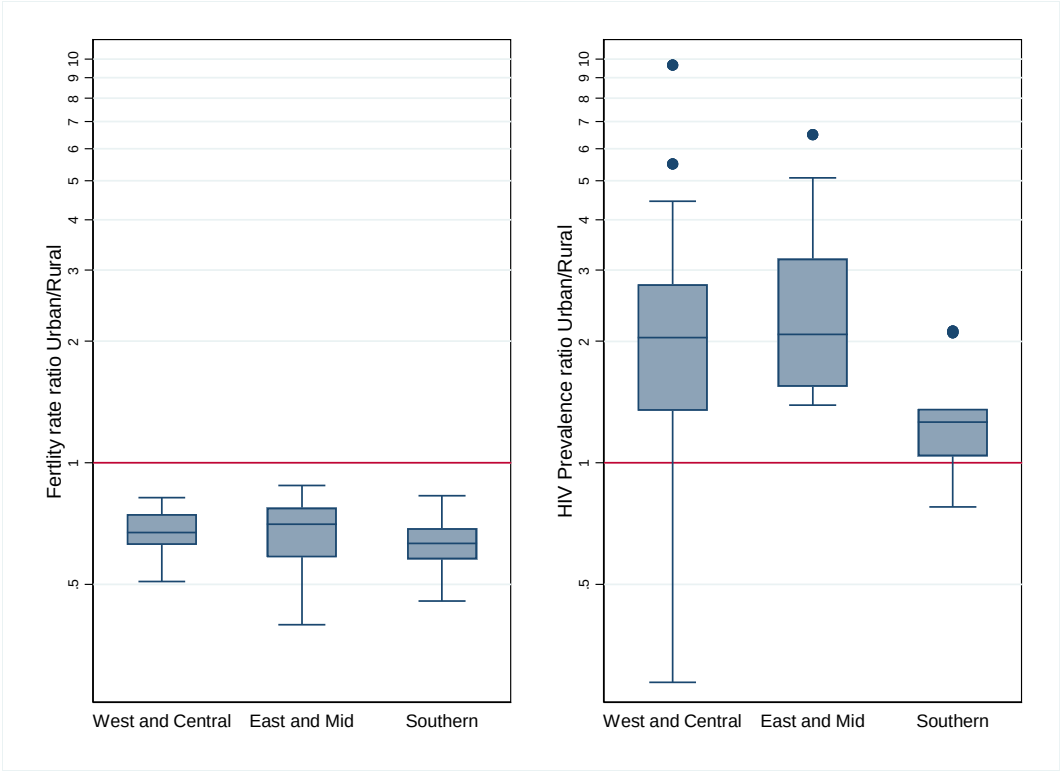


Figure 7.3: Urban, rural fertility rate ratio for HIV negative women (left) and HIV prevalence urban rural ratio (right) on the log scale. In all regions, HIV prevalence was higher while fertility was lower in urban areas than rural. This suggests that the lower fertility among HIV positive women may be partially confounded by urban/rural differences in fertility and HIV.



ART coverage and HIV subfertility

The fertility differences between HIV positive and HIV negative women slightly reduced as ART coverage increased. With ART coverage at over 50% the fertility rate ratio was 1.09 times higher (95% CI 1.01-1.18), compared to when ART coverage was below 20%. However, overall the fertility of HIV positive women remained significantly lower than that of HIV-negative women in recent surveys with high ART coverage. For example in urban Southern Africa the fertility rate ratio increased from 0.70 (95%CI 0.59-0.82) in 30-34 year olds in a time with less than 20% national ART coverage to 0.76 (95%CI 0.64-0.91) when there was 50% ART coverage (Figure 7.4, Table 7.2; Table 7.3). There was no evidence that the level of ART coverage affected the age-pattern of relative fertility (Wald test F=1.23, p=0.253)

Figure 7.4: Adjusted Age specific fertility rate ratios for Southern Africa comparing HIV positive women to negative women by region and National ART coverage (Adjusted for Region, place of residence, the effect of five year age group on HIV status and place of residence, ART coverage, Country, Calendar year)

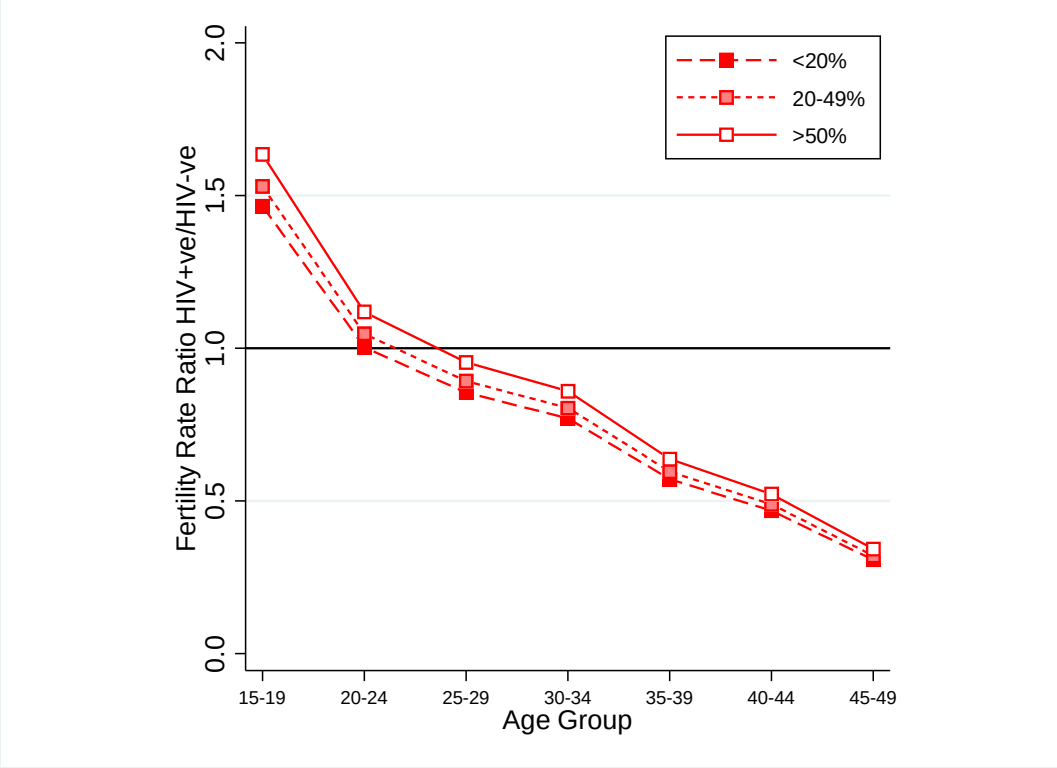


Table 7.3: Adjusted age specific fertility rate ratio comparing HIV positive to HIV negative women.

	Southern Africa			East and Mid Africa			West and Central Africa	
	<20%	20-49%	>50%	<20%	20-49%	>50%	>20%	20-49%
Urban								
15-19	1.65 (1.36- 2.01)	1.72 (1.41- 2.11)	1.84 (1.51- 2.24)	1.48 (1.22- 1.80)	1.55 (1.27- 1.89)	1.65 (1.35- 2.01)	1.48 (1.21- 1.80)	1.54 (1.26- 1.88)
20-24	1.07 (0.93- 1.22)	1.11 (0.96- 1.29)	1.19 (1.03- 1.36)	0.96 (0.84- 1.09)	1.00 (0.87- 1.15)	1.07 (0.93- 1.21)	0.96 (0.83- 1.09)	1.00 (0.86- 1.15)
25-29	0.90 (0.79- 1.02)	0.94 (0.81- 1.07)	1.00 (0.87- 1.14)	0.80 (0.71- 0.91)	0.84 (0.73- 0.96)	0.89 (0.78- 1.02)	0.80 (0.70- 0.91)	0.84 (0.73- 0.96)
30-34	0.69 (0.58- 0.81)	0.72 (0.60- 0.86)	0.76 (0.65- 0.90)	0.62 (0.53- 0.72)	0.64 (0.54- 0.76)	0.68 (0.58- 0.80)	0.61 (0.52- 0.72)	0.64 (0.54- 0.76)
35-39	0.53 (0.42- 0.67)	0.56 (0.44- 0.70)	0.59 (0.47- 0.74)	0.48 (0.38- 0.60)	0.50 (0.40- 0.63)	0.53 (0.42- 0.67)	0.48 (0.38- 0.60)	0.50 (0.39- 0.63)
40-44	0.44 (0.28- 0.69)	0.46 (0.29- 0.72)	0.49 (0.31- 0.77)	0.39 (0.25- 0.62)	0.41 (0.26- 0.65)	0.44 (0.28- 0.69)	0.39 (0.25- 0.62)	0.41 (0.26- 0.65)
45-49	0.07 (0.01- 0.61)	0.07 (0.01- 0.64)	0.07 (0.01- 0.68)	0.06 (0.01- 0.55)	0.06 (0.01- 0.57)	0.07 (0.01- 0.61)	0.06 (0.01- 0.55)	0.06 (0.01- 0.57)
Rural								
15-19	1.40 (1.19- 1.66)	1.46 (1.23- 1.74)	1.56 (1.31- 1.85)	1.26 (1.06- 1.49)	1.31 (1.11- 1.56)	1.40 (1.18- 1.66)	1.25 (1.05- 1.49)	1.31 (1.09- 1.56)
20-24	0.98 (0.88- 1.10)	1.02 (0.91- 1.15)	1.09 (0.97- 1.23)	0.88 (0.79- 0.98)	0.92 (0.82- 1.04)	0.98 (0.87- 1.10)	0.88 (0.77- 1.00)	0.92 (0.80- 1.04)
25-29	0.83 (0.75- 0.91)	0.86 (0.78- 0.96)	0.92 (0.82- 1.02)	0.74 (0.67- 0.82)	0.77 (0.70- 0.86)	0.82 (0.74- 0.92)	0.74 (0.65- 0.84)	0.77 (0.68- 0.87)
30-34	0.81 (0.73- 0.91)	0.85 (0.75- 0.96)	0.90 (0.80- 1.02)	0.73 (0.65- 0.82)	0.76 (0.68- 0.86)	0.81 (0.72- 0.92)	0.73 (0.64- 0.83)	0.76 (0.67- 0.86)
35-39	0.60 (0.50- 0.71)	0.62 (0.53- 0.74)	0.66 (0.56- 0.79)	0.54 (0.45- 0.63)	0.56 (0.47- 0.66)	0.60 (0.50- 0.71)	0.53 (0.44- 0.64)	0.56 (0.47- 0.67)
40-44	0.49 (0.35- 0.70)	0.51 (0.36- 0.73)	0.55 (0.39- 0.77)	0.44 (0.31- 0.63)	0.46 (0.32- 0.65)	0.49 (0.34- 0.70)	0.44 (0.31- 0.63)	0.46 (0.32- 0.66)
45-49	0.39 (0.17- 0.87)	0.41 (0.18- 0.91)	0.43 (0.19- 0.97)	0.35 (0.16- 0.78)	0.36 (0.16- 0.82)	0.39 (0.17- 0.87)	0.35 (0.15- 0.78)	0.36 (0.16- 0.82)

Model: hivstatusXagegrp hivstatusXagegrpXresidence coverageXhivstatus epigrpXhivstatus yearbeforeXi.hivstatusXagegrp_fiveyr year country

HIV and fertility among women who have ever had sex

Across surveys, we observed consistently higher median age at first sex among young women in urban areas compared to rural areas and in southern African countries compared to east Africa and west and central Africa (Table 7.1). This suggests that some of the variation in the relative fertility of HIV positive women at the youngest ages (Figure 7.2a) may be attributable to systematic differences in the age at sexual debut. We replicated the above models, excluding person years prior to first sex (Table 7.4). Removing the person years of women who had not become sexually active completely explained the higher fertility among HIV positive women aged under 25 compared to HIV negative women (figure 1b shows the stratum specific rate ratios derived from Table 7.4, model 2). In all regional, place of residence and ART coverage groups, the fertility of HIV positive women aged 15-19 was not significantly different to that of HIV negative women when excluding person time prior to first sex (Table 7.4, Figure 7.2b; Table 7.5). Excluding person time prior to first sex gave a relative fertility rate ratio of 0.92 (95% CI 0.76-1.11) for 15-19 year old women in urban areas, compared to 1.49 (95% CI 1.22-1.82) when analysing all women. Similarly, in rural areas the FRR for 15-19 year olds was 0.89 (95%CI 0.76-1.05) after excluding person years prior to first sex, compared to 1.23 (95%CI 1.04-1.47) for all person years. For 20-24 year olds, the relative fertility of HIV positive women fell, and in many cases was significantly lower than that of HIV-negative women ($p<0.05$) when restricted to sexually active women (Figure 7.2b; Table 7.5). The effect of age on the interaction between place of residence remained but was reduced at younger ages. After restricting to person years for women after first sex, the differences in the relative fertility for women under age 25 by place of residence and differences by region were substantially reduced (Figure 7.2b; Table 7.3 and Table 7.5). For example for 15-19 year olds the relative fertility rate ratio was the same in the urban and rural areas (interaction term 0.95, 95%CI 0.80-1.13 compared to 0.83, 95%CI 0.69-0.995 when including all women's person time).

Table 7.4: Adjusted fertility rate ratios for those women aged 15-49 excluding person years prior to first sex

	Model 1		Model 2	
	FRR	95 %CI	FRR	95 %CI
HIV status				
HIV negative	1		1	
HIV Positive	0.69	(0.62-0.77)	0.59	(0.51-0.69)
Effects of HIV by age				
15-19, HIV positive	1.33	(1.11-1.60)	1.55	(1.21-1.98)
20-24, HIV positive	1.20	(1.05-1.38)	1.36	(1.13-1.63)
25-29, HIV positive	1.12	(0.97-1.29)	1.29	(1.06-1.56)
30-34, HIV positive	1		1	
35-39, HIV positive	0.77	(0.63-0.92)	0.81	(0.62-1.04)
40-44, HIV positive	0.62	(0.44-0.88)	0.67	(0.41-1.10)
45-49, HIV positive	0.42	(0.18-0.96)	0.10	(0.01-0.96)
Effects of HIV by Place of residence				
Urban, HIV positive			1	
Rural, HIV positive			1.21	(1.05-1.40)
Effects of Place of residence on age and HIV status interaction				
Rural, HIV positive,15-19			0.78	(0.63-0.98)
Rural, HIV positive,20-24			0.82	(0.69-0.98)
Rural, HIV positive,25-29			0.78	(0.65-0.93)
Rural, HIV positive,30-34			1	
Rural, HIV positive,35-39			0.90	(0.71-1.16)
Rural, HIV positive,40-44			0.90	(0.57-1.42)
Rural, HIV positive,45-49			4.65	(0.6-36.32)
Effects of HIV by Region				
Southern, HIV positive			1.09	(1.02-1.16)
Eastern, HIV positive			1	
Western, HIV positive			1.05	(0.96-1.14)
Effects of HIV by ART Coverage				
<20%, HIV positive			1	
20-49%, HIV positive			1.04	(0.98-1.11)
>50%, HIV positive			1.13	(1.05-1.22)
Age Group				
15-19	1.20	(1.15-1.24)	1.16	(1.10-1.22)
20-24	1.22	(1.17-1.26)	1.16	(1.10-1.22)
25-29	1.15	(1.11-1.20)	1.14	(1.08-1.20)
30-34	1		1	
35-39	0.76	(0.73-0.80)	0.69	(0.64-0.74)
40-44	0.33	(0.31-0.35)	0.25	(0.23-0.28)
45-49	0.08	(0.07-0.10)	0.06	(0.04-0.07)
Place of residence				
Urban			1	
Rural			1.32	(1.27-1.37)
Effects of age by Place of residence				
Rural, 15-19			1.05	(1.00-1.10)
Rural, 20-24			1.08	(1.04-1.13)
Rural, 25-29			1.03	(0.98-1.08)
Rural, 30-34			1	
Rural, 35-39			1.13	(1.06-1.21)
Rural, 40-44			1.37	(1.22-1.53)
Rural, 45-49			1.59	(1.22-2.07)
Region				
Southern			0.74	(0.71-0.77)
Eastern			1	
Western			0.72	(0.68-0.76)
ART Coverage				
<20%			1	
20-49%			0.96	(0.92-0.99)
>50%			0.76	(0.72-0.80)

Results from exponential regression of fertility rates as a function of HIV status, age controlling for Country and calendar year. Also not shown is the additional interaction between years before the survey, HIV status and age group. Model 2 has an additional interaction between place of residence, age group and HIV status, region and HIV status, and ART coverage and HIV status.

Table 7.5: Adjusted age specific fertility rate ratio comparing HIV positive to HIV negative excluding person time prior to first sex.

Sexually	Southern Africa			East and Mid Africa			West and Central Africa	
Active	<20%	20-49%	>50%	<20%	20-49%	>50%	>20%	20-49%
Urban								
15-19	0.99 (0.82-1.20)	1.02 (0.84-1.24)	1.13 (0.93-1.37)	0.92 (0.76-1.11)	0.95 (0.78-1.15)	1.05 (0.86-1.27)	0.97 (0.80-1.17)	1.00 (0.83-1.21)
20-24	0.87 (0.76-0.99)	0.90 (0.77-1.04)	0.99 (0.86-1.13)	0.81 (0.71-0.91)	0.83 (0.72-0.96)	0.92 (0.81-1.04)	0.85 (0.74-0.97)	0.88 (0.76-1.01)
25-29	0.82 (0.72-0.93)	0.84 (0.74-0.97)	0.93 (0.82-1.06)	0.76 (0.67-0.86)	0.78 (0.68-0.89)	0.86 (0.76-0.98)	0.80 (0.70-0.91)	0.83 (0.72-0.94)
30-34	0.63 (0.54-0.75)	0.66 (0.55-0.78)	0.72 (0.61-0.85)	0.59 (0.50-0.69)	0.61 (0.51-0.72)	0.67 (0.57-0.78)	0.62 (0.53-0.73)	0.64 (0.54-0.76)
35-39	0.50 (0.40-0.62)	0.51 (0.41-0.64)	0.56 (0.45-0.70)	0.46 (0.37-0.58)	0.48 (0.38-0.60)	0.52 (0.42-0.66)	0.48 (0.39-0.61)	0.50 (0.40-0.63)
40-44	0.41 (0.26-0.64)	0.42 (0.27-0.66)	0.46 (0.30-0.73)	0.38 (0.24-0.59)	0.39 (0.25-0.62)	0.43 (0.27-0.68)	0.40 (0.25-0.63)	0.41 (0.26-0.65)
45-49	0.06 (0.01-0.58)	0.06 (0.01-0.60)	0.07 (0.01-0.66)	0.06 (0.01-0.54)	0.06 (0.01-0.56)	0.07 (0.01-0.62)	0.06 (0.01-0.57)	0.06 (0.01-0.59)
Rural								
15-19	0.96 (0.82-1.13)	0.99 (0.84-1.17)	1.10 (0.93-1.29)	0.89 (0.76-1.05)	0.92 (0.78-1.09)	1.02 (0.86-1.20)	0.94 (0.80-1.11)	0.97 (0.82-1.15)
20-24	0.86 (0.78-0.96)	0.89 (0.80-1.01)	0.99 (0.88-1.11)	0.80 (0.72-0.89)	0.83 (0.74-0.93)	0.91 (0.81-1.03)	0.85 (0.75-0.96)	0.88 (0.77-0.99)
25-29	0.77 (0.70-0.85)	0.79 (0.72-0.88)	0.88 (0.79-0.98)	0.71 (0.64-0.79)	0.74 (0.67-0.82)	0.81 (0.73-0.91)	0.75 (0.66-0.85)	0.78 (0.69-0.88)
30-34	0.77 (0.69-0.86)	0.80 (0.71-0.90)	0.88 (0.78-0.99)	0.72 (0.64-0.80)	0.74 (0.66-0.83)	0.81 (0.72-0.92)	0.75 (0.66-0.86)	0.78 (0.69-0.89)
35-39	0.55 (0.47-0.66)	0.57 (0.48-0.68)	0.63 (0.53-0.75)	0.51 (0.43-0.61)	0.53 (0.45-0.63)	0.59 (0.49-0.70)	0.54 (0.45-0.65)	0.56 (0.47-0.67)
40-44	0.46 (0.32-0.65)	0.47 (0.33-0.67)	0.52 (0.37-0.74)	0.42 (0.30-0.60)	0.44 (0.31-0.62)	0.48 (0.34-0.69)	0.45 (0.31-0.64)	0.46 (0.32-0.66)
45-49	0.37 (0.17-0.83)	0.39 (0.17-0.86)	0.42 (0.19-0.95)	0.35 (0.15-0.78)	0.36 (0.16-0.80)	0.39 (0.18-0.88)	0.36 (0.16-0.82)	0.38 (0.17-0.85)

Model: hivstatusXagegrp hivstatusXagegrpXresidence coverageXhivstatus epigrpXhivstatus yearbeforeXi.hivstatusXagegrp_fiveyr year country if sexually active

7.1.5 Discussion

This analysis has shown that overall subfertility attributable to HIV is slightly less pronounced than previously thought, and we find that it varies across settings. Consistent regional and urban/rural differences have been found, which are largely explained by variation in age at first sex. The fertility differential between HIV positive and HIV negative women appears to have narrowed in recent years as ART coverage has increased, however caution is required in attributing this directly to ART.

We corroborated patterns found in previous studies showing increasing HIV-associated subfertility with age[41, 43, 72]. Also consistent with these other studies, we find that in the youngest age group HIV positive women have higher fertility than their HIV negative counterparts as many women in this age group are not sexually active and therefore are not exposed to either HIV or pregnancy. Chen and Walker reported a strong relationship between the percentage of 15-19 year olds who are sexually active and the fertility rate ratio among this age group[41]. We extended this to show that when restricting analysis of fertility to women who had sexually debuted there was no difference in the fertility of HIV-positive and HIV-negative women, suggesting that selection for sexually active women completely explains the increased fertility of HIV positive women in this age group. Variation in age at first sex largely explained regional and place of residence differences in relative fertility. West and Central Africa overall have a much lower median age at first sex than both East and Southern Africa at around 15-16 years old compared to 18-19 years old in the Southern African countries (Table 1). The median age at sexual debut is higher in urban compared to rural areas (Table 1), and again, once person years before sexual debut are removed from the analysis there is no significant difference in relative fertility between urban and rural residency for women under 30. At older ages, HIV-associated subfertility is more pronounced in the urban areas. This could be explained by differences in sexual activity between rural and urban areas[168], influenced by differences in social norms, desired family size, knowledge of HIV status and access to services that may influence contraceptive use or abstinence from sex. In addition to systematic differences in sexual debut, regions also differed in the scale of HIV epidemics and the stage of the epidemic at the time when surveys have been collected. This analysis suggests that the relationship between HIV and fertility has attenuated slightly since the introduction of ART, but overall fertility remains significantly lower among HIV positive women than HIV negative women. These reductions are somewhat less dramatic than predicted by current estimates of PMTCT need published by UNAIDS using the Spectrum model, which assumes that women on ART for more than six months have the same fertility as HIV negative women of the same age. For example, under this assumption a 50% increase in ART coverage would attenuate the overall FRR of HIV

positive women from 0.7 times that of HIV negative women to 0.85. This is an increase of 1.21 times, somewhat greater than the 1.11 times increase that we estimated for survey periods with ART coverage >50% compared to those <20%. There was no evidence that the effect of ART coverage on HIV subfertility varied by age. Since the differences in HIV-associated subfertility by national ART coverage are small it is possible that we did not have the power to detect any further differences by age. National ART coverage is an ecological variable. It does not measure individual exposure to treatment, and hence we are cautious about attributing causality, for example countries with better roll out of ART may also have other things in common such as good health systems, with better provision of family planning services.

We find substantially less HIV-associated subfertility compared to Chen and Walker[41] in women aged below 35 and more HIV-associated subfertility at older ages. A number of factors can explain these differences. Chen and Walker had fewer surveys than were used in this analysis and did not adjust for place of residence or region, which we showed confounds the relationship between HIV and fertility because of systematically lower fertility in urban areas which also have higher HIV prevalence. The surveys used in the Chen and Walker analysis were predominantly from East, West and Central Africa where HIV-associated subfertility is more pronounced than in Southern Africa. We looked at data for the three years prior to the survey when constructing our models as did Chen and Walker, however we only report results from the first year before the survey due to evidence that using data beyond one year exaggerated the HIV-associated subfertility in younger women (see document, Supplemental Digital Content 1). We also find substantially lower subfertility using the DHS data than we did using data from the demographic surveillance sites in Eastern and Southern Africa[43]. Much of these DSS data are from rural populations around Lake Victoria in East Africa that experienced early and severe HIV epidemics, all factors that we expect to be associated with greater subfertility based on this multi-country analysis.

There are a number of recommendations arising from these analyses for improving estimates and predictions of need for PMTCT services. We found evidence for variation across regions, with less HIV associated sub fertility in Southern Africa, but no evidence of differences by age pattern. This suggests that scaling the estimated age pattern of relative fertility of HIV-positive women to reflect overall prevalence among pregnant women observed through routine HIV testing may be a reasonable approach to calibrating and reflecting variation across countries and settings. There are significant differences in the pattern of relative fertility by urban/rural residency, which appeared to be largely explained by older sexual debut in urban areas. This should be accounted for

in planning and allocating resources for PMTCT at the subnational level and evaluating local progress towards MTCT elimination. Finally, the relationship between HIV and fertility has attenuated slightly since ART has been introduced, supporting the current practice to account for ART coverage when predicting fertility of HIV positive women and need for PMTCT. However, overall the reductions are somewhat less dramatic than predicted by current Spectrum assumptions and fertility remains lower among HIV positive women than HIV negative women at older ages. Overall, we have characterised the fertility patterns of HIV positive women over time and across regions in sub-Saharan Africa as ART scaled up from the mid 2000s through 2015. However, they could continue to evolve rapidly as HIV treatment and prevention programmes enter a new era. Improving timely data about the fertility patterns of HIV positive women and deeper understanding of the mechanisms underlying changes will be important to plan and evaluate PMTCT policy and monitor epidemic trends.

7.1.6 Acknowledgements

M.M. and J.W.E. conceived the analysis, M.M. did the analysis. J.W.E. reviewed the analysis and supported the development of the manuscript. M.M. and J.W.E. wrote the manuscript. BZ commented on drafts and supported the development of the manuscript.

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7.2 Possible biases in the analysis of HIV and fertility (Appendix one of PAPER E expanded)

7.2.1 Introduction

Analysis of population level effects of HIV on fertility has relied on two types of studies, first retrospective data from demographic and health surveys (DHS)[1] with HIV testing[2], second data from community based HIV cohort studies[3, 4]. Demographic and Health Surveys have the advantage that they are large nationally representative surveys across sub Saharan Africa whereas community based cohort studies are usually not nationally representative and do not cover much of sub-Saharan Africa. However, community based HIV cohort studies could be seen as the gold standard as they prospectively test participants for HIV and record births and other demographic characteristics. This means that HIV status of the mother at the birth of the child is known, in contrast to using retrospective data, which requires us to assume that the HIV status of the women at time of interview is the same as her HIV status in the time prior to the survey. Retrospective surveys are also subject to survivorship bias, since not all women of childbearing age in the sample households survive to time of interview. Women who die prematurely are likely to have experienced a serious illness, such as AIDS, and during the time of serious illness they are likely to have low fertility. Both data sources can be affected by underreporting of young infant deaths, which are more likely to occur to HIV positive women, due to recall bias [5]. However if we use only the most recent years before the surveys it is possible that DHS data are less affected by this bias as they directly ask the woman herself about her births as opposed to community based cohort studies which often use proxy respondents to report experiences of family members.

7.2.2 Methods

Identifying biases in retrospective data used to analyse HIV subfertility

We started the analysis reported in the manuscript using the standard cut off of three years prior to the survey. This standard is used by DHS in reporting general fertility rates[6], and was adopted by previous studies of HIV and fertility[2]. This cut off for fertility analysis is chosen to balance the desire for maximizing the retrospective person years of observation while minimizing biases from using retrospective data. Table A1 summarises the potential biases that are known to occur in using retrospective birth reports to analyse fertility, many of which vary with age.

Using the same methods as outlined in the main paper we used exponential regression to estimate the interaction between single years before the survey and its effect on the age pattern of HIV subfertility. The model included HIV status and five year age group, single years before the survey and adjusted for country and survey year.

Using DHS data to model the possible extent of bias in DSS data due to under-reporting of early infant deaths.

Whereas all the bias categories listed in Table 7.6 can affect retrospective fertility data collected in DHS, only the last one (under-reporting of births leading to infant deaths) can occur in prospectively collected data, such as are obtained in demographic surveillance systems (DSS). This kind of under-reporting will occur if the birth and the subsequent infant death occur within the same inter-survey interval, and may be more severe if proxy reporting is allowed, rather than obtaining reports from the mother herself. Early infant deaths will disproportionality affect HIV positive women due to high mortality of children who are vertically infected with HIV[13], and this concentration of infant deaths would be more pronounced in the years prior to antiretroviral treatment given for the prevention of mother to child transmission (PMTCT).

We ran our analysis using a similar model to Marston et al[43] allowing for interaction between HIV status and five-year age group and adjusting for place of residence, country and calendar year. We used data for only one year before the DHS survey simulating a DSS survey with an inter survey interval of one year, with no key informant reporting events during the inter-survey interval. We ran the model to simulate a total lack of reporting of births resulting in neonatal deaths and then more extreme scenarios, excluding any birth than resulted in a death within half a year and within one year.

Table 7.6: Biases affecting the use of retrospective data to measure HIV-associated subfertility

Nature of bias	Direction of bias	Age groups affected
Survivorship bias: women who have been infected for longer are more likely to have died before being interviewed. They are also more likely to have much lower fertility due to illness, but are not included in the analysis	Fertility of HIV positive women is over-estimated, so HIV-associated sub-fertility is understated	More in older women as they are more likely to have been infected for longer and are thus at higher risk of dying
Age eligibility: survey eligibility is limited to ages of 15-49, therefore women aged 47+ in the three years prior to the survey may no longer be eligible to participate on the survey date. The composition of the oldest age group skews to the younger ages, where fertility is higher.	Fertility of HIV positive women is over-estimated, so HIV-associated sub-fertility is understated	Only the 45-49 year old age group is affected
HIV status miss-classification (i): women who sero-convert in the analysis interval, and who have a birth before sero-conversion will be wrongly classified as contributing births (and person-years) to HIV positive fertility	Fertility of HIV positive women is over-estimated, so HIV-associated sub-fertility is understated	This bias would be greatest at ages in which HIV incidence is highest, generally ages 20-34.
HIV status miss-classification (ii): women who sero-convert in the analysis interval, and who have a birth after sero-conversion will have too many person-years (but not too few births) classified as contributing to HIV positive fertility	Fertility of HIV positive women is under-estimated, so HIV-associated sub-fertility is exaggerated	This bias will be greatest if sero-conversion occurs close to the age of sexual debut, or formation of first regular sexual union, when births are more likely to occur after sero-conversion, so the age group most strongly affected will be 15-24

Nature of bias	Direction of bias	Age groups affected
HIV status miss-classification (iii): Women who sero-convert in the analysis interval, and who have no birth will have too many person-years classified as contributing to HIV positive fertility.	Fertility of HIV positive women is under-estimated, so HIV-associated sub-fertility is exaggerated	This bias would be greatest at ages in which HIV incidence is highest, generally ages 20-34.
Under-reporting of births of infants who die: Births that result in early neonatal and infant deaths tend to be underreported especially those which occurred further back in time. Since children of HIV positive women have higher mortality, especially before PMTCT services were widespread, this kind of under-reporting will be more frequent in HIV positive women	Fertility of HIV positive women is under-estimated, so HIV-associated sub-fertility is exaggerated	Affects all age groups, but likely to diminish in importance over time, as roll-out of PMTCT services improves mortality of children of HIV positive mothers

7.2.3 Results

Analysis of biases using retrospective data to analyse HIV subfertility

First, we investigated possible biases in using the retrospective data for three years prior to the survey. We fitted a simple model with HIV status, age group and the interaction between the two, adjusted for country and calendar year as shown in section 7.1 (Table 7.2, Model 1). We introduced the variable representing the first, second and third year before the survey and tested it's interaction with HIV status, this showed a significant decrease in the fertility rate ratio comparing HIV positive women to HIV negative women of 0.91 (0.85-0.98) and 0.94 (0.87-1.01) times in the second and third year compared to the first year respectively (Wald test for interaction p=0.073).

We also looked at how age affected the interaction between years before the survey and HIV status (Table 7.7, model 1). We found that the interaction between HIV status and years before the survey appeared to work in different directions. For women under 30 years HIV-associated subfertility was more pronounced if we used data further back than one year compared to the first year. The fertility rate ratio comparing positives to negatives decreasing by 0.86 (95%CI 0.79-0.94) and 0.89 (95%CI 0.81-0.97) in the 2nd and 3rd year respectively (Table 7.7, Model 2). For those aged 30 years and over, HIV-associated subfertility was less pronounced as a result of using data going back further than one year, although this was not significant (Table 7.7, Model 3). Table 7.8 and Figure 7.5 show the resultant adjusted age specific rate ratios by years used prior to the survey.

Analysis of possible biases in DSS due to under reporting of births ending in early infant deaths

Births that occurred in the year before the surveys ended in death for a higher percentage of HIV positive women compared to HIV negative women. Excluding deaths occurring to children born in the interval before the age of six months, the effects were largest in the women aged 25-29 years, with 10.2% of births excluded in HIV positive women compared to 3.3% in HIV negative women (Table 7.9). The exclusion of births that ended in neonatal death gave an increase in subfertility of 5.5% in the youngest age group and was lowest at 1.1% in the 20-24 year old age group. The extreme of excluding any birth that ended in a death in the interval gave an 11% increase in subfertility in the 15-19 year olds, 8.2% in the 30-34 year olds and between 3-6% in the remaining groups (Table 7.9).

Table 7.7: Adjusted fertility rate ratios for all women, women under 30 and women over 30 to demonstrate the significant decrease in HIV subfertility in women under 30 when looking beyond one year prior to the survey.

	All women			All women			Women <30			Women 30+		
	FRR	95 %CI	Wald	FRR	95 %CI	Wald	FRR	95 %CI	Wald	FRR	95 %CI	Wald
HIV status												
HIV negative				1			1			1		
HIV Positive	0.74(0.68-0.79)	*>0.001*		0.70(0.63-0.78)	*>0.001*		0.77(0.71-0.82)	*>0.001*		0.73(0.67-0.80)	*>0.001*	
Age group												
15-19	0.59(0.57-0.60)			0.57(0.55-0.59)			0.51(0.50-0.52)					
20-24	1.12(1.10-1.14)			1.08(1.04-1.12)			0.97(0.95-0.99)					
25-29	1.15(1.13-1.17)			1.13(1.09-1.17)			1.00	*>0.001*				
30-34	1			1						1		
35-39	0.76(0.75-0.78)			0.77(0.73-0.80)						0.76(0.75-0.78)		
40-44	0.35(0.34-0.36)			0.33(0.31-0.36)						0.35(0.34-0.36)		
45-49	0.11(0.10-0.12)	*>0.001*		0.09(0.07-0.10)	*>0.001*					0.11(0.10-0.12)	*>0.001*	
Effects of HIV by age												
15-19, HIV positive	1.83(1.66-2.03)			1.97(1.64-2.37)			1.79(1.62-1.97)					
20-24, HIV positive	1.22(1.12-1.32)			1.33(1.16-1.53)			1.18(1.09-1.27)					
25-29, HIV positive	1.03(0.95-1.11)			1.13(0.98-1.29)			1	*>0.001*				
30-34, HIV positive	1			1						1		
35-39, HIV positive	0.81(0.73-0.91)			0.75(0.62-0.91)						0.81(0.73-0.91)		
40-44, HIV positive	0.65(0.53-0.78)			0.60(0.43-0.85)						0.65(0.53-0.78)		
45-49, HIV positive	0.41(0.24-0.69)	*>0.001*		0.41(0.18-0.94)	*>0.001*					0.41(0.25-0.69)	*>0.001*	
Year before survey												
1st	1			1			1			1		
2nd	0.94(0.92-0.96)			0.89(0.86-0.94)			0.96(0.94-0.98)			0.90(0.87-0.93)		
3rd	0.95(0.94-0.97)	*>0.001*		0.94(0.90-0.98)	*>0.001*		0.96(0.94-0.98)	*>0.001*		0.95(0.91-0.98)	*>0.001*	

Effects of HIV by years before survey								
2nd year, HIV positive	0.92(0.86-0.99)		0.96(0.81-1.15)		0.87(0.79-0.95)		1.03(0.91-1.18)	
3rd year, HIV positive	0.94(0.88-1.01)	*0.073*	1.05(0.90-1.21)	*0.639*	0.89(0.82-0.97)	*0.003*	1.04(0.93-1.17)	*0.764*
Effects of yearbefore on age and HIV status interaction								
2nd year, HIV positive, 15-19			0.94(0.71-1.24)					
2nd year, HIV positive, 20-24			0.90(0.72-1.13)					
2nd year, HIV positive, 25-29			0.89(0.71-1.11)					
2nd year, HIV positive, 30-34			1					
2nd year, HIV positive, 35-39			1.29(0.96-1.73)					
2nd year, HIV positive, 40-44			1.03(0.63-1.69)					
2nd year, HIV positive, 45-49			1.66(0.54-5.06)					
3rd year, HIV positive, 15-19			0.86(0.67-1.11)					
3rd year, HIV positive, 20-24			0.85(0.70-1.03)					
3rd year, HIV positive, 25-29			0.85(0.70-1.05)					
3rd year, HIV positive,30-34			1					
3rd year, HIV positive, 35-39			0.99(0.76-1.29)					
3rd year, HIV positive, 40-44			1.20(0.76-1.90)					
3rd year, HIV positive, 45-49			0.34(0.06-2.07)	*0.146*				

Note: The country and calendar year variables are not shown

Table 7.8: Fertility rate ratios by five year age group and year before the survey from exponential regression model using all women in Table 7.7

Age group	Year before the survey					
	1st year		2nd year		3rd year	
	FRR	95% CI	FRR	95% CI	FRR	95% CI
15-19	1.38	(1.19-1.61)	1.25	(1.08-1.44)	1.25	(1.09-1.43)
20-24	0.93	(0.85-1.03)	0.81	(0.73-0.89)	0.83	(0.75-0.91)
25-29	0.79	(0.72-0.86)	0.68	(0.61-0.74)	0.71	(0.63-0.79)
30-34	0.70	(0.63-0.78)	0.68	(0.59-0.77)	0.73	(0.66-0.82)
35-39	0.53	(0.45-0.62)	0.65	(0.55-0.77)	0.55	(0.47-0.64)
40-44	0.42	(0.30-0.59)	0.42	(0.30-0.58)	0.53	(0.40-0.71)
45-49	0.29	(0.13-0.66)	0.46	(0.22-0.97)	0.10	(0.02-0.52)

Figure 7.5: Fertility rate ratios by five year age group and year before the survey from exponential regression model using all women in Table 7.7

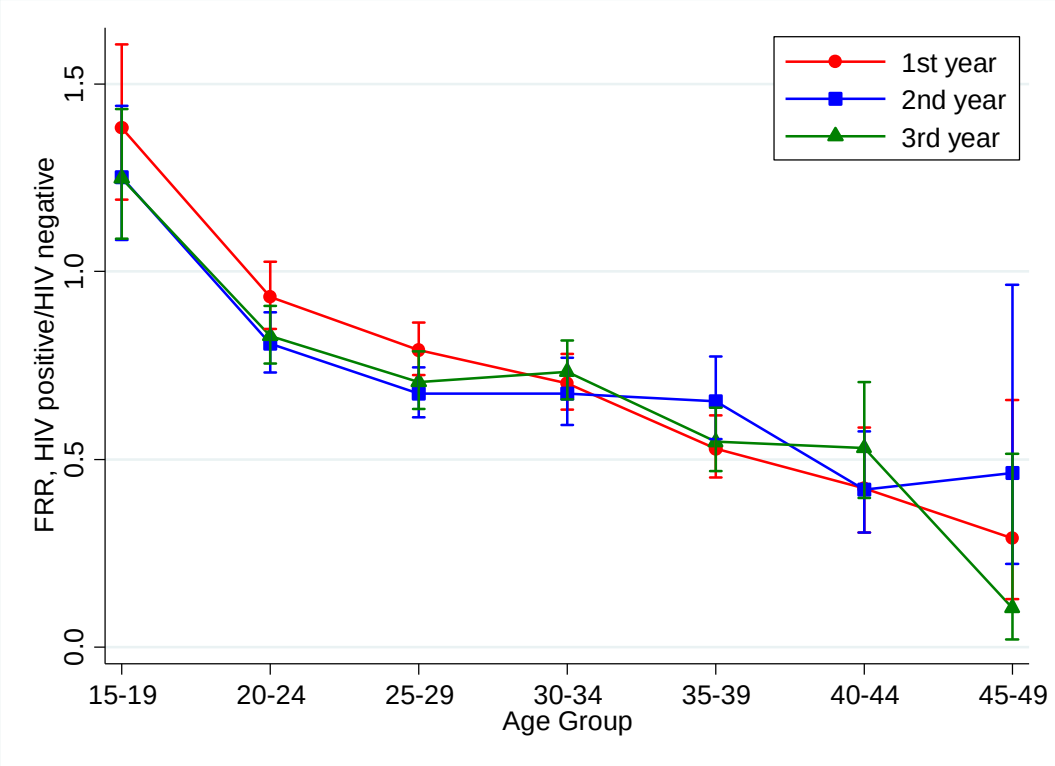

Table 7.9: Change in Age Specific fertility rate ratio if and birth ending in neonatal, less than six or twelve months in the previous year to the survey was missed.

Womens age	No exclusion		Neonatal deaths					Deaths before six months					Deaths before one year					
	FRR	95% CI	Births excluded (%) HIV -ve	Births excluded (%) HIV +ve	FRR	95% CI	Decrease in FRR (%)	Births excluded (%) HIV -ve	Births excluded (%) HIV +ve	FRR	95% CI	decrease in FRR (%)	Births excluded (%) HIV -ve	Births excluded (%) HIV +ve	FRR	95% CI	Decrease in FRR (%)
15-19	1.41	(1.22-1.64)	4.1	9.2	1.33	(1.14-1.56)	5.5	5.1	12.8	1.30	(1.11-1.52)	8.2	5.1	12.8	1.26	(1.07-1.48)	11.0
20-24	0.98	(0.89-1.08)	3.0	3.9	0.97	(0.87-1.07)	1.1	3.8	6.9	0.94	(0.85-1.05)	3.2	3.8	6.9	0.94	(0.85-1.04)	3.8
25-29	0.84	(0.77-0.92)	2.6	6.0	0.81	(0.74-0.89)	3.6	3.3	10.2	0.78	(0.71-0.85)	7.4	3.3	10.2	0.77	(0.70-0.85)	8.2
30-34	0.75	(0.68-0.84)	3.1	4.2	0.74	(0.67-0.83)	1.4	4.1	8.2	0.72	(0.64-0.80)	4.5	4.1	8.2	0.71	(0.64-0.79)	5.8
35-39	0.57	(0.49-0.67)	4.0	6.3	0.56	(0.47-0.65)	2.6	4.7	9.0	0.54	(0.46-0.64)	4.9	4.7	9.0	0.54	(0.46-0.64)	4.8
40-44	0.45	(0.33-0.62)	4.2	6.6	0.44	(0.31-0.62)	2.7	5.6	6.6	0.44	(0.32-0.62)	1.5	5.6	6.6	0.43	(0.30-0.61)	4.9
45-49	0.30	(0.13-0.68)	11.3	0.0	0.34	(0.15-0.77)	-12.4	14.1	0.0	0.35	(0.15-0.79)	-16.0	14.1	0.0	0.35	(0.15-0.79)	-15.8

Model: hivstatusXagegrp_fiveyr resid year country if yearbefore==1

7.2.4 Discussion

We found evidence of biases when using retrospective data for analysis of subfertility. Using data beyond one year increased the subfertility in younger women and slightly increased it for older women although this was not significant. Older women are likely to have been infected with HIV for longer than younger women – this means that survivorship bias would be greater for older women, as with longer duration of infection they are likely to be less fertile [4] and less likely to survive to be interviewed. For younger women the assumption that they have been HIV positive for several years before the survey will be less true than for older women who are more likely to have sero converted long ago. Therefore the assumption of constant retrospective HIV status at younger ages would be expected to cause a larger misclassification of person years by HIV status: more negative person years will be wrongly classified as HIV positive in younger women, which would tend to decrease the apparent extent of their subfertility. However, we found the overall bias in the measurement of subfertility in younger women related to increasing the number of years of retrospective data used in the analysis went in the opposite direction. One possible reason for this is that the HIV negative time for younger women immediately prior to sero conversion is dominated by time prior to entry into first sexual union, or indeed prior to sexual debut, when women are not yet exposed to risk of conception or HIV acquisition. This coupled with all the person years when a women does not have a birth during a sero conversion interval being assigned to HIV positive women, would tend to exaggerate the extent of subfertility in the HIV positive group mirroring our observations.

Researchers should be aware of the many possible biases when analysing population based data on HIV and fertility, and try to minimise them. The biases found in this study show that biases in estimates of HIV sub fertility are strongly influenced by the age of the woman, and can be minimised by curtailing the analysis to the year immediately preceding the survey.

We also used the DHS data to investigate the impact of missing neonatal and young infant deaths in when using Demographic Surveillance to estimate the extent of HIV-associated subfertility. Our modelling showed that such omissions cannot explain the differences in the estimates obtained from the present analysis of the pooled DHS data to the estimates obtained in the analysis of community based cohort studies by Marston et al [43]

8 PAPER F: Relative patterns of sexual activity and fertility among HIV positive and negative women – evidence from 46 DHS

For objective 7 of the PhD: To identify how behaviour contributes to HIV subfertility in order to gain a better understanding of the contribution it makes to differences in fertility by HIV status; an analysis was conducted using data from demographic and health surveys and has been submitted to PLoS ONE:

8.1 Introduction to paper

Both papers C and E found at the population level only a slight narrowing of the differences between HIV positive and HIV negative women in the era of ART. This along with a systematic review[73] which concluded that that evidence indicated that fertility increases after the first year on ART but remains lower than in HIV negative women of the same age, stimulated a call for more research to try to understand the mechanisms behind the differences in fertility by HIV status. This is necessary in order to better estimate and project the number of pregnant women in need of PMTCT services and to estimate the incidence and prevalence of paediatric HIV[48]. Paper E provided evidence of regional and urban and rural variation in HIV subfertility. It also showed that these differences at younger ages could be largely be explained by varying age at sexual debut, demonstrating that at young ages sexual behaviour has an impact on fertility differentials by HIV status. In order to shed more light on the mechanisms for the differences in fertility by HIV status it is important to assess how much of the HIV subfertility seen in populations with generalised HIV epidemics could be directly due to sexual behaviour.

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

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SECTION A – Student Details

Student	Camilla Marston
Principal Supervisor	Basia Zaba
Thesis Title	Demographic Determinants of Paediatric HIV in Generalised HIV epidemics

If the Research Paper has previously been published please complete Section B, If not please complete Section C

SECTION B

Where was the work published?			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	PLoS One
Please list the paper's authors in the intended authorship order:	Milly Marston, Jeffrey W. Eaton, Basia Zaba.
Stage of publication	**Submitted**

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 conceived the analysis, prepared the data and carried out the analysis, co-authors commented on analysis and edited drafts.

Student Signature: [redacted] **Date:** 27/03/18

Supervisor Signature: [redacted] **Date:** 27.03.2018

Relative patterns of sexual activity and fertility among HIV positive and negative women – evidence from 46 DHS

Milly MARSTON [1],Basia ZABA[1], Jeffrey W EATON[2].

1 London School of Hygiene and Tropical Medicine, London

2 Department of Infectious Disease Epidemiology, Imperial College, London

Corresponding Author: Milly Marston, London School of Hygiene and Tropical Medicine, London, UK, WC1E 7HT. Tel: +44 (0)207 299 4665

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Fertility; HIV; Demographic and Health surveys; HIV Infections/prevention & control; Antiretroviral Therapy, Highly Active; HIV Infections/therapy; Sexual behaviour; Reproductive Behaviour

8.2 Abstract

Objectives

Projections of fertility of HIV positive women as ART scales up are needed to plan prevention of mother-to-child transmission (PMTCT) services. We describe differences in exposure to pregnancy between HIV positive and HIV negative women by age, region and national ART coverage to evaluate the extent to which behavioural differences explain lower fertility among HIV positive women and assess whether exposure to pregnancy has changed with antiretroviral treatment (ART) scale-up.

Methods

We analysed 46 nationally representative household surveys in sub-Saharan Africa conducted between 2003 and 2015 to estimate risk of exposure to recent sex and pregnancy of HIV positive and HIV negative women by age using a log Poisson model. We tested for regional and urban/rural differences and associations with national ART Coverage. We estimated an adjusted fertility rate ratio of HIV positive to HIV negative women adjusting for differences in exposure to pregnancy.

Results

Exposure to pregnancy differs significantly between HIV positive and negative women by age, modified by region. Younger HIV positive women have a higher exposure to pregnancy that HIV negative women and the opposite is true at older ages. The switch occurs at 25-29 for rural women and 30-34 for urban women. There was no evidence that exposure to pregnancy of HIV positive women have changed as national ART coverage increased. The inferred rate of fecundity of HIV positive women when adjusted for differences in exposure to pregnancy were lower than unadjusted fertility rate ratios in women aged 20-29 and 20-24 in urban and rural areas respectively varying between 0.6 and 0.9 over regions.

Discussion

The direct effects of HIV on fertility are broadly similar across ages, while the dramatic age gradient that has frequently been observed is largely attributable to variation in relative sexual exposure by age.

8.3 Background

Numerous studies have demonstrated that the relationship between HIV and fertility varies with age. Among the youngest women aged 15-19 years, fertility is higher among HIV positive women, while above age 25 the fertility of HIV positive women becomes increasingly lower than that of their HIV negative counterparts, termed 'HIV associated subfertility'. Population based studies have also identified differences in HIV subfertility by region[43, 45], urban and rural area[45] and speculated whether changes are associated with increased antiretroviral treatment (ART) roll out [45, 79, 169].

Accurate short-term projections for the number of HIV positive women are important for HIV surveillance and policy, for example to plan local provision of prevention of mother-to-child transmission (PMTCT) services and interpret HIV surveillance data for pregnant women to infer wider epidemic trends. Beyond documenting the empirical relationships between HIV and fertility, such projections require characterization of the mechanisms that explain the complex relationship between HIV and fertility in order to predict how this will change as the epidemic context evolves, in particular with the rapid scale-up of ART and changes in eligibility policy. The Spectrum model supported by UNAIDS currently assumes that the fertility of women on ART for longer than six months is the same fertility as HIV-negative women of the same age. A number of cohort studies have reported high rates of conception among women on long-term treatment[121, 152]. However, direct comparisons with fertility of HIV-negative women in the same population are not readily available. A recent systematic review concluded that evidence was scant, but suggested lower fertility in HIV positive women on ART [73]. Marston et al [45] estimated that with national ART coverage at high levels, the gap between fertility of HIV positive and HIV negative women has narrowed, but that fertility of HIV positive women remained lower than would be expected if HIV positive women on ART had the same fertility as HIV negative women.

A variety of biological and socio-behavioural explanations have been hypothesised to explain HIV subfertility, and, as ART roll out increases, both causes of HIV subfertility could be affected. The physiological and immunological fertility reducing effects of HIV could be attenuated if ART lessens the severity of women's HIV disease. Reduced widowhood and divorce together with increased sexual activity due to improved health could increase exposure to pregnancy for HIV positive women compared to the pre-ART era.

It is well documented that at younger ages, age at sexual debt largely explains the relatively higher fertility in HIV positive women compared to their HIV negative

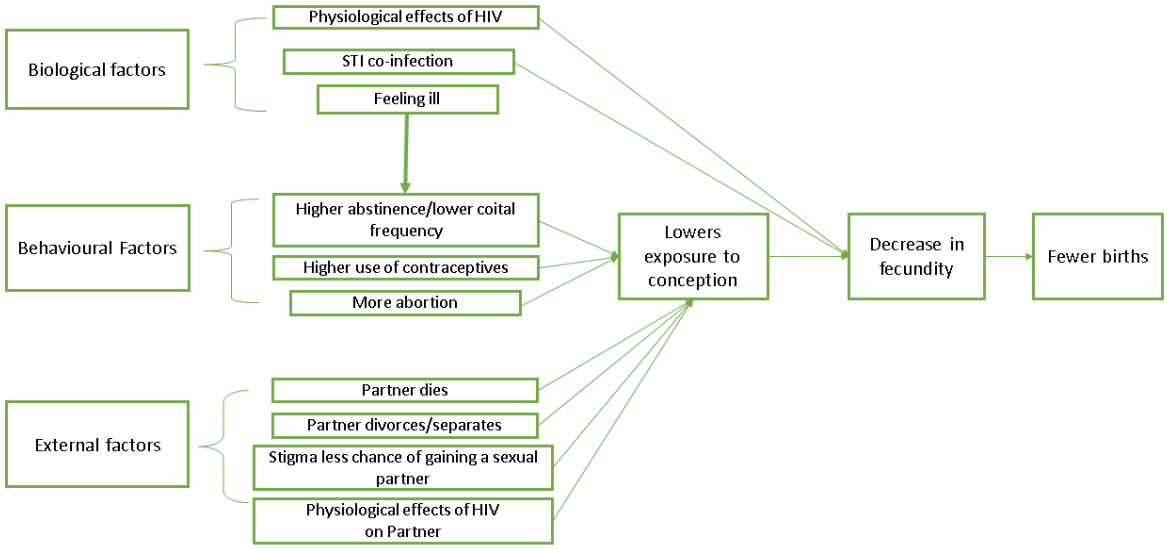
counterparts[41, 43, 72, 144]. However, at older ages the contribution of differences in sexual behaviour to lower fertility in HIV positive women has been less thoroughly analysed. Sexual intercourse has been reported as less frequent in HIV positive women compared to HIV negative women [107, 108] but also modern contraceptive use is generally lower[107, 170]. The proximate determinants of fertility through which behavioural factors must act are (i) sexual intercourse and (ii) non-use of contraception. Therefore, quantifying the differences between HIV positive and HIV negative women's exposure to sex without the use of contraceptives and a comparison of the ensuing pregnancy rates sheds light on the contribution of sexual behaviour to HIV subfertility, and may explain some regional differences in HIV subfertility and predict how this could change in the era of ART.

We use 46 nationally representative surveys from sub-Saharan Africa to estimate levels and trends of exposure to sex and to pregnancy outcome comparing HIV positive women to HIV negative women by region, place of residence and national ART coverage to assess how much of the HIV subfertility seen in these populations could be directly due to sexual behaviour.

8.4 Methods

Figure 8.1 describes a simple conceptual framework for the possible effects of HIV on fertility. In this analysis, we aim to estimate the extent to which lower fertility is attributable to lower exposure to pregnancy due to behaviour modification associated with HIV, compared to biological factors decreasing fecundity which could potentially be directly ameliorated by successful ART. The ideal study to evaluate this would be to analyse individual-level conception rates during periods of exposure to pregnancy for HIV positive and HIV negative women. This is not possible in survey data because sexual activity and contraceptive use are only measured at the time of the survey, not over the duration of exposure to pregnancy.

Figure 8.1: A simple Conceptual framework for pathways to lower fertility in HIV positive women



Instead, to assess the contribution of differences in sexual behaviour (coital frequency and contraceptive use) to lower fertility in HIV positive women, we evaluate the relationship between age-specific exposure to recent sex (defined as sex in the last four weeks) and age-specific fertility rates of HIV positive women compared to HIV negative women. We work with the hypothesis that at the population level, exposure to recent sex is a measure of direct behavioural actions that lead to the possibility of a pregnancy. Therefore, if behavioural differences were the only factor determining differences in fertility, we would expect the relative rate of recent sex by HIV status to be the same as the relative fertility rates. On the other hand, if biological effects of HIV completely explained differences in fertility, we expect to see no difference in recent sexual activity between HIV positive and HIV negative women. Since contraceptive use may differ between HIV positive and HIV negative women we also study exposure to recent sex without contraceptive use. We make the following assumptions:

- The relationship between the binary measure of sex in the last four weeks (yes/no) and an integer measure of coital frequency is the same for HIV positive and HIV negative women at the population level
- For an individual current contraceptive use is equivalent to contraceptive use in the last four weeks
- Contraceptive use efficacy is equal for HIV positive and HIV negative women.

We test our assumptions about recent sex as a proxy for coital frequency by repeating the analyses outlined below restricting it to married women, as marital status would likely

affect the relationship between recent sex and coital frequency, so if marital patterns are different by HIV status, this relationship may also differ.

Data

We analysed data from 46 Demographic and Health surveys (DHS) and AIDS indicator surveys (AIS) from 26 countries in sub-Saharan Africa that included both HIV testing data and questions about recent sexual intercourse and current contraceptive use (Table 8.1). Four surveys with HIV testing (Tanzania 2008 and 2012, Cote D'Ivoire 2005 and Uganda 2011) were excluded as they did not include questions on current contraceptive use.

Table 8.1: Summary of Demographic and Health surveys used

Region	Survey	Year	n	HIV prevalence Women 15-49 (95% CI)*	Estimated female adults 15+ ART
Southern Africa					
	Lesotho	2004	3030	26.3 (24.5-28.2)	1 (1-1)
	Lesotho	2009	3778	26.7 (25.0-28.6)	27 (25-29)
	Lesotho	2014	3175	29.7 (27.7-31.8)	40 (37-43)
	Namibia	2013	4051	16.9 (15.4-18.4)	62 (50-70)
	Swaziland	2006-07	4424	31.1 (29.4-32.9)	10 (8-11)
	Zimbabwe	2005-06	6947	21.1 (19.7-22.6)	2 (2-3)
	Zimbabwe	2010-11	7313	17.7 (16.6-18.8)	31 (24-38)
	Zimbabwe	2015	8667	16.7 (15.6-17.8)	72 (57-84)
East and Mid Africa					
	Burundi	2010	4533	1.7 (1.4-2.1)	33 (26-40)
	Kenya	2003	3151	8.7 (7.6-10.0)	0 (0-0)
	Kenya	2008-09	3641	8 (6.8-9.3)	16 (15-18)
	Malawi	2004	2686	13.3 (12.0-14.8)	1 (1-2)
	Malawi	2010	7091	12.9 (11.8-14.1)	31 (29-33)
	Malawi	2015-16	7737	10.8 (9.9-11.7)	66 (63-71)
	Rwanda	2005	5641	3.6 (3.1-4.2)	9 (8-11)
	Rwanda	2010	6917	3.7 (3.3-4.2)	45 (39-51)
	Rwanda	2014-15	6752	3.6 (3.2-4.1)	67 (59-76)
	Zambia	2007	5502	16.1 (14.7-17.5)	20 (19-22)
	Zambia	2013-14	14719	15.1 (14.2-16.0)	53 (50-56)]
West and Central Africa and Ethiopia					
	Burkina	2003	4086	1.5 (1.2-2.0)	1 (1-1)
	Burkina	2010	8298	1.2 (0.9-1.5)	32 (25-40)
	Cameroon	2004	5128	6.6 (5.9-7.4)	2 (2-3)
	Cameroon	2011	7221	5.6 (5.0-6.3)	18 (15-20)
	Chad	2014-15	5656	1.8 (1.4-2.2)	50 (42-59)
	Cote Ivoire	2011-12	4509	4.6 (3.9-5.4)	25 (22-27)
	DRC	2007	4492	1.6 (1.2-2.2)	5 (4-6)
	DRC	2013-14	9264	1.6 (1.2-2.2)	24 (19-29)
	Ethiopia	2005	5736	1.9 (1.4-2.4)	2 (2-3)
	Ethiopia	2011	14695	1.9 (1.5-2.3)	41 (32-51)
	Gabon	2012	5459	5.8 (4.7-7.1)	32 (26-38)
	Gambia	2013	4089	2.1 (1.6-2.8)	24 (18-30)
	Ghana	2003	5097	2.3 (1.9-2.8)	0 (0-0)
	Guinea	2005	3742	1.9 (1.4-2.6)	2 (1-2)
	Guinea	2012	4622	2.1 (1.7-2.6)	28 (21-34)
	Liberia	2007	6382	1.8 (1.4-2.1)	3 (2-3)
	Liberia	2013	4397	2 (1.5-2.8)	19 (15-24)
	Mali	2006	4528	1.4 (1.0-2.0)	8 (6-10)
	Mali	2012-13	4806	1.3 (1.0-1.8)	32 (24-40)]
	Niger	2006	4406	0.6 (0.4-0.9)	3 (2-4)
	Niger	2012	5000	0.4 (0.2-0.5)	27 (20-32)
	Sao Tome	2009	2378	1.3 (0.8-2.0)	.
	Senegal	2005	4229	0.7 (0.4-1.0)	0 (0-0)
	Senegal	2010-11	5326	0.6 (0.4-0.8)	33 (25-40)
	Sierra Leone	2008	3448	1.7 (1.3-2.3)	4 (3-5)
	Sierra Leone	2013	7695	1.7 (1.3-2.0)	21 (13-29)
	Togo	2013-14	4737	3.1 (2.6-3.7)	37 (27-49)

*** Estimated HIV prevalence, see methods section**

† http://aidsinfo.unaids/, accessed 07 September 2017. Note for those surveys running over two years the earlier year is given

‡ICF International, 2015. The DHS Program STATcompiler. http://www.statcompiler.com. September 07 2017

Outcome variables

Exposure to sex: We created a binary variable "had recent sexual intercourse" defined as reporting having had sexual intercourse in the last four weeks.

Married: Marital status was defined as a binary variable: currently married (including cohabiting couples) and not currently married.

Current modern Contraceptive use: Modern contraceptive use conformed to the DHS definition and included the pill, IUD, injections, diaphragm, condom, female sterilization, male sterilization, implants, female condom, Foam/Jelly and lactational amenorrhea.

Exposure to pregnancy: A binary outcome "exposure to pregnancy" was defined as those who reported recent intercourse and reported not to be currently using any modern contraceptive. This definition assumes that current contraceptive use was constant in the 4 weeks prior to the survey.

Condom use: This binary outcome defined as women reporting currently using condoms among women who had reported recent sex and currently using a modern contraceptive.

Fertility Rates: This is measured using the retrospective birth histories and calculated as births per person year in the three years preceding the survey.

Other Variables

Other variables included women's HIV status at the time of the survey, five-year age group at time of survey, calendar year, place of residence (urban/rural), ART coverage using UNAIDS estimates[167] of national female adult ART coverage at the time of each survey stratified into categories <20%, 20-49%, and >50%, and Region. Region was grouped into Southern (Zimbabwe, Lesotho, Swaziland and Namibia), East and Mid Africa (Tanzania, Kenya, Uganda, Rwanda, Burundi, Malawi and Zambia) and West and Central Africa with Ethiopia (Table 1). HIV epidemics in the East and Mid African countries occurred earlier than in Southern Africa. West and central Africa along with Ethiopia have lower prevalence and their HIV transmission is likely to be more concentrated in high risk groups.

Women who were pregnant at the time of the survey (0.9%); those infected with HIV-2 (0.9%); and those whose HIV test was indeterminate (0.04%) were excluded from the analysis.

Data analysis

For each outcome variable, we used log Poisson regression to estimate the interaction between HIV status and five-year age group, place of residence, region and national ART coverage for the outcome variables recent sex, recent exposure to pregnancy, and fertility rate[45]. Each model was adjusted for country and survey year. Relative exposure to pregnancy by HIV status were compared to the fertility rate ratios by HIV status in order to estimate how much of the reduced fertility in HIV positive women compared to HIV negative women at the population level could be attributed to less exposure to sex. For regressions of fertility rate, fertility data for the three years before the survey were modelled, with an additional categorical variable for each year before the survey interacted with the age groups below 25 years and above 25 years[45]. Estimated fertility rate ratios by HIV status pertain to estimated fertility rate for the year preceding the survey.

We further analysed the outcomes of modern contraceptive use and marital status using the same log Poisson regression models in order to evaluate the extent to which differences in exposure to pregnancy between HIV positive and HIV negative women were mediated by differences in these intermediate outcomes. Finally, we investigate differences in contraceptive type between HIV positive and HIV negative women and the potential implications of this for contraceptive efficacy. We assess differences in type of modern contraceptives used between HIV positive and HIV negative women by analysing differences in condom use among women who reported having recent sex and currently using a modern contraceptive.

Decomposition of fertility differences

Due to the cross-sectional nature of the data we are unable to directly measure the contribution of recent sex to differences in fertility by HIV status as the outcome. The only possible measures of fertility relate to births in the years before the survey, so they come before the exposure, sex in the last four weeks. Instead, we have estimated relative fertility rates and relative exposure to pregnancy between HIV positive and HIV negative women within a given age, location, and time period. Comparing these risk ratios allows us to decompose the fertility differences by HIV status into differences in exposure to pregnancy and inferred differences in fecundity, as shown below.

The probability of having a live birth for an HIV negative women is:

$$F_{-ve} = E_{-ve} \times B_{-ve}$$

$$\therefore\ B_{-ve} = \frac{F_{-ve}}{E_{-ve}} \qquad (1)$$

Where E_{-ve} is the probability of being sexually exposed to pregnancy and B_{-ve} the probability of becoming pregnant and having a live birth given exposure.

For an HIV positive women

$$F_{+ve} = E_{+ve} \times B_{+ve}$$

$$F_{+ve} = E_{+ve} \times B_{-ve} \times \beta \qquad (2)$$

Where β is the additional risk factor of being HIV positive.

Rearranging (2) and substituting in (1)

$$\beta = \frac{F_{+ve}}{E_{+ve} \times B_{-ve}} = \frac{F_{+ve} \times E_{-ve}}{F_{-ve} \times E_{+ve}}$$

$$\approx \frac{Fertility\ rate\ ratio\ (+ve/-ve)}{Risk\ ratio\ of\ exposure\ to\ pregnancy\ (+ve/-ve)}$$

To obtain estimates of the relative difference in fecundity for HIV positive women, we use the risk ratios of being exposed to pregnancy analysed in this analysis along with the fertility rate ratios from Marston et al [45] .

8.5 Ethical Approval

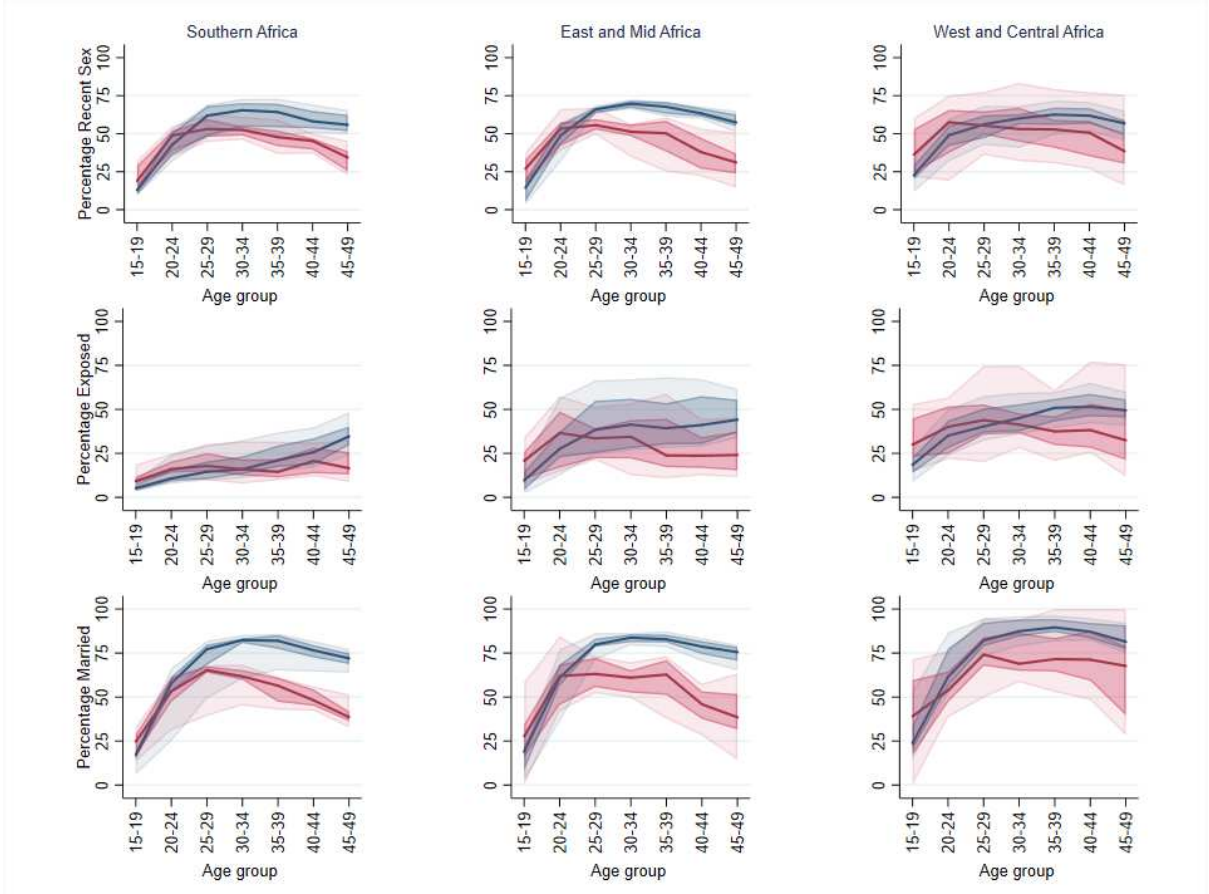
Ethical approval was obtained from the London School of Hygiene and Tropical Medicine ethics committee 2nd May 2017. DHS obtained the required local ethical approval and permission for each survey.

8.6 Results

Recent sex by HIV status

In Eastern, Mid and Southern Africa the median percentage of women reporting recent sex across the 46 surveys was around 25% at age 15-19. This peaked in the age range 25-34 at around 70% in HIV negative women and 50% in HIV positive women and then declined after this age. For West and Central Africa the peak occurred at slightly older ages, in 30-39 year olds (Figure 8.2).

Figure 8.2: Cross-survey median percentages for recent sex, Exposure to Pregnancy (Exposed) and being married by HIV status (blue negative, red positive) by HIV status and region. Also shown is the interquartile range and the 10th to 90th percentile range.



Differences in recent sex between HIV positive and HIV negative women varied with age, residence and region, although the general patterns are similar. Younger HIV positive women were more likely to have had recent sex compared to HIV negative women. This switched at around 20-24 for rural women and 25- 29 for urban women after which HIV positive women had a lower risk of recent sex than HIV negative women (See Table 8.2, model 2, Figure 8.3 and appendix Table 8.5). In southern Africa, the difference between HIV positive and HIV negative women was smaller (interaction term 1.06 95%CI 1.01-1.12). For example, in the 30-34 year age group, East and Mid African HIV positive women in urban areas were 0.90 (95%CI 0.85-0.96) less likely to have had recent sex compared to 0.96 (95%CI 0.89-1.02) in Southern Africa. There was no evidence of variation of an interaction between HIV status and region by age. There was no evidence of any change in the relative probability of recent sex between HIV positive women to HIV negative women by ART coverage (Table 8.2, model 3).

Figure 8.3: Adjusted Risk ratio for recent sex and exposure to a live birth, comparing HIV positive women to negative women with Fertility rate ratio

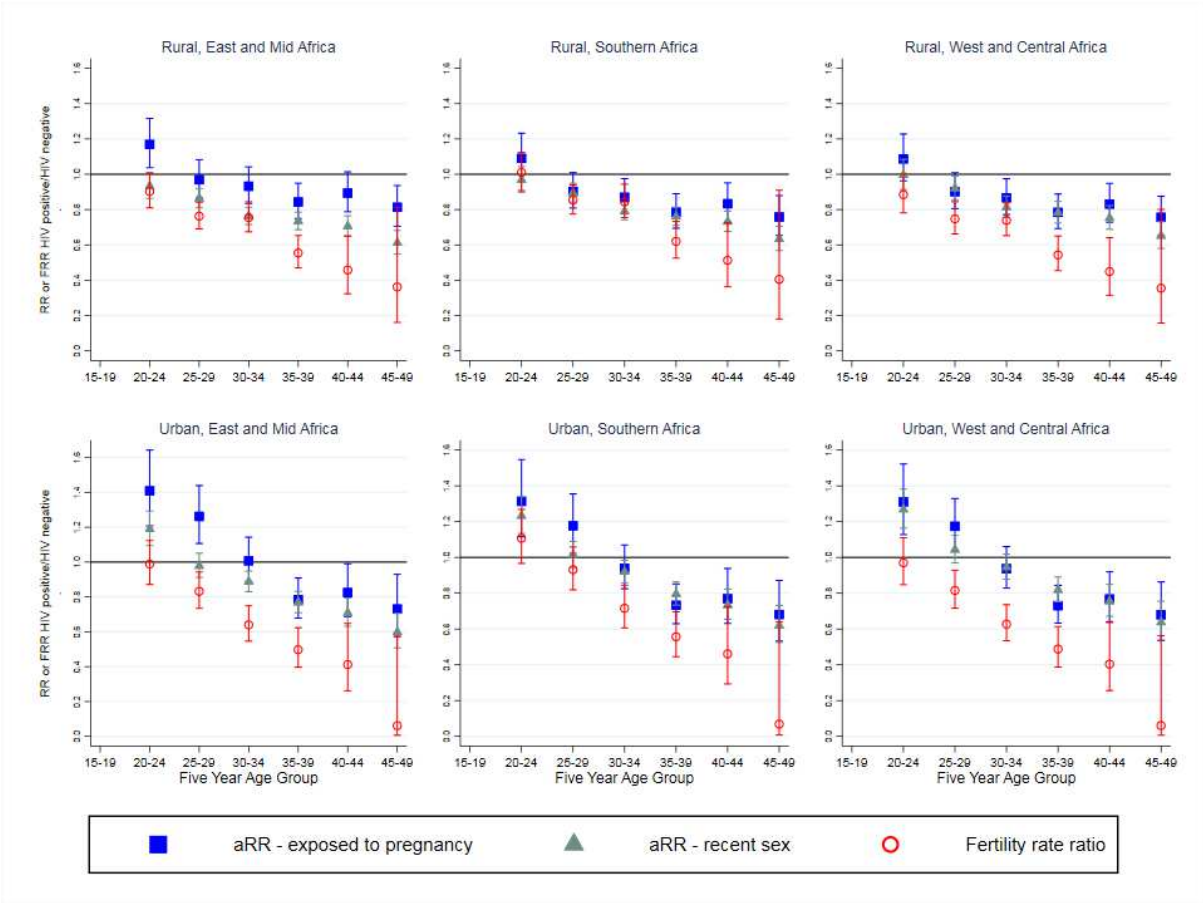


Table 8.2: Adjusted Risk ratios of recent sex, using Log Poisson model

	Model 1		Model 2		Model 3	
	RR	95 %CI	RR	95 %CI	RR	95 %CI
HIV status						
HIV negative	1		1		1	
HIV Positive	0.85	(0.82-0.89)	0.90	(0.85-0.94)	0.90	(0.85-0.96)
Effects of HIV by age						
15-19, HIV positive	1.72	(1.51-1.95)	1.72	(1.51-1.95)	1.53	(1.23-1.92)
20-24, HIV positive	1.25	(1.17-1.33)	1.25	(1.17-1.33)	1.31	(1.19-1.44)
25-29, HIV positive	1.11	(1.05-1.17)	1.10	(1.04-1.17)	1.10	(1.01-1.19)
30-34, HIV positive	1		1		1	
35-39, HIV positive	0.93	(0.87-0.99)	0.93	(0.88-0.99)	0.88	(0.80-0.96)
40-44, HIV positive	0.86	(0.80-0.93)	0.87	(0.81-0.93)	0.81	(0.72-0.91)
45-49, HIV positive	0.74	(0.67-0.81)	0.74	(0.68-0.81)	0.69	(0.59-0.81)
Effects of HIV by Place of residence						
rural, HIV positive			0.88	(0.85-0.92)	0.85	(0.78-0.92)
Effects of Place of residence on age and HIV status interaction						
rural, HIV positive,15-19					1.27	(0.97-1.67)
rural, HIV positive,20-24					0.96	(0.85-1.10)
rural, HIV positive,25-29					1.04	(0.93-1.16)
rural, HIV positive,30-34					1	
rural, HIV positive,35-39					1.13	(1.00-1.27)
rural, HIV positive,40-44					1.16	(1.00-1.35)
rural, HIV positive,45-49					1.14	(0.94-1.39)
Effects of HIV by Region						
Southern, HIV positive			1.06	(1.01-1.11)	1.06	(1.01-1.11)
Eastern, HIV positive			1		1	
Western, HIV positive			1.03	(0.98-1.09)	1.03	(0.98-1.09)
Effects of HIV by ART Coverage						
<20%, HIV positive					1	
20-49%, HIV positive					1.01	(0.96-1.06)
>50%, HIV positive					0.99	(0.94-1.05)
Age Group						
15-19	0.29	(0.28-0.30)	0.29	(0.28-0.30)	0.26	(0.25-0.27)
20-24	0.74	(0.73-0.76)	0.75	(0.73-0.76)	0.68	(0.66-0.70)
25-29	0.94	(0.93-0.96)	0.94	(0.93-0.96)	0.90	(0.88-0.93)
30-34	1		1		1	
35-39	1.01	(0.99-1.02)	1.01	(0.99-1.02)	1.00	(0.97-1.03)
40-44	0.99	(0.97-1.01)	0.99	(0.97-1.00)	0.95	(0.91-0.98)
45-49	0.90	(0.88-0.92)	0.90	(0.88-0.91)	0.87	(0.84-0.91)
Place of residence						
urban					1	
rural			1.08	(1.06-1.09)	1.01	(0.98-1.04)
Effects of age by Place of residence						
rural, 15-19					1.16	(1.09-1.24)
rural, 20-24					1.15	(1.11-1.20)
rural, 25-29					1.06	(1.03-1.10)
rural, 30-34					1	
rural, 35-39					1.01	(0.97-1.05)
rural, 40-44					1.05	(1.01-1.10)
rural, 45-49					1.04	(0.99-1.09)
Region						
Southern			0.92	(0.87-0.98)	0.93	(0.86-1.00)
Eastern			1		1	
Western			0.78	(0.73-0.84)	0.78	(0.72-0.85)
ART Coverage						
<20%					1	
20-49%					0.92	(0.87-0.98)
>50%					0.93	(0.84-1.02)

*All models also adjusted for calendar year (categorical) and country

Differences in modern contraceptive use for those who have had recent sex

Among women who reported recent sex, overall HIV positive women were less likely to report current use of modern contraceptives (appendix Table 8.6, Figure 8.6). However, these differences varied by age, region and place of residence. In urban areas for Southern and East and Mid Africa HIV positive women under 35 years old reported lower modern contraceptive use than HIV negative women (aRR ranging from 0.63, 95%CI 0.56-0.71 to 0.87, 95%CI 0.82-0.93). This pattern was similar in East and Mid Africa for older women but in Southern African women over 35 years old there was little or no difference in contraceptive use. In West and Mid Africa there was no evidence of a difference between current modern contraceptive use comparing HIV positive women to HIV negative women. In rural areas the pattern is different. Among younger women there was very little evidence of any difference between HIV positive and negative women's current contraceptive use. For East and Mid Africa the risk ratios were below one for all ages indicating lower use of modern contraceptives among HIV positive women but this only reaches statistical significance ($p<0.05$) at ages 30 to 34 years. Among rural women older than 35 in southern Africa, HIV positive women are more likely to be currently using modern contraceptives than HIV negative women (for example 35-39 year old aRR is 1.15 (95%CI 1.06-1.25) (see appendix Table 8.6-Table 8.7,Figure 8.6).

Differences in condom use amongst modern contraceptive users

Of the women reporting having had recent sex and currently using modern contraceptives, HIV positive women were more likely to be using condoms than HIV negative women at all ages. The magnitude of this different varied by age, region and rural and urban residency (Appendix, Figure 8.7)

Recent exposure to pregnancy

Relative differences in recent exposure to pregnancy between HIV positive and HIV negative women were different from the relative patterns in recent sex, due to HIV positive women in many exposure groups having lower use of modern contraceptives than their HIV negative counterparts. Figure 8.2 shows the cross-survey median percentages of exposure to pregnancy by HIV status and region.

Rural HIV positive women aged 15-24 had a higher risk of recent exposure to pregnancy compared to HIV negative women (Table 8.3, model 7 and Figure 8.3). This switched around age 25-34 where HIV positive women are less exposed to pregnancy than the

HIV negative women with a general trend of an increase in this gap with age. There was some evidence for regional variation with a slightly increased difference in recent exposure to pregnancy between HIV positive and HIV negative women Southern African and Western African HIV positive women with interaction terms 0.95 (95%CI 0.87-1.04) and 0.91 (95%CI 0.84-0.99). There was no evidence of a variation of region and HIV by age, though statistical power was limited to detect such an interaction. Young urban women also had higher exposure to pregnancy at young ages and lower exposure at older ages, but the crossover occurred at an older age group of around age 30-39, with some regional variation. There was no evidence of change in the relationship of HIV positive women to HIV negative women's exposure to pregnancy by ART coverage (Table 8.3, model 6).

Table 8.3: Risk ratios of exposure to pregnancy, using Log Poisson model

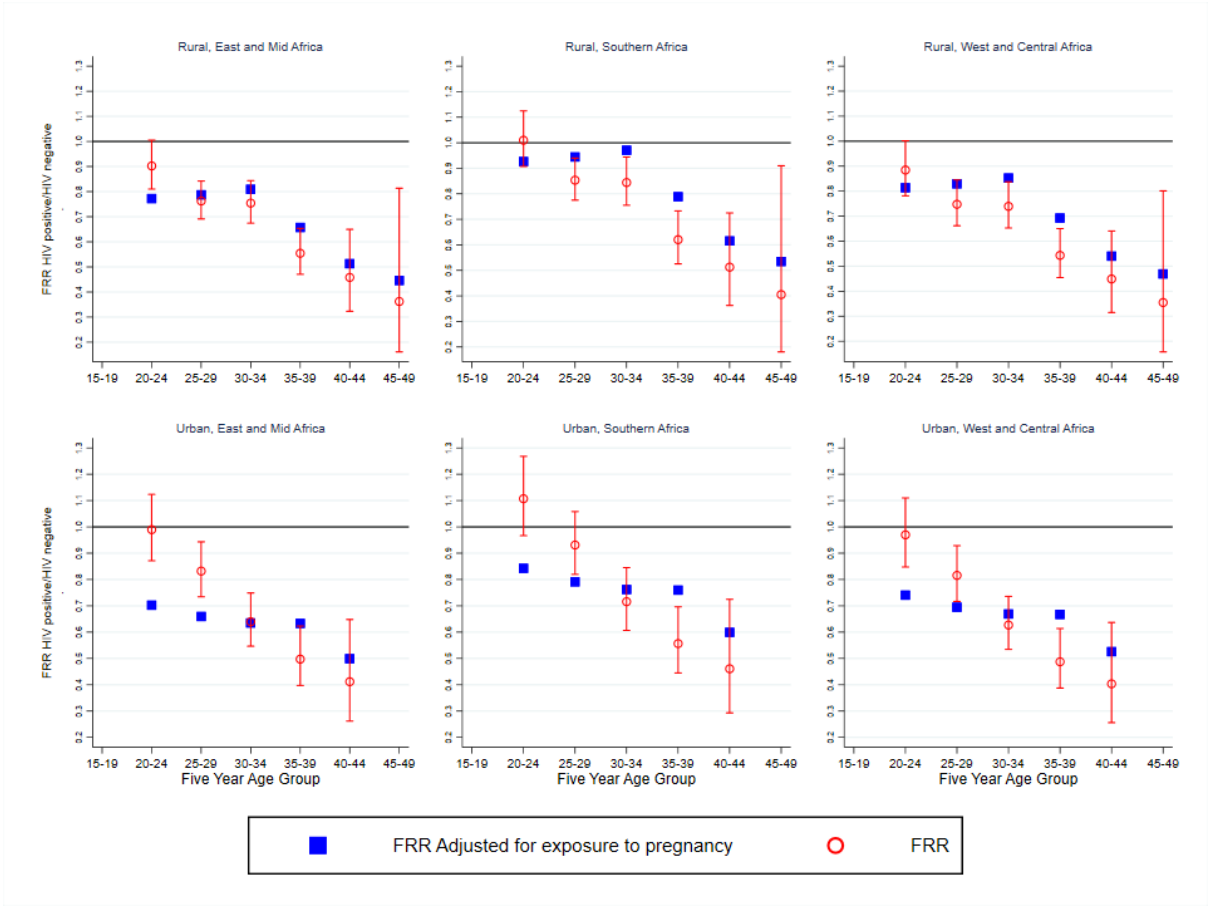
	Model 4		Model 5		Model 6	
	RR	95 %CI	RR	95 %CI	RR	95 %CI
HIV status						
HIV negative	1		1		1	
HIV Positive	0.91	(0.84-0.98)	1.03	(0.91-1.17)	1.03	(0.90-1.18)
Effects of HIV by age						
15-19, HIV positive	1.86	(1.54-2.25)	1.79	(1.25-2.55)	1.79	(1.25-2.55)
20-24, HIV positive	1.30	(1.16-1.46)	1.39	(1.16-1.66)	1.39	(1.16-1.66)
25-29, HIV positive	1.12	(1.01-1.25)	1.25	(1.06-1.48)	1.25	(1.06-1.48)
30-34, HIV positive	1		1		1	
35-39, HIV positive	0.85	(0.76-0.95)	0.78	(0.65-0.93)	0.78	(0.65-0.93)
40-44, HIV positive	0.91	(0.80-1.03)	0.83	(0.68-1.02)	0.83	(0.67-1.02)
45-49, HIV positive	0.82	(0.71-0.94)	0.73	(0.57-0.94)	0.73	(0.57-0.94)
Effects of HIV by Place of residence						
rural, HIV positive			0.91	(0.78-1.06)	0.91	(0.78-1.06)
Effects of Place of residence on age and HIV status interaction						
rural, HIV positive,15-19			1.09	(0.72-1.66)	1.09	(0.72-1.66)
rural, HIV positive,20-24			0.91	(0.72-1.14)	0.91	(0.72-1.14)
rural, HIV positive,25-29			0.82	(0.66-1.02)	0.82	(0.66-1.02)
rural, HIV positive,30-34			1		1	
rural, HIV positive,35-39			1.16	(0.92-1.46)	1.16	(0.92-1.46)
rural, HIV positive,40-44			1.16	(0.89-1.50)	1.16	(0.89-1.50)
rural, HIV positive,45-49			1.20	(0.89-1.62)	1.20	(0.89-1.62)
Effects of HIV by Region						
Southern, HIV positive			0.95	(0.87-1.04)	0.95	(0.86-1.04)
Eastern, HIV positive			1		1	
Western, HIV positive			0.91	(0.84-0.99)	0.91	(0.83-1.00)
Effects of HIV by ART Coverage						
<20%, HIV positive					1	
20-49%, HIV positive					1.04	(0.96-1.14)
>50%, HIV positive					0.96	(0.86-1.08)
Age Group						
15-19	0.33	(0.32-0.34)	0.28	(0.26-0.30)	0.28	(0.26-0.30)
20-24	0.75	(0.73-0.77)	0.66	(0.62-0.70)	0.66	(0.62-0.70)
25-29	0.93	(0.91-0.96)	0.87	(0.83-0.92)	0.87	(0.83-0.92)
30-34	1		1		1	
35-39	1.08	(1.05-1.11)	1.10	(1.04-1.16)	1.10	(1.04-1.16)
40-44	1.14	(1.11-1.17)	1.13	(1.07-1.20)	1.13	(1.07-1.20)
45-49	1.16	(1.13-1.19)	1.15	(1.09-1.23)	1.15	(1.09-1.23)
Place of residence						
urban			1		1	
rural			1.24	(1.18-1.29)	1.24	(1.18-1.29)
Effects of age by Place of residence						
rural, 15-19			1.28	(1.18-1.4)	1.28	(1.18-1.4)
rural, 20-24			1.23	(1.16-1.31)	1.23	(1.16-1.31)
rural, 25-29			1.11	(1.05-1.18)	1.11	(1.05-1.18)
rural, 30-34			1		1	
rural, 35-39			0.97	(0.91-1.03)	0.97	(0.91-1.03)
rural, 40-44			0.98	(0.92-1.05)	0.98	(0.92-1.05)
rural, 45-49			0.99	(0.93-1.06)	0.99	(0.93-1.06)
Region						
Southern			0.38	(0.34-0.42)	0.38	(0.34-0.42)
Eastern			1		1	
Western			0.95	(0.84-1.08)	0.95	(0.84-1.08)
ART Coverage						
<20%					1	
20-49%			0.88	(0.79-0.99)	0.88	(0.79-0.99)
>50%			0.81	(0.70-0.95)	0.81	(0.69-0.95)

*All models also adjusted for calendar year and country

Estimating fertility rate ratios if exposure was the same for recent sex and exposure to pregnancy

Figure 8.4 shows the inferred relative fecundity of HIV positive women compared to HIV negative, when adjusted for differences in exposure to pregnancy. The estimated fecundity for HIV positive women under 35 was between 0.6 and 0.9 compared to that of HIV negative women. This varied by place of residence and region with greater reductions in fertility in urban areas compared to rural areas. The estimated fecundity reduction was less in Southern Africa compared to the two other regions. After the age of 35 the estimated fecundity reduction intensified gradually as age increases.

Figure 8.4: Adjusted Fertility rate ratios (FRR) with adjusted fertility rate ratios adjusted for exposure to pregnancy (FRR/RR)



Marriage

Figure 8.2 shows the median percentage married across surveys by age, HIV status and region. These showed a slightly higher or similar median percentage of women married among HIV positive women up to the ages of 20-24. After this age HIV negative women were more likely to be married with the gap increasing with age.

Rural HIV positive women aged 20-49 are less likely to report being currently married compared to HIV negative women with this difference widening as age increases (appendix, Table 8.10 and Table 8.11, Figure 8.10). For example in Southern Africa, the relative probability of being married for HIV positive women was 0.88 (95% CI 0.84-0.94) at 20-24 years old to 0.62 (95% CI 0.57-0.68) at age 45-49. Young urban HIV positive women below the age of 30 have a higher or similar risk of being married compared to their HIV negative counterparts but after 30 their probability of marriage becomes lower than that of HIV negative women, with the relative difference increasing with age. There is some regional variation with Western and Central Africa having a slightly reduced difference. There is some evidence that the gap between positive and negative women has narrowed with increased ART coverage.

Married women differences between recent sex and exposure to pregnancy

The analysis of recent sex and exposure to pregnancy among married women only was restricted to 20-44 year olds due to very small sample size for married HIV positive women in the 15-19 and 45-49 year age group. When restricted to married women only, differences in recent sexual activity were much smaller between HIV positive women and HIV negative women than when considering all women (Appendix,Table 8.12-Table 8.15, Figure 8.11-Figure 8.14). For rural married women there was no evidence of a difference by HIV status for ages 20-34 and a slightly lower risk of recent sex for HIV positive married women aged 35-44. However, for rural HIV positive women there was a higher risk of exposure to a pregnancy for women of all ages apart from 35-39 year olds. For West Africa the pattern was the same but differences were not statistically significant. For urban married women aged 20-34 in Southern Africa there was evidence of an increased risk of recent sex compared to HIV negative married women, with no evidence of a difference at older ages 35-44. This pattern was the same in the other regions but did not reach statistical significance.

Estimating the fecundity reduction for married women

Estimates of the fecundity reduction estimated among married women only gave broadly similar results as for all women although implying slightly larger fecundity reduction for HIV positive rural women in Eastern and Mid and Southern Africa (appendix, Figure 8.15 and Figure 8.16). Detailed results are further reported in the appendix, including all models, stratified rate ratios and graphs.

8.7 Discussion

This analysis has shown that patterns of sexual exposure between HIV positive and HIV negative women by age, region and place of residence strongly mirror the patterns of relative fertility rates between the two groups. We have also shown that after adjusting for differences in exposure to recent sexual activity, young HIV positive women may have somewhat lower rates of conception and fertility than HIV negative counterparts, similar to that observed among women in older age groups.

Many studies have found higher fertility rates in young HIV positive women 15-19 compared to HIV negative women. This is due to selection effects where women who begin sexual activity are exposed to both the risk of pregnancy and HIV[41, 45, 72, 171] Where median age at first sex is higher these selection effects can also have some impact in the 20-24 year age group[45]. Others have shown that some HIV subfertility is due to widowhood and separation from a partner, or lower sexual activity due to illness[107] – it is speculated that declines in coital frequency are larger with increases in age. This analysis confirms both these aspects of behaviour. Rural HIV positive women have an increasingly lower probability of recent sex as age increases and urban HIV positive women have a higher risk of recent sex in 20-24 year olds followed by a lower risk after the age of 30. A different pattern emerges when examining exposure to pregnancy, taking into account modern contraceptive use. Modern contraceptive use is lower among HIV positive women, resulting in much higher exposure to pregnancy for younger HIV positive women compared to HIV negative women up to the age of around 25 years old for rural areas and 30 for urban areas. For older women the exposure to pregnancy remains lower for HIV positive women than HIV negative women although their risk of recent exposure to pregnancy was slightly closer than their risk of recent sex. These differences in recent exposure to pregnancy appear to disguise the direct effects of HIV on fertility. With the assumptions that the relationship between recent sex and coital frequency is the same at population level for HIV positive and HIV negative women and that the effectiveness of contraceptive use is the same across the two groups, we estimate that the impact of HIV on fecundity is much higher in younger women than might

be gauged from HIV-associated subfertility measured in general populations, without taking into account sexual behaviour [41, 45, 72] and slightly lower in older women. Taken together, this suggests that the direct effects of HIV on fertility are more similar across ages, while the dramatic age gradient that has frequently been observed is largely attributable to variation in relative sexual exposure by age. We estimate that in these younger women, if biological factors impacting fecundity were the only effect on fertility, the fertility risk ratio comparing HIV positive women to HIV negative women would be around 0.7 to 0.9. This appears to vary by region and urban and rural residency, with a greater estimated biological impact on fecundity in urban areas and a lower estimated biological impact in Southern Africa.

A possible explanation for a biological impact of HIV on fecundity in women at the earlier stages of HIV infection may be co-infection or past infection with other sexually transmitted infections (STI). The role of STIs in HIV subfertility has been discussed previously[172-174]. HIV positive women are more likely to be infected with another STI than HIV negative women as STI have similar risk factors to HIV. STI such as Chlamydia and Gonorrhoea cause Pelvic inflammatory disease that can impair fertility soon after infection and if left untreated can then go on to cause permanent infertility due to tubal damage[85]. Other STI such as syphilis are linked to adverse fetal outcomes: miscarriage and still birth[91]. These STIs in women are generally asymptomatic[175] and therefore may go untreated, but also lack of access to health facilities or social stigma may contribute to lack of treatment. Variation in biological subfertility by place of residence and region may be explained by the prevalence and type of STIs and access to treatment.

These results also shed light on the persistent fertility differences between HIV positive and HIV negative women in the era of ART[45, 73, 74]. Although it is possible that high coverage has not been sustained for long enough to observe a dramatic recovery in fertility yet, it is also possible that although ART improves the health of HIV positive women, it may not immediately change their prospects for sexual activity and exposure to pregnancy, or it may not ameliorate the long-term impacts of previous STIs on impaired fertility. There was no evidence of an effect of ART coverage or timing of ART roll-out in this analysis indicating that the relative difference in recent exposure to pregnancy between HIV positive and HIV negative women has not changed over time. There are few DHS studies in countries that have achieved a high ART roll out for a sustained amount of time, therefore it is possible that it is too soon to detect behavioural changes due to the presence of ART.

As this analysis uses cross sectional data we are unable to model sexual behaviour as an explanatory factor for individual-level fertility outcomes. Our measure of fertility comes from birth histories in the year before the survey, the explanatory variable recent sex relates to the four weeks prior to the survey, and current contraceptive use is measured at the time of the survey. Therefore our estimates of the biological effect of HIV on fecundity are indirect, depending on ratio comparisons of fertility rates and rates of exposure to unprotected sex.

For this analysis we assume that the relationship between recent sex and coital frequency is the same by HIV status of the women. However, apart from 15-19 year olds, HIV positive women were generally less likely to be married than HIV negative women, therefore we might find that the relationship between recent sex and coital frequency may be different if the latter were to be measured directly. To reduce the possibility of this biasing our analysis, we also restricted the analysis to married women only, which yielded broadly similar results for the estimated effect of HIV on fertility. However coital frequency may also be determined by a variety of other factors such as partner mobility, polygamy, duration of marriage and desire for children which we have not yet investigated.

We used reported current modern contraceptive use as a proxy for the contraceptive behaviour during the four weeks prior to the survey. Although this may be a reasonable assumption it is possible that consistency and contraceptive efficacy varies by type of contraceptives. Of the women who had reported recent sex and currently using modern contraceptives, HIV positive women were more likely to be using condoms than HIV negative women. Condom are both less effective than other modern contraceptives as they are more likely to be incorrectly used and used differently with different partners so may be less likely to have been used consistently over the previous four weeks. With condom use more prevalent in HIV positive women it is possible that they have a higher exposure to pregnancy risk relative to HIV negative women, even if the exposure to pregnancy variable used in this analysis is similar. This may have more of an effect in areas where prevalence of condom use is higher.

We have shown that differences in sexual activity between HIV positive and HIV negative women by age largely explain the steep gradient in fertility rate ratios by age that has been previously described, as well as regional and urban/rural differences in relative fertility. Moreover, recent sexual activity and exposure to pregnancy for HIV positive women has not increased significantly since ART was scaled-up. This may go some way explain why we have not observed the rapid increases in fertility of HIV positive women

that would be predicted by mathematical models which assume women on ART will have the same fertility as HIV negative women of the same age. We also hypothesize that long-term fertility impairment due to other STIs or lasting immunological effects of HIV may contribute to the continuing lower average fertility of HIV positive women. These dynamics could continue to evolve as both women and men initiate ART earlier, widowhood and marriage dissolution decrease, and norms around sexual behaviour and HIV continue to change.

8.8 Appendix

Recent sex by HIV status

Table 8.4: Risk ratios of recent sex, using Log Poisson model

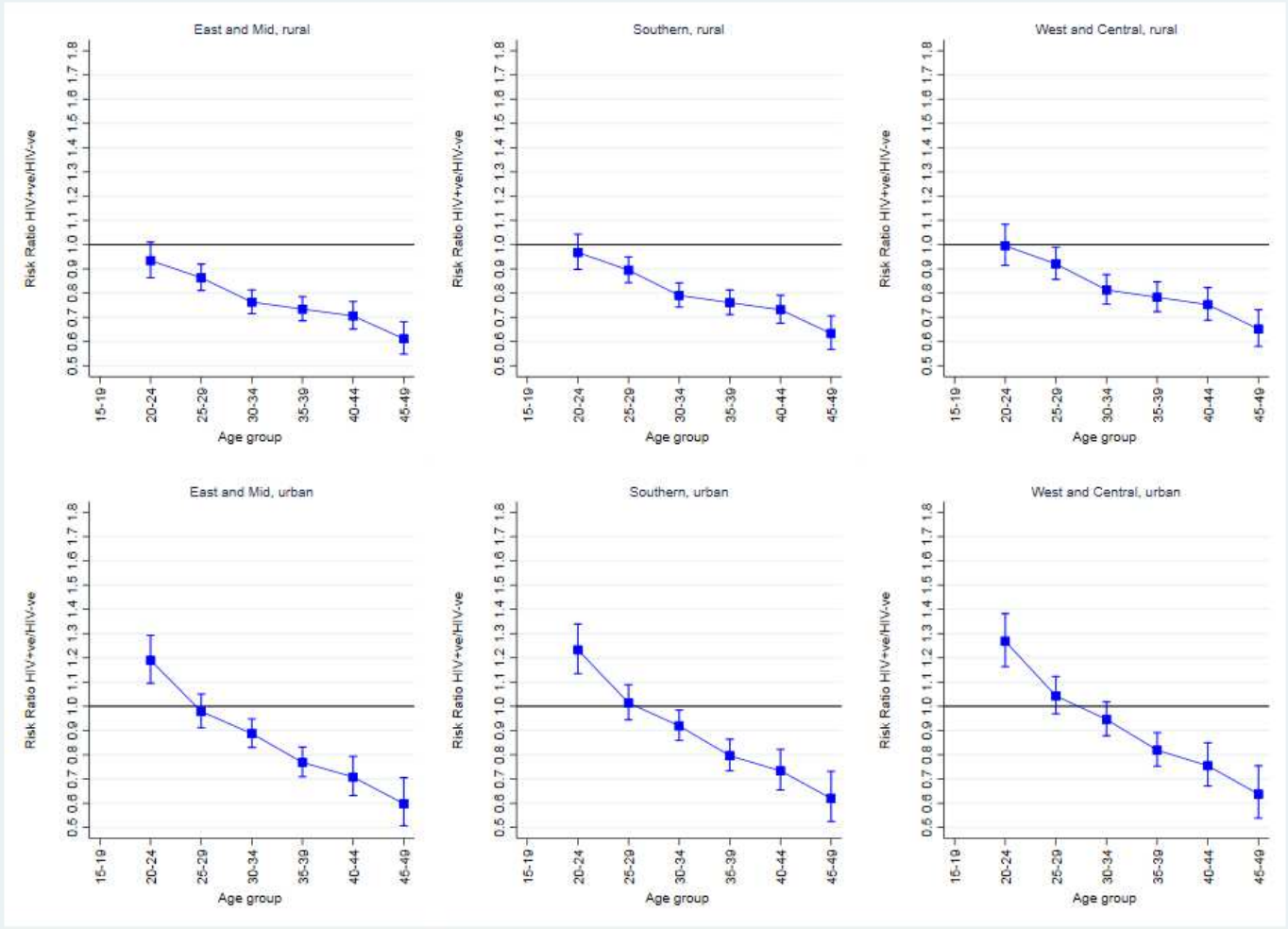
	Model 1		Model 2		Model 3		Model 4	
	FRR	95 %CI	FRR	95 %CI	FRR	95 %CI	FRR	95 %CI
HIV status								
HIV negative	1		1		1		1	
HIV Positive	0.85	(0.82-0.89)	0.90	(0.85-0.94)	0.90	(0.85-0.96)	0.90	(0.84-0.97)
Effects of HIV by age								
15-19, HIV positive	1.72	(1.51-1.95)	1.72	(1.51-1.95)	1.53	(1.23-1.92)	1.54	(1.23-1.92)
20-24, HIV positive	1.25	(1.17-1.33)	1.25	(1.17-1.33)	1.31	(1.19-1.44)	1.31	(1.19-1.44)
25-29, HIV positive	1.11	(1.05-1.17)	1.10	(1.04-1.17)	1.10	(1.01-1.19)	1.10	(1.01-1.19)
30-34, HIV positive	1		1		1		1	
35-39, HIV positive	0.93	(0.87-0.99)	0.93	(0.88-0.99)	0.88	(0.80-0.96)	0.88	(0.80-0.96)
40-44, HIV positive	0.86	(0.80-0.93)	0.87	(0.81-0.93)	0.81	(0.72-0.91)	0.81	(0.72-0.91)
45-49, HIV positive	0.74	(0.67-0.81)	0.74	(0.68-0.81)	0.69	(0.59-0.81)	0.69	(0.59-0.81)
Effects of HIV by Place of residence								
rural, HIV positive			0.88	(0.85-0.92)	0.85	(0.78-0.92)	0.85	(0.78-0.92)
Effects of Place of residence on age and HIV status interaction								
rural, HIV positive,15-19					1.27	(0.97-1.67)	1.27	(0.97-1.67)
rural, HIV positive,20-24					0.96	(0.85-1.10)	0.96	(0.85-1.10)
rural, HIV positive,25-29					1.04	(0.93-1.16)	1.04	(0.93-1.16)
rural, HIV positive,30-34					1		1	
rural, HIV positive,35-39					1.13	(1.00-1.27)	1.13	(1.00-1.27)
rural, HIV positive,40-44					1.16	(1.00-1.35)	1.16	(1.00-1.35)
rural, HIV positive,45-49					1.14	(0.94-1.39)	1.14	(0.94-1.39)
Effects of HIV by Region								
Southern, HIV positive			1.06	(1.01-1.11)	1.06	(1.01-1.11)	1.06	(1.01-1.11)
Eastern, HIV positive			1		1		1	
Western, HIV positive			1.03	(0.98-1.09)	1.03	(0.98-1.09)	1.03	(0.97-1.09)
Effects of HIV by ART Coverage								
<20%, HIV positive					1		1	
20-49%, HIV positive					1.01	(0.96-1.06)	1.01	(0.97-1.06)
>50%, HIV positive					0.99	(0.94-1.05)	0.99	(0.94-1.05)
Age Group								
15-19	0.29	(0.28-0.30)	0.29	(0.28-0.30)	0.26	(0.25-0.27)	0.26	(0.25-0.27)

20-24	0.74(0.73-0.76)	0.75(0.73-0.76)	0.68(0.66-0.70)	0.68(0.66-0.70)
25-29	0.94(0.93-0.96)	0.94(0.93-0.96)	0.90(0.88-0.93)	0.90(0.88-0.93)
30-34	1	1	1	1
35-39	1.01(0.99-1.02)	1.01(0.99-1.02)	1.00(0.97-1.03)	1.00(0.97-1.03)
40-44	0.99(0.97-1.01)	0.99(0.97-1.00)	0.95(0.91-0.98)	0.95(0.91-0.98)
45-49	0.90(0.88-0.92)	0.90(0.88-0.91)	0.87(0.84-0.91)	0.87(0.84-0.91)
Place of residence				
urban			1	1
rural		1.08(1.06-1.09)	1.01(0.98-1.04)	1.01(0.98-1.04)
Effects of age by Place of residence				
rural, 15-19			1.16(1.09-1.24)	1.16(1.09-1.24)
rural, 20-24			1.15(1.11-1.20)	1.15(1.11-1.20)
rural, 25-29			1.06(1.03-1.10)	1.06(1.03-1.10)
rural, 30-34			1	1
rural, 35-39			1.01(0.97-1.05)	1.01(0.97-1.05)
rural, 40-44			1.05(1.01-1.10)	1.05(1.01-1.10)
rural, 45-49			1.04(0.99-1.09)	1.04(0.99-1.09)
Region				
Southern		0.92(0.87-0.98)	0.93(0.86-1.00)	0.93(0.86-1.00)
Eastern		1	1	1
Western		0.78(0.73-0.84)	0.78(0.72-0.85)	0.78(0.72-0.85)
ART Coverage				
<20%			1	1
20-49%			0.92(0.87-0.98)	0.92(0.87-0.97)
>50%			0.93(0.84-1.02)	0.93(0.84-1.02)

Table 8.5: Stratum specific risk ratios from Model 2, recent sex

recent sex - nopreg				
		Southern Africa	East and Mid	West and central
Urban				
	15-19	1.46 (1.16-1.83)	1.39 (1.11-1.74)	1.44 (1.15-1.80)
	20-24	1.28 (1.18-1.39)	1.22 (1.12-1.33)	1.26 (1.16-1.37)
	25-29	1.05 (0.98-1.13)	1.01 (0.94-1.08)	1.04 (0.97-1.12)
	30-34	0.96 (0.89-1.02)	0.91 (0.85-0.97)	0.94 (0.88-1.01)
	35-39	0.83 (0.77-0.90)	0.79 (0.73-0.86)	0.82 (0.75-0.89)
	40-44	0.76 (0.68-0.86)	0.73 (0.65-0.82)	0.75 (0.67-0.85)
	45-49	0.64 (0.55-0.76)	0.61 (0.52-0.72)	0.63 (0.54-0.75)
Rural				
	15-19	1.25 (0.98-1.59)	1.19 (0.93-1.52)	1.23 (0.96-1.56)
	20-24	1.09 (0.97-1.23)	1.04 (0.93-1.17)	1.08 (0.95-1.22)
	25-29	0.90 (0.81-1.00)	0.86 (0.77-0.95)	0.89 (0.80-0.99)
	30-34	0.82 (0.77-0.87)	0.78 (0.73-0.83)	0.80 (0.75-0.87)
	35-39	0.71 (0.63-0.80)	0.68 (0.60-0.76)	0.70 (0.62-0.79)
	40-44	0.65 (0.57-0.75)	0.62 (0.54-0.72)	0.64 (0.56-0.74)
	45-49	0.55 (0.46-0.66)	0.52 (0.44-0.63)	0.54 (0.45-0.65)

Figure 8.5: Risk ratio of recent sex, comparing HIV positive women to HIV negative women



Differences in modern contraceptive use for those who have had recent sex

Table 8.6: Risk of using a current modern use of contraceptives for those who have had recent sex, comparing HIV positive to HIV negative women

	Model 1		Model 2		Model 3		Model 4	
	RR	95 %CI	RR	95 %CI	RR	95 %CI	RR	95 %CI
HIV status								
HIV negative	1		1		1		1	
HIV Positive	0.92	(0.87-0.97)	0.63	(0.56-0.71)	0.66	(0.58-0.75)	0.66	(0.57-0.75)
Effects of HIV by age								
15-19, HIV positive	0.98	(0.81-1.19)	1.31	(0.92-1.87)	1.11	(0.72-1.71)	1.11	(0.72-1.71)
20-24, HIV positive	0.96	(0.88-1.05)	1.19	(1.00-1.41)	1.16	(0.96-1.41)	1.17	(0.96-1.41)
25-29, HIV positive	0.99	(0.91-1.07)	1.14	(0.96-1.35)	1.00	(0.83-1.21)	1.01	(0.84-1.21)
30-34, HIV positive	1		1		1		1	
35-39, HIV positive	1.12	(1.03-1.22)	1.21	(1.02-1.43)	1.20	(1.00-1.45)	1.20	(0.99-1.45)
40-44, HIV positive	1.06	(0.96-1.18)	1.17	(0.96-1.42)	1.13	(0.89-1.42)	1.12	(0.89-1.41)
45-49, HIV positive	1.21	(1.05-1.40)	1.16	(0.87-1.55)	1.02	(0.73-1.43)	1.01	(0.72-1.42)
Effects of HIV by Place of residence								
rural, HIV positive			1.22	(1.15-1.29)	1.13	(1.02-1.25)	1.13	(1.02-1.26)
Effects of Place of residence on age and HIV status interaction								
rural, HIV positive,15-19					1.27	(0.86-1.87)	1.26	(0.86-1.86)
rural, HIV positive,20-24					1.01	(0.85-1.20)	1.01	(0.85-1.20)
rural, HIV positive,25-29					1.25	(1.08-1.46)	1.25	(1.08-1.46)
rural, HIV positive,30-34					1		1	
rural, HIV positive,35-39					1.01	(0.86-1.19)	1.01	(0.86-1.19)
rural, HIV positive,40-44					1.07	(0.87-1.31)	1.07	(0.87-1.32)
rural, HIV positive,45-49					1.19	(0.88-1.62)	1.20	(0.89-1.63)
Effects of HIV by Region								
Southern, HIV positive			1.38	(1.21-1.58)	1.37	(1.20-1.56)	1.38	(1.21-1.58)
Western, HIV positive			1.37	(1.02-1.85)	1.30	(0.96-1.77)	1.34	(0.99-1.83)
Effects of Region on age and HIV status interaction								
Southern Africa, Positive, 15-19			0.68	(0.44-1.04)	0.70	(0.45-1.07)	0.70	(0.45-1.07)

Southern Africa, Positive, 20-24		0.75(0.61-0.92)	0.76(0.62-0.93)	0.76(0.62-0.93)
Southern Africa, Positive, 25-29		0.81(0.67-0.98)	0.82(0.68-0.99)	0.82(0.68-0.99)
Southern Africa, Positive, 30-34		1	1	1
Southern Africa, Positive, 35-39		0.90(0.74-1.09)	0.90(0.74-1.09)	0.90(0.74-1.09)
Southern Africa, Positive, 40-44		0.82(0.64-1.03)	0.82(0.65-1.04)	0.82(0.65-1.04)
Southern Africa, Positive, 45-49		1.01(0.72-1.42)	1.04(0.74-1.46)	1.05(0.75-1.47)
West and Central Africa, Positive, 15-19		1.09(0.56-2.13)	1.17(0.59-2.33)	1.16(0.59-2.30)
West and Central Africa, Positive, 20-24		0.98(0.65-1.46)	1.05(0.70-1.58)	1.04(0.70-1.57)
West and Central Africa, Positive, 25-29		0.93(0.63-1.37)	1.04(0.70-1.54)	1.03(0.69-1.53)
West and Central Africa, Positive, 30-34		1	1	1
West and Central Africa, Positive, 35-39		0.99(0.65-1.52)	1.04(0.68-1.61)	1.04(0.67-1.60)
West and Central Africa, Positive, 40-44		1.11(0.68-1.82)	1.14(0.69-1.90)	1.15(0.69-1.91)
West and Central Africa, Positive, 45-49		0.67(0.27-1.69)	0.53(0.19-1.44)	0.53(0.20-1.46)
Effects of HIV by ART Coverage				
20-49%, HIV positive				0.96(0.89-1.04)
>50%, HIV positive				1.04(0.97-1.12)
Age Group				
15-19	0.86(0.82-0.90)	0.68(0.62-0.75)	0.82(0.74-0.92)	0.82(0.74-0.92)
20-24	1.00(0.97-1.04)	0.90(0.85-0.95)	0.96(0.90-1.03)	0.96(0.90-1.03)
25-29	1.00(0.97-1.03)	0.95(0.90-1.00)	1.01(0.95-1.08)	1.01(0.95-1.08)
30-34	1	1	1	1
35-39	0.89(0.85-0.92)	0.93(0.88-0.99)	0.94(0.87-1.01)	0.94(0.87-1.01)
40-44	0.77(0.74-0.80)	0.85(0.80-0.91)	0.85(0.78-0.93)	0.85(0.78-0.93)
45-49	0.52(0.49-0.55)	0.59(0.54-0.65)	0.70(0.62-0.79)	0.70(0.62-0.79)
Place of residence				
urban		1	1	1
rural		0.68(0.67-0.70)	0.71(0.68-0.75)	0.71(0.68-0.75)
Effects of age by Place of residence				
rural, 15-19			0.75(0.69-0.83)	0.75(0.69-0.83)

rural, 20-24		0.92(0.86-0.98)	0.92(0.86-0.98)
rural, 25-29		0.93(0.88-0.99)	0.93(0.88-0.99)
rural, 30-34		1	1
rural, 35-39		0.98(0.91-1.05)	0.98(0.91-1.05)
rural, 40-44		0.98(0.90-1.07)	0.98(0.90-1.07)
rural, 45-49		0.80(0.71-0.89)	0.80(0.71-0.89)
Region			
Southern	1.59(1.41-1.79)	1.54(1.22-1.93)	1.54(1.22-1.94)
Eastern	1	1	1
Western	0.55(0.48-0.63)	0.54(0.43-0.69)	0.54(0.43-0.69)
Effects of age by Region			
Southern Africa, 15-19	1.22(1.09-1.37)	1.19(1.06-1.34)	1.19(1.06-1.34)
Southern Africa, 20-24	1.10(1.03-1.17)	1.08(1.01-1.15)	1.08(1.01-1.15)
Southern Africa, 25-29	1.06(0.99-1.12)	1.04(0.98-1.10)	1.04(0.98-1.10)
Southern Africa, 30-34	1	1	1
Southern Africa, 35-39	0.94(0.88-1.01)	0.94(0.88-1.01)	0.94(0.88-1.01)
Southern Africa, 40-44	0.94(0.87-1.02)	0.94(0.86-1.02)	0.94(0.86-1.02)
Southern Africa, 45-49	0.96(0.85-1.08)	0.93(0.82-1.05)	0.93(0.82-1.04)
West and Central Africa, 15-19	1.46(1.30-1.64)	1.40(1.24-1.57)	1.40(1.24-1.57)
West and Central Africa, 20-24	1.19(1.10-1.29)	1.16(1.07-1.26)	1.16(1.07-1.26)
West and Central Africa, 25-29	1.04(0.96-1.12)	1.01(0.94-1.09)	1.01(0.94-1.09)
West and Central Africa, 30-34	1	1	1
West and Central Africa, 35-39	0.93(0.85-1.01)	0.92(0.85-1.00)	0.92(0.85-1.00)
West and Central Africa, 40-44	0.83(0.75-0.92)	0.83(0.75-0.93)	0.83(0.75-0.93)
West and Central Africa, 45-49	0.77(0.67-0.88)	0.74(0.64-0.85)	0.74(0.64-0.85)
ART Coverage			
<20%		1	1
20-49%		1.17 (1.01-1.37)	1.18 (1.02-1.38)
>50%		1.14 (0.85-1.53)	1.14 (0.85-1.53)

Table 8.7: Stratified rate ratios for the risk of using a current modern use of contraceptives for those who have had recent sex, comparing HIV positive to HIV negative women

		Risk ratios by region		
		Southern Africa	East and Mid	West and central
Urban				
	15-19	0.77 (0.61-0.98)	0.82 (0.59-1.15)	1.23 (0.75-2.01)
	20-24	0.77 (0.71-0.85)	0.75 (0.65-0.85)	1.00 (0.78-1.29)
	25-29	0.81 (0.75-0.87)	0.72 (0.63-0.82)	0.91 (0.73-1.15)
	30-34	0.87 (0.82-0.93)	0.63 (0.56-0.71)	0.86 (0.66-1.14)
	35-39	0.95 (0.87-1.03)	0.76 (0.68-0.86)	1.04 (0.79-1.37)
	40-44	0.83 (0.74-0.93)	0.73 (0.62-0.86)	1.12 (0.78-1.61)
	45-49	1.02 (0.86-1.22)	0.73 (0.56-0.95)	0.68 (0.29-1.56)
Rural				
	15-19	0.94 (0.74-1.19)	1.00 (0.72-1.40)	1.50 (0.91-2.45)
	20-24	0.94 (0.86-1.03)	0.91 (0.80-1.03)	1.21 (0.94-1.57)
	25-29	0.98 (0.91-1.05)	0.87 (0.77-0.99)	1.11 (0.89-1.39)
	30-34	1.06 (0.99-1.13)	0.77 (0.68-0.87)	1.05 (0.80-1.38)
	35-39	1.15 (1.06-1.25)	0.93 (0.82-1.04)	1.26 (0.96-1.66)
	40-44	1.01 (0.90-1.13)	0.89 (0.76-1.05)	1.36 (0.95-1.95)
	45-49	1.24 (1.05-1.48)	0.89 (0.69-1.16)	0.82 (0.36-1.91)

Figure 8.6: Risk ratio of currently using modern contraceptives for women reporting recent sex, comparing HIV positive women to HIV negative women

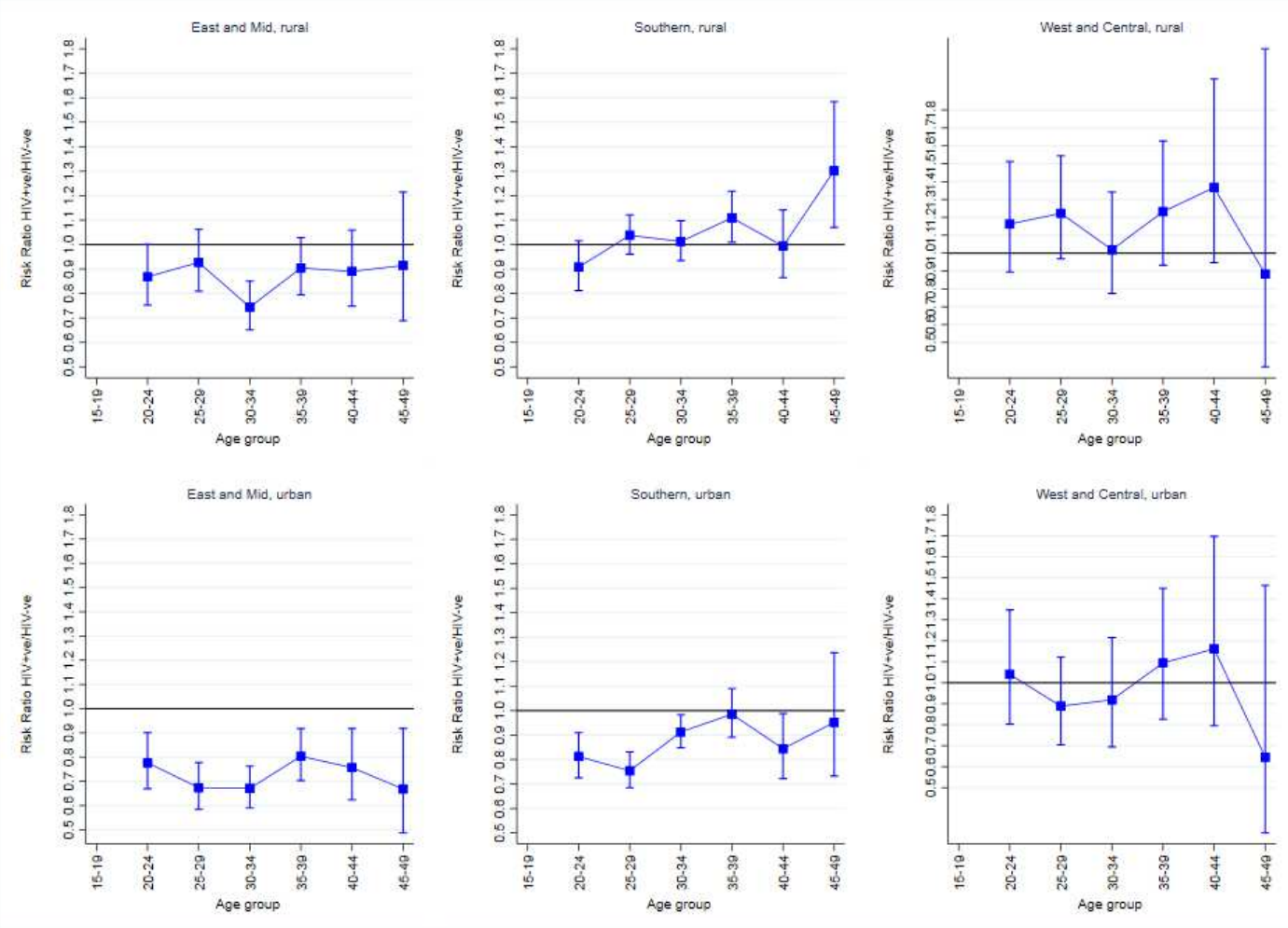
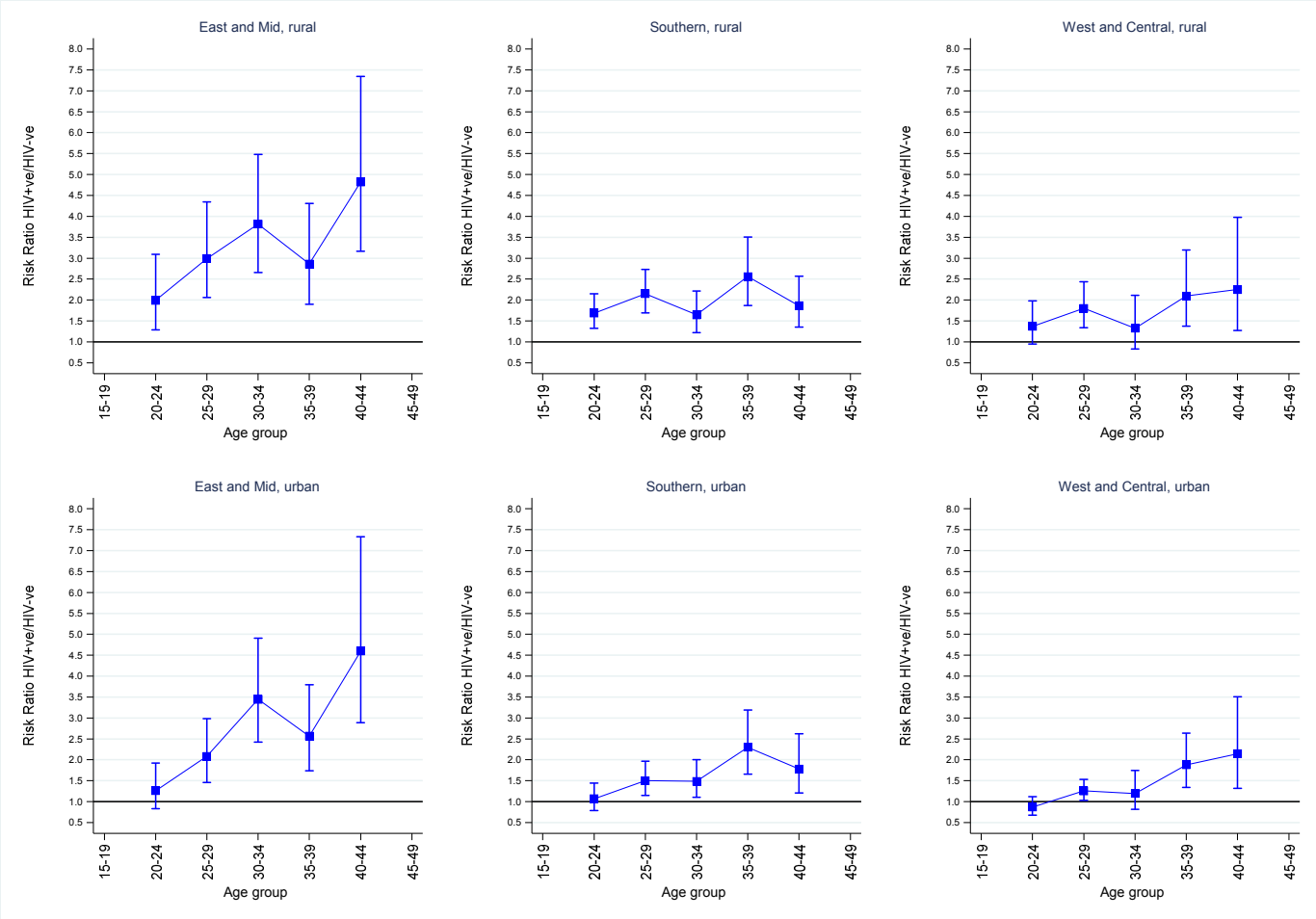


Figure 8.7: Risk ratio of using a condom for women who report having recent sex and currently using a modern contraceptive (HIV+ve/HIV-ve)



outcome= recent_sex_modern_usecondom, model: hivstatusXageagroup residXi.hivstatusXagegroup regionXhivstatusXagegroup year country

Recent exposure to pregnancy

Table 8.8: Risk ratios of recent exposure to a live birth, using Log Poisson model

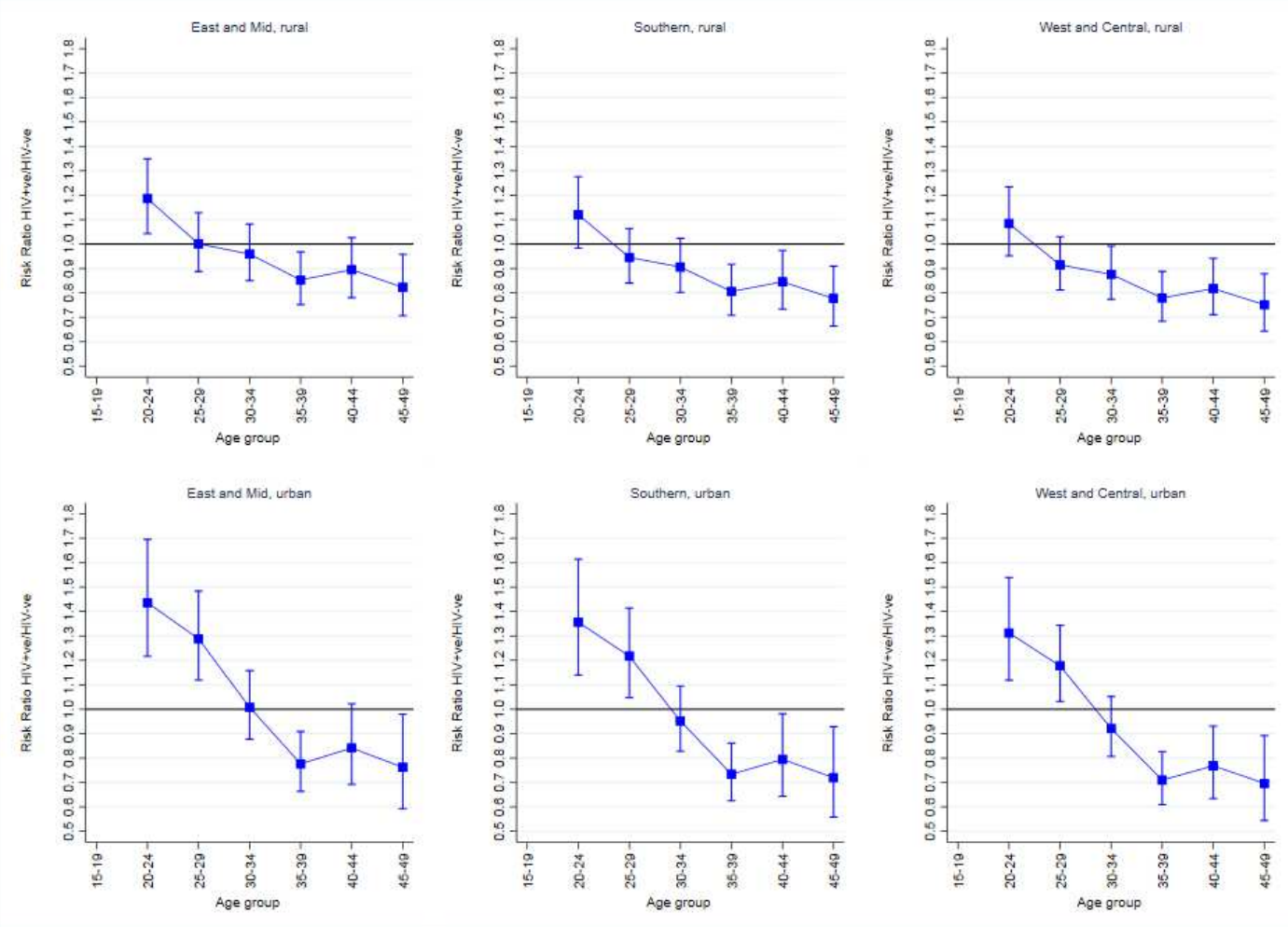
Exposed - nopreg	Model 5		Model 6		Model 7		Model 8	
	FRR	95 %CI	FRR	95 %CI	FRR	95 %CI	FRR	95 %CI
HIV status								
HIV negative	1		1		1		1	
HIV Positive	0.91	(0.84-0.98)	1.03	(0.90-1.16)	1.03	(0.91-1.17)	1.03	(0.90-1.18)
Effects of HIV by age								
15-19, HIV positive	1.86	(1.54-2.25)	1.78	(1.24-2.54)	1.79	(1.25-2.55)	1.79	(1.25-2.55)
20-24, HIV positive	1.30	(1.16-1.46)	1.40	(1.17-1.67)	1.39	(1.16-1.66)	1.39	(1.16-1.66)
25-29, HIV positive	1.12	(1.01-1.25)	1.25	(1.06-1.48)	1.25	(1.06-1.48)	1.25	(1.06-1.48)
30-34, HIV positive	1		1		1		1	
35-39, HIV positive	0.85	(0.76-0.95)	0.78	(0.65-0.93)	0.78	(0.65-0.93)	0.78	(0.65-0.93)
40-44, HIV positive	0.91	(0.80-1.03)	0.82	(0.67-1.01)	0.83	(0.68-1.02)	0.83	(0.67-1.02)
45-49, HIV positive	0.82	(0.71-0.94)	0.72	(0.56-0.94)	0.73	(0.57-0.94)	0.73	(0.57-0.94)
Effects of HIV by Place of residence								
rural, HIV positive			0.92	(0.79-1.07)	0.91	(0.78-1.06)	0.91	(0.78-1.06)
Effects of Place of residence on age and HIV status interaction								
rural, HIV positive,15-19			1.08	(0.71-1.65)	1.09	(0.72-1.66)	1.09	(0.72-1.66)
rural, HIV positive,20-24			0.90	(0.71-1.13)	0.91	(0.72-1.14)	0.91	(0.72-1.14)
rural, HIV positive,25-29			0.83	(0.67-1.03)	0.82	(0.66-1.02)	0.82	(0.66-1.02)
rural, HIV positive,30-34			1		1		1	
rural, HIV positive,35-39			1.16	(0.92-1.46)	1.16	(0.92-1.46)	1.16	(0.92-1.46)
rural, HIV positive,40-44			1.17	(0.90-1.51)	1.16	(0.89-1.50)	1.16	(0.89-1.50)
rural, HIV positive,45-49			1.20	(0.89-1.63)	1.20	(0.89-1.62)	1.20	(0.89-1.62)
Effects of HIV by Region								
Southern, HIV positive			0.95	(0.87-1.04)	0.95	(0.87-1.04)	0.95	(0.86-1.04)
Eastern, HIV positive			1		1		1	
Western, HIV positive			0.91	(0.84-0.99)	0.91	(0.84-0.99)	0.91	(0.83-1.00)
Effects of HIV by ART Coverage								
<20%, HIV positive							1	
20-49%, HIV positive							1.04	(0.96-1.14)
>50%, HIV positive							0.96	(0.86-1.08)
Age Group								
15-19	0.33	(0.32-0.34)	0.28	(0.26-0.30)	0.28	(0.26-0.30)	0.28	(0.26-0.30)

20-24	0.75(0.73-0.77)	0.66(0.62-0.69)	0.66(0.62-0.70)	0.66(0.62-0.70)
25-29	0.93(0.91-0.96)	0.87(0.83-0.92)	0.87(0.83-0.92)	0.87(0.83-0.92)
30-34	1	1	1	1
35-39	1.08(1.05-1.11)	1.09(1.03-1.16)	1.10(1.04-1.16)	1.10(1.04-1.16)
40-44	1.14(1.11-1.17)	1.15(1.09-1.21)	1.13(1.07-1.20)	1.13(1.07-1.20)
45-49	1.16(1.13-1.19)	1.15(1.08-1.22)	1.15(1.09-1.23)	1.15(1.09-1.23)
Place of residence				
urban		1	1	1
rural		1.22(1.17-1.27)	1.24(1.18-1.29)	1.24(1.18-1.29)
Effects of age by Place of residence				
rural, 15-19		1.29(1.18-1.41)	1.28(1.18-1.40)	1.28(1.18-1.4)
rural, 20-24		1.24(1.16-1.32)	1.23(1.16-1.31)	1.23(1.16-1.31)
rural, 25-29		1.11(1.05-1.18)	1.11(1.05-1.18)	1.11(1.05-1.18)
rural, 30-34		1	1	1
rural, 35-39		0.98(0.92-1.04)	0.97(0.91-1.03)	0.97(0.91-1.03)
rural, 40-44		0.98(0.92-1.04)	0.98(0.92-1.05)	0.98(0.92-1.05)
rural, 45-49		1.01(0.94-1.08)	0.99(0.93-1.06)	0.99(0.93-1.06)
Region				
Southern		0.38(0.35-0.43)	0.38(0.34-0.42)	0.38(0.34-0.42)
Eastern		1	1	1
Western		1.00(0.89-1.12)	0.95(0.84-1.08)	0.95(0.84-1.08)
ART Coverage				
<20%				1
20-49%			0.88(0.79-0.99)	0.88(0.79-0.99)
>50%			0.81(0.70-0.95)	0.81(0.69-0.95)

Table 8.9: Stratum specific risk ratios from Model 5, exposure to live birth

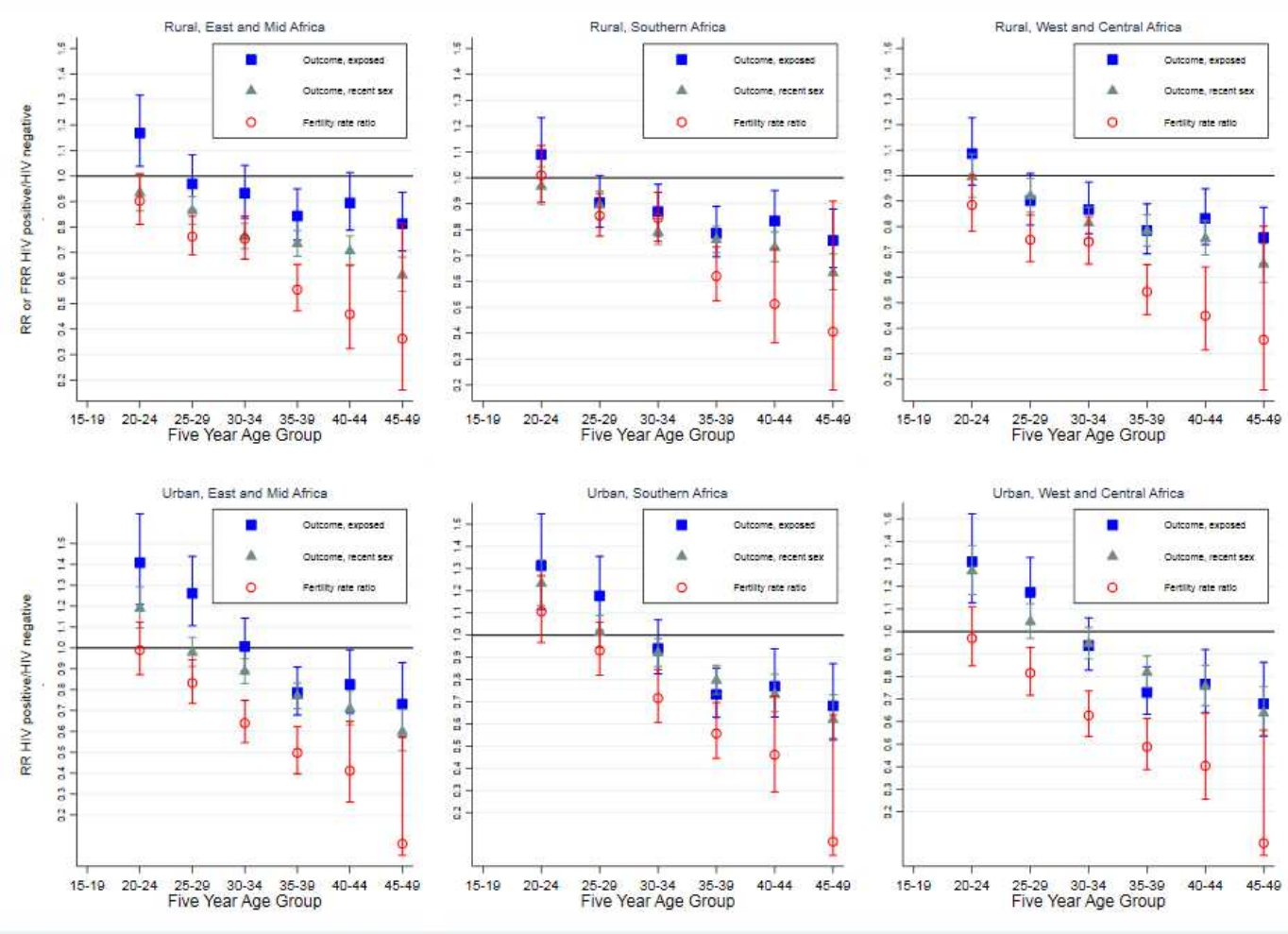
		Southern Africa	East and Mid	West and central
Urban				
	15-19	1.73 (1.24-2.42)	1.82 (1.30-2.54)	1.66 (1.19-2.31)
	20-24	1.36 (1.16-1.60)	1.43 (1.23-1.67)	1.31 (1.13-1.52)
	25-29	1.22 (1.06-1.41)	1.29 (1.13-1.47)	1.17 (1.04-1.33)
	30-34	0.97 (0.86-1.11)	1.03 (0.90-1.16)	0.93 (0.83-1.06)
	35-39	0.76 (0.66-0.89)	0.80 (0.69-0.93)	0.73 (0.63-0.84)
	40-44	0.80 (0.66-0.97)	0.84 (0.70-1.01)	0.77 (0.64-0.92)
	45-49	0.71 (0.55-0.90)	0.74 (0.58-0.95)	0.68 (0.53-0.86)
Rural				
	15-19	1.72 (1.40-2.13)	1.81 (1.47-2.23)	1.65 (1.34-2.03)
	20-24	1.13 (1.00-1.27)	1.18 (1.05-1.33)	1.08 (0.96-1.22)
	25-29	0.93 (0.84-1.04)	0.98 (0.88-1.10)	0.90 (0.80-1.00)
	30-34	0.90 (0.80-1.01)	0.94 (0.85-1.06)	0.86 (0.77-0.97)
	35-39	0.81 (0.72-0.92)	0.86 (0.76-0.96)	0.78 (0.69-0.88)
	40-44	0.86 (0.75-0.98)	0.91 (0.80-1.03)	0.83 (0.72-0.94)
	45-49	0.78 (0.68-0.91)	0.82 (0.71-0.95)	0.75 (0.65-0.87)

Figure 8.8: Risk ratio of exposure to pregnancy, comparing HIV positive women to HIV negative women



outcome= outcome_exposed_nopreg. model:outcome_exposed_nopreg hivstatusXageagroup residXi.hivstatusXagegroup regionXhivstatus year country

Figure 8.9: Adjusted Risk ratio for recent sex and exposure to a live birth, comparing HIV positive women to negative women with Fertility rate ratio



Married

Table 8.10: Risk ratios of being married using Log Poisson model

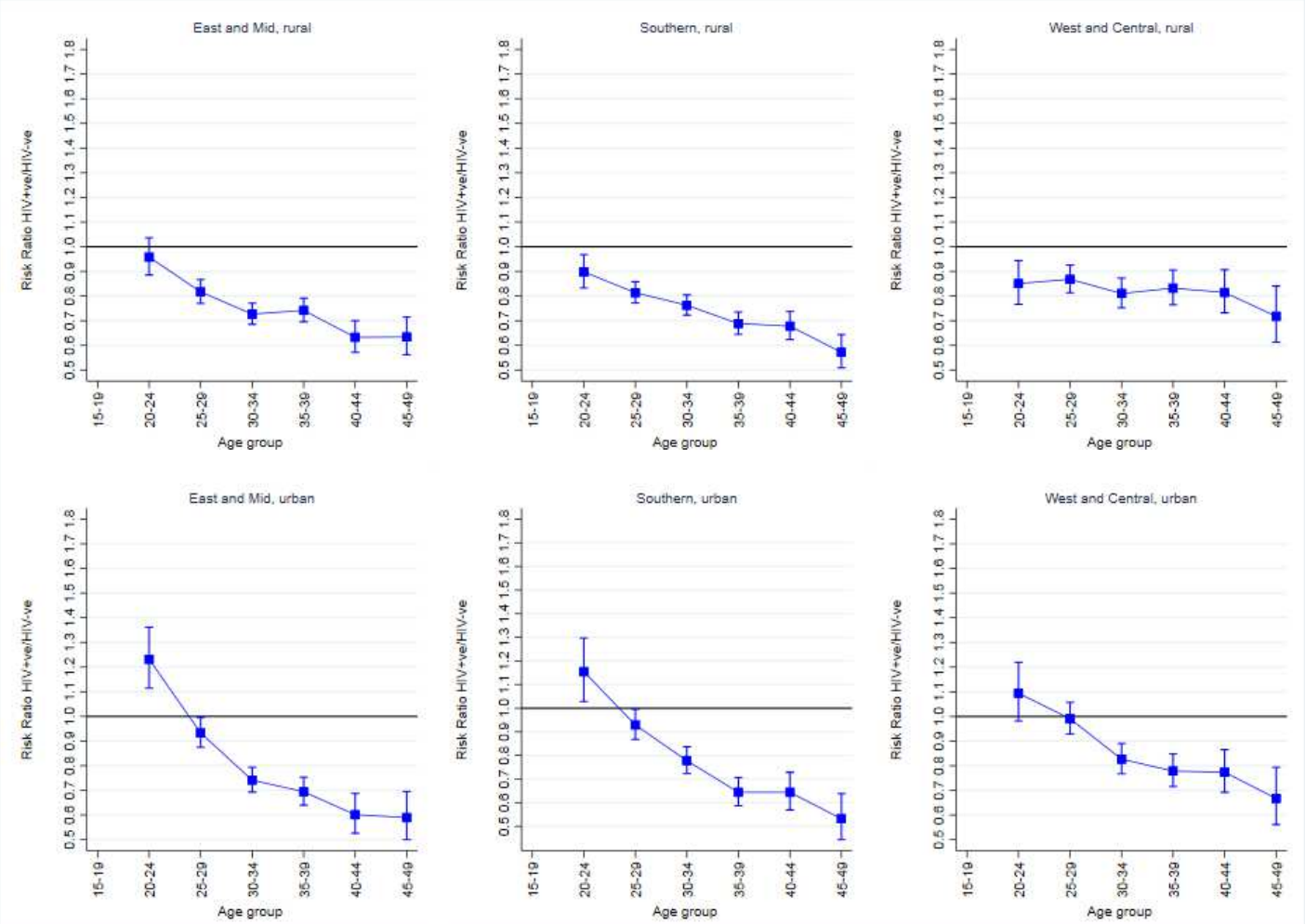
	Model 1		Model 2		Model 3	
	RR	95 %CI	RR	95 %CI	RR	95 %CI
HIV status						
HIV negative	1		1		1	
HIV Positive	0.78	(0.76-0.81)	0.79	(0.75-0.84)	0.77	(0.72-0.82)
Effects of HIV by age						
15-19, HIV positive	1.80	(1.61-2.01)	2.14	(1.73-2.65)	2.15	(1.74-2.66)
20-24, HIV positive	1.19	(1.13-1.26)	1.37	(1.25-1.51)	1.39	(1.26-1.53)
25-29, HIV positive	1.10	(1.05-1.14)	1.18	(1.10-1.27)	1.19	(1.11-1.28)
30-34, HIV positive	1		1		1	
35-39, HIV positive	0.92	(0.88-0.97)	0.88	(0.81-0.96)	0.89	(0.81-0.96)
40-44, HIV positive	0.86	(0.81-0.92)	0.84	(0.75-0.93)	0.84	(0.75-0.94)
45-49, HIV positive	0.78	(0.73-0.84)	0.75	(0.66-0.87)	0.76	(0.66-0.87)
Effects of HIV by Place of residence						
rural, HIV positive			0.99	(0.93-1.06)	0.99	(0.93-1.06)
Effects of Place of residence on age and HIV status interaction						
rural, HIV positive,15-19			0.80	(0.62-1.02)	0.80	(0.63-1.03)
rural, HIV positive,20-24			0.82	(0.73-0.92)	0.82	(0.73-0.92)
rural, HIV positive,25-29			0.89	(0.82-0.97)	0.88	(0.81-0.96)
rural, HIV positive,30-34			1		1	
rural, HIV positive,35-39			1.07	(0.97-1.19)	1.07	(0.96-1.18)
rural, HIV positive,40-44			1.04	(0.92-1.18)	1.03	(0.91-1.17)
rural, HIV positive,45-49			1.04	(0.88-1.23)	1.03	(0.87-1.21)
Effects of HIV by Region						
Southern, HIV positive			1.01	(0.98-1.05)	1.02	(0.98-1.05)
Western, HIV positive			1.06	(1.01-1.10)	1.07	(1.02-1.12)
Effects of HIV by ART Coverage						
<20%, HIV positive					1	
20-49%, HIV positive					1.03	(0.99-1.07)
>50%, HIV positive					1.06	(1.02-1.11)
Age Group						
15-19	0.26	(0.26-0.27)	0.18	(0.17-0.19)	0.18	(0.17-0.19)
20-24	0.73	(0.73-0.74)	0.60	(0.58-0.61)	0.59	(0.58-0.61)

25-29	0.95	(0.94-0.95)	0.89	(0.87-0.91)	0.89	(0.87-0.91)
30-34	1		1		1	
35-39	1.01	(1.00-1.02)	1.04	(1.02-1.06)	1.04	(1.02-1.06)
40-44	0.97	(0.96-0.98)	1.00	(0.98-1.02)	1.00	(0.98-1.02)
45-49	0.92	(0.91-0.93)	0.93	(0.90-0.95)	0.93	(0.90-0.95)
Place of residence						
urban			1		1	
rural			1.13	(1.11-1.15)	1.13	(1.11-1.15)
Effects of age by Place of residence						
rural, 15-19			1.73	(1.62-1.85)	1.72	(1.61-1.85)
rural, 20-24			1.37	(1.33-1.41)	1.38	(1.34-1.42)
rural, 25-29			1.09	(1.07-1.12)	1.10	(1.08-1.12)
rural, 30-34			1		1	
rural, 35-39			0.96	(0.94-0.98)	0.96	(0.94-0.98)
rural, 40-44			0.95	(0.93-0.98)	0.96	(0.93-0.98)
rural, 45-49			0.98	(0.95-1.01)	0.98	(0.95-1.01)
Region						
Southern			1.03	(0.99-1.08)	1.02	(0.97-1.08)
Eastern			1		1	
Western			1.19	(1.13-1.24)	1.20	(1.13-1.26)
ART Coverage						
<20%					1	
20-49%					1.05	(1.02-1.09)
>50%					1.05	(0.99-1.13)

Table 8.11: Stratum specific risk ratios of being married comparing HIV positive women to HIV negative women.

		Risk ratios by region		
		Southern Africa	East and Mid	West and central
Urban				
	15-19	1.71(1.38-2.12)	1.70(1.37-2.10)	1.79(1.44-2.23)
	20-24	1.12(1.02-1.22)	1.11(1.01-1.21)	1.17(1.07-1.28)
	25-29	0.96(0.90-1.01)	0.95(0.90-1.00)	1.00(0.95-1.06)
	30-34	0.80(0.76-0.85)	0.80(0.75-0.85)	0.84(0.80-0.90)
	35-39	0.71(0.66-0.77)	0.71(0.66-0.76)	0.75(0.70-0.81)
	40-44	0.67(0.61-0.74)	0.67(0.60-0.74)	0.71(0.64-0.78)
	45-49	0.59(0.51-0.68)	0.59(0.51-0.68)	0.62(0.54-0.72)
Rural				
	15-19	1.33(1.17-1.51)	1.32(1.16-1.50)	1.40(1.22-1.59)
	20-24	0.88(0.84-0.94)	0.88(0.83-0.93)	0.93(0.87-0.99)
	25-29	0.84(0.80-0.88)	0.83(0.80-0.87)	0.88(0.84-0.93)
	30-34	0.79(0.76-0.83)	0.79(0.75-0.82)	0.83(0.79-0.87)
	35-39	0.75(0.72-0.79)	0.75(0.71-0.79)	0.79(0.75-0.83)
	40-44	0.70(0.65-0.74)	0.69(0.65-0.74)	0.73(0.68-0.78)
	45-49	0.62(0.57-0.68)	0.62(0.57-0.67)	0.65(0.60-0.71)

Figure 8.10: Adjusted Risk ratio for being married, comparing HIV positive women to negative women.



Married recent sex and exposure to pregnancy

Table 8.12: Risk ratios of recent sex for married women, using Log Poisson model

	Model 1		Model 2		Model 3		Model 4	
	RR	95 %CI	RR	95 %CI	RR	95 %CI	RR	95 %CI
HIV status								
HIV negative	1		1		1		1	
HIV Positive	1.00	(0.96-1.04)	0.99	(0.95-1.04)	0.99	(0.94-1.03)	1.06	(0.99-1.12)
Effects of HIV by age								
15-19, HIV positive	1.09	(0.98-1.22)	1.11	(0.99-1.23)	1.11	(1.00-1.24)	0.87	(0.72-1.06)
20-24, HIV positive	1.05	(0.99-1.12)	1.06	(0.99-1.12)	1.06	(1.00-1.12)	1.01	(0.93-1.11)
25-29, HIV positive	1.03	(0.98-1.08)	1.03	(0.98-1.09)	1.03	(0.98-1.09)	0.98	(0.91-1.05)
30-34, HIV positive	1		1		1		1	
35-39, HIV positive	0.96	(0.91-1.01)	0.96	(0.92-1.02)	0.97	(0.92-1.02)	0.94	(0.87-1.02)
40-44, HIV positive	0.95	(0.90-1.01)	0.96	(0.91-1.02)	0.96	(0.91-1.02)	0.91	(0.83-1.00)
45-49, HIV positive	0.92	(0.85-1.00)	0.93	(0.86-1.01)	0.93	(0.86-1.01)	0.86	(0.74-0.99)
Effects of HIV by Place of residence								
rural, HIV positive			0.95	(0.92-0.99)	0.96	(0.92-1.00)	0.88	(0.81-0.94)
Effects of Place of residence on age and HIV status interaction								
rural, HIV positive,15-19							1.45	(1.15-1.83)
rural, HIV positive,20-24							1.07	(0.95-1.20)
rural, HIV positive,25-29							1.10	(0.99-1.22)
rural, HIV positive,30-34							1	
rural, HIV positive,35-39							1.07	(0.96-1.20)
rural, HIV positive,40-44							1.12	(0.99-1.28)
rural, HIV positive,45-49							1.17	(0.98-1.40)
Effects of HIV by Region								
Southern, HIV positive			1.04	(1.00-1.08)	1.04	(1.00-1.08)	1.04	(0.99-1.08)
Western, HIV positive			1.01	(0.95-1.06)	1.01	(0.96-1.07)	1.00	(0.94-1.06)
Effects of HIV by ART Coverage								
20-49%, HIV positive							0.99	(0.94-1.03)
>50%, HIV positive							0.95	(0.91-1.00)
Age Group								
15-19	0.87	(0.85-0.89)	0.88	(0.85-0.90)	0.87	(0.85-0.89)	0.96	(0.91-1.01)
20-24	0.94	(0.93-0.96)	0.95	(0.93-0.96)	0.94	(0.93-0.96)	0.99	(0.96-1.01)

25-29	0.98(0.97-0.99)	0.98(0.96-0.99)	0.98(0.96-0.99)	0.98(0.95-1.01)
30-34	1	1	1	1
35-39	1.01(1.00-1.03)	1.01(1.00-1.03)	1.01(0.99-1.03)	0.99(0.96-1.02)
40-44	1.02(1.01-1.04)	1.03(1.01-1.04)	1.03(1.01-1.04)	0.97(0.94-1.01)
45-49	0.99(0.97-1.01)	0.99(0.97-1.01)	0.99(0.98-1.01)	0.97(0.93-1.01)
Place of residence				
urban		1	1	1
rural		0.92(0.91-0.93)	0.91(0.90-0.93)	0.92(0.90-0.95)
Effects of age by Place of residence				
rural, 15-19				0.88(0.82-0.94)
rural, 20-24				0.94(0.91-0.97)
rural, 25-29				0.99(0.96-1.03)
rural, 30-34				1
rural, 35-39				1.03(0.99-1.07)
rural, 40-44				1.08(1.03-1.12)
rural, 45-49				1.03(0.99-1.08)
Region				
Southern		0.99(0.96-1.02)	0.99(0.96-1.02)	0.99(0.97-1.02)
Eastern		1	1	1
Western		0.91(0.85-0.98)	0.91(0.85-0.98)	0.91(0.85-0.98)
ART Coverage				
<20%			1	1
20-49%			0.99 (0.93-1.06)	0.99(0.93-1.06)
>50%			0.98 (0.89-1.08)	0.99(0.90-1.09)

Table 8.13: Risk ratios of exposure to a live birth, for married women,, using Log Poisson model

	Model 1		Model 2		Model 3		Model 4	
	RR	95 %CI	RR	95 %CI	RR	95 %CI	RR	95 %CI
HIV status								
HIV negative	1		1		1		1	
HIV Positive	1.09	(1.01-1.17)	1.19	(1.08-1.32)	1.20	(1.09-1.32)	1.25	(1.10-1.42)
Effects of HIV by age								
15-19, HIV positive	1.18	(0.99-1.40)	1.19	(1.00-1.42)	1.19	(1.00-1.42)	0.99	(0.74-1.34)
20-24, HIV positive	1.08	(0.97-1.21)	1.08	(0.97-1.21)	1.07	(0.96-1.20)	1.03	(0.87-1.23)
25-29, HIV positive	1.00	(0.90-1.11)	1.00	(0.90-1.11)	1.00	(0.90-1.10)	1.06	(0.90-1.24)
30-34, HIV positive	1		1		1		1	
35-39, HIV positive	0.87	(0.78-0.97)	0.87	(0.78-0.98)	0.87	(0.78-0.98)	0.82	(0.69-0.97)
40-44, HIV positive	1.00	(0.89-1.12)	1.00	(0.89-1.12)	1.01	(0.90-1.13)	0.95	(0.78-1.14)
45-49, HIV positive	0.98	(0.86-1.11)	0.97	(0.85-1.11)	0.98	(0.86-1.12)	0.90	(0.71-1.15)
Effects of HIV by Place of residence								
rural, HIV positive			0.98	(0.91-1.05)	0.97	(0.90-1.04)	0.93	(0.80-1.07)
Effects of Place of residence on age and HIV status interaction								
rural, HIV positive,15-19							1.32	(0.91-1.92)
rural, HIV positive,20-24							1.02	(0.80-1.29)
rural, HIV positive,25-29							0.88	(0.70-1.10)
rural, HIV positive,30-34							1	
rural, HIV positive,35-39							1.12	(0.89-1.42)
rural, HIV positive,40-44							1.06	(0.82-1.37)
rural, HIV positive,45-49							1.08	(0.80-1.45)
Effects of HIV by Region								
Southern, HIV positive			0.95	(0.86-1.05)	0.95	(0.87-1.05)	0.94	(0.86-1.04)
Western, HIV positive			0.86	(0.79-0.94)	0.86	(0.79-0.94)	0.84	(0.77-0.93)
Effects of HIV by ART Coverage								
20-49%, HIV positive							0.99	(0.91-1.07)
>50%, HIV positive							0.96	(0.87-1.06)
Age Group								
15-19	1.02	(0.98-1.06)	1.01	(0.98-1.05)	1.01	(0.97-1.04)	1.05	(0.97-1.14)
20-24	0.96	(0.94-0.99)	0.96	(0.93-0.98)	0.96	(0.93-0.98)	0.97	(0.92-1.02)
25-29	0.98	(0.96-1.00)	0.98	(0.96-1.00)	0.98	(0.96-1.00)	0.96	(0.91-1.01)
30-34	1		1		1		1	
35-39	1.08	(1.05-1.10)	1.07	(1.05-1.10)	1.07	(1.05-1.10)	1.08	(1.02-1.14)
40-44	1.17	(1.14-1.20)	1.16	(1.13-1.19)	1.16	(1.13-1.19)	1.14	(1.08-1.21)

45-49	1.26(1.23-1.29)	1.25(1.22-1.29)	1.25(1.22-1.28)	1.26(1.19-1.33)
Place of residence				
urban		1	1	1
rural		1.12(1.10-1.14)	1.13(1.10-1.15)	1.13(1.08-1.18)
Effects of age by Place of residence				
rural, 15-19				0.95(0.87-1.03)
rural, 20-24				0.99(0.93-1.05)
rural, 25-29				1.03(0.97-1.09)
rural, 30-34				1
rural, 35-39				0.99(0.94-1.06)
rural, 40-44				1.01(0.95-1.08)
rural, 45-49				0.99(0.93-1.06)
Region				
Southern		0.57(0.53-0.61)	0.60(0.56-0.65)	0.60(0.56-0.65)
Eastern		1	1	1
Western		1.90(1.71-2.12)	1.90(1.70-2.12)	1.90(1.70-2.12)
ART Coverage				
<20%			1	1
20-49%			0.84 (0.76-0.94)	0.85(0.76-0.94)
>50%			0.76 (0.66-0.87)	0.76(0.66-0.88)

Table 8.14: Stratum specific risk ratios, recent sex, married women, exclude pregnancy

		Southern Africa	East and Mid	West and central
Urban				
	15-19	1.14 (1.02-1.27)	1.10 (0.98-1.22)	1.10 (0.99-1.23)
	20-24	1.09 (1.03-1.15)	1.05 (0.99-1.11)	1.05 (0.99-1.12)
	25-29	1.07 (1.02-1.12)	1.02 (0.98-1.07)	1.03 (0.98-1.09)
	30-34	1.03 (0.98-1.08)	0.99 (0.95-1.04)	1.00 (0.94-1.06)
	35-39	1.00 (0.95-1.05)	0.96 (0.91-1.00)	0.96 (0.91-1.02)
	40-44	0.99 (0.94-1.05)	0.95 (0.90-1.01)	0.96 (0.90-1.02)
	45-49	0.96 (0.89-1.05)	0.93 (0.85-1.00)	0.93 (0.85-1.02)
Rural				
	15-19	1.09 (0.98-1.21)	1.05 (0.94-1.17)	1.05 (0.95-1.17)
	20-24	1.04 (0.99-1.09)	1.00 (0.95-1.06)	1.01 (0.94-1.07)
	25-29	1.02 (0.97-1.06)	0.98 (0.93-1.02)	0.99 (0.93-1.04)
	30-34	0.99 (0.94-1.03)	0.95 (0.90-0.99)	0.95 (0.90-1.01)
	35-39	0.95 (0.91-1.00)	0.91 (0.87-0.96)	0.92 (0.87-0.98)
	40-44	0.95 (0.90-1.00)	0.91 (0.86-0.96)	0.92 (0.86-0.98)
	45-49	0.92 (0.85-0.99)	0.88 (0.82-0.96)	0.89 (0.82-0.97)

Table 8.15: Stratum specific risk ratios, Exposed, married women, exclude pregnancy

Exposed - Married Women		Southern Africa	East and Mid	West and central
Urban				
	15-19	1.33 (1.12-1.59)	1.42 (1.20-1.68)	1.24 (1.06-1.46)
	20-24	1.21 (1.07-1.37)	1.29 (1.16-1.44)	1.13 (1.02-1.25)
	25-29	1.12 (1.01-1.26)	1.20 (1.09-1.32)	1.05 (0.96-1.15)
	30-34	1.12 (1.01-1.25)	1.19 (1.08-1.32)	1.04 (0.95-1.15)
	35-39	0.98 (0.87-1.09)	1.04 (0.94-1.16)	0.91 (0.82-1.01)
	40-44	1.12 (0.99-1.27)	1.20 (1.07-1.34)	1.05 (0.94-1.16)
	45-49	1.09 (0.95-1.26)	1.16 (1.02-1.32)	1.02 (0.89-1.16)
Rural				
	15-19	1.30 (1.10-1.54)	1.39 (1.18-1.64)	1.21 (1.03-1.43)
	20-24	1.18 (1.06-1.31)	1.26 (1.14-1.39)	1.10 (0.99-1.22)
	25-29	1.10 (1.00-1.21)	1.17 (1.07-1.28)	1.02 (0.93-1.12)
	30-34	1.09 (1.00-1.20)	1.17 (1.06-1.28)	1.02 (0.93-1.12)
	35-39	0.95 (0.86-1.06)	1.02 (0.92-1.12)	0.89 (0.80-0.99)
	40-44	1.09 (0.98-1.22)	1.17 (1.05-1.29)	1.02 (0.92-1.13)
	45-49	1.06 (0.94-1.21)	1.14 (1.01-1.28)	0.99 (0.88-1.13)

Figure 8.11: Adjusted Risk ratio for recent sex,, comparing HIV positive women to negative women with Fertility rate ratio for married women

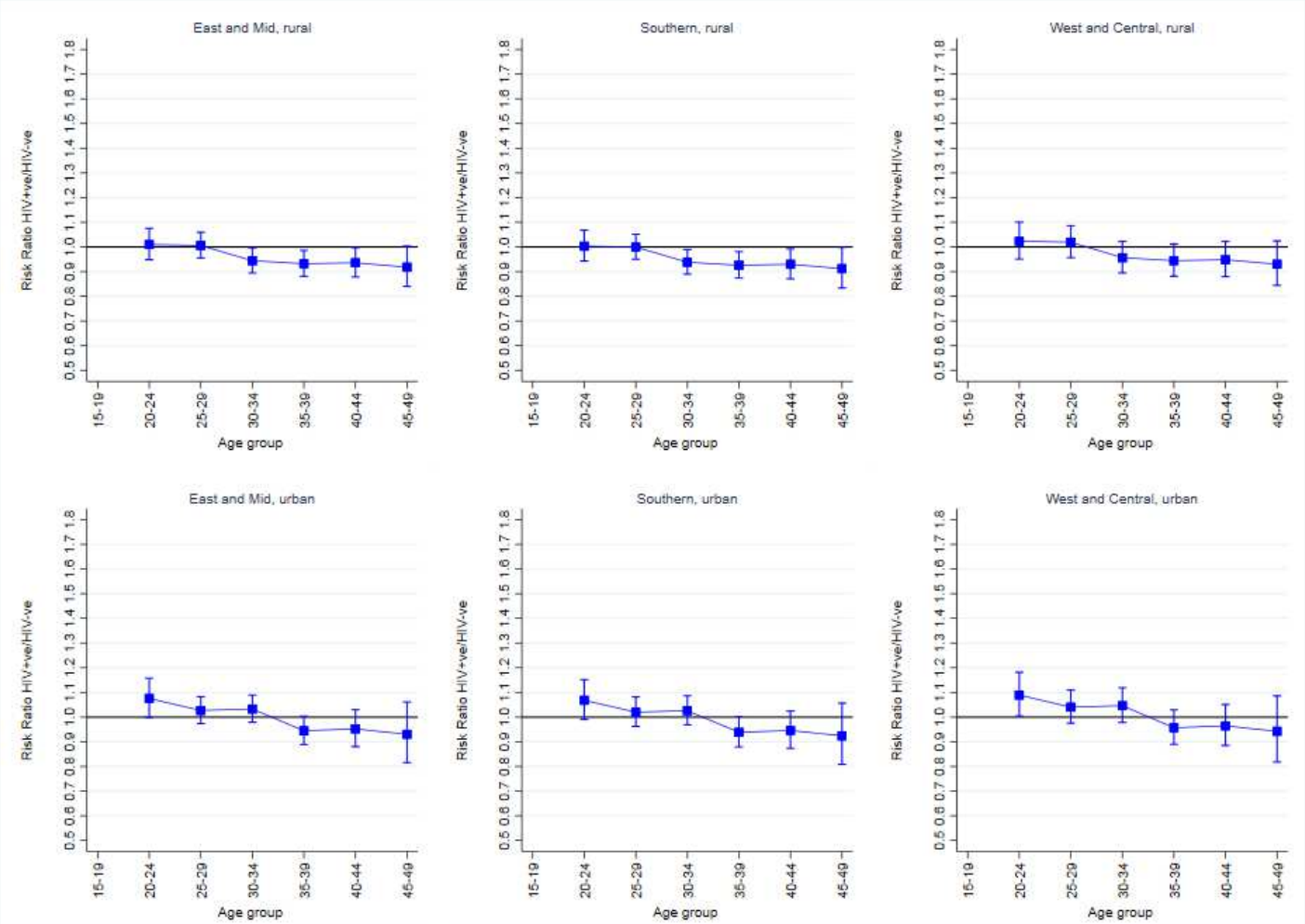


Figure 8.12: Risk ratio of currently using modern contraceptives for married women reporting recent sex, comparing HIV positive women to HIV negative women

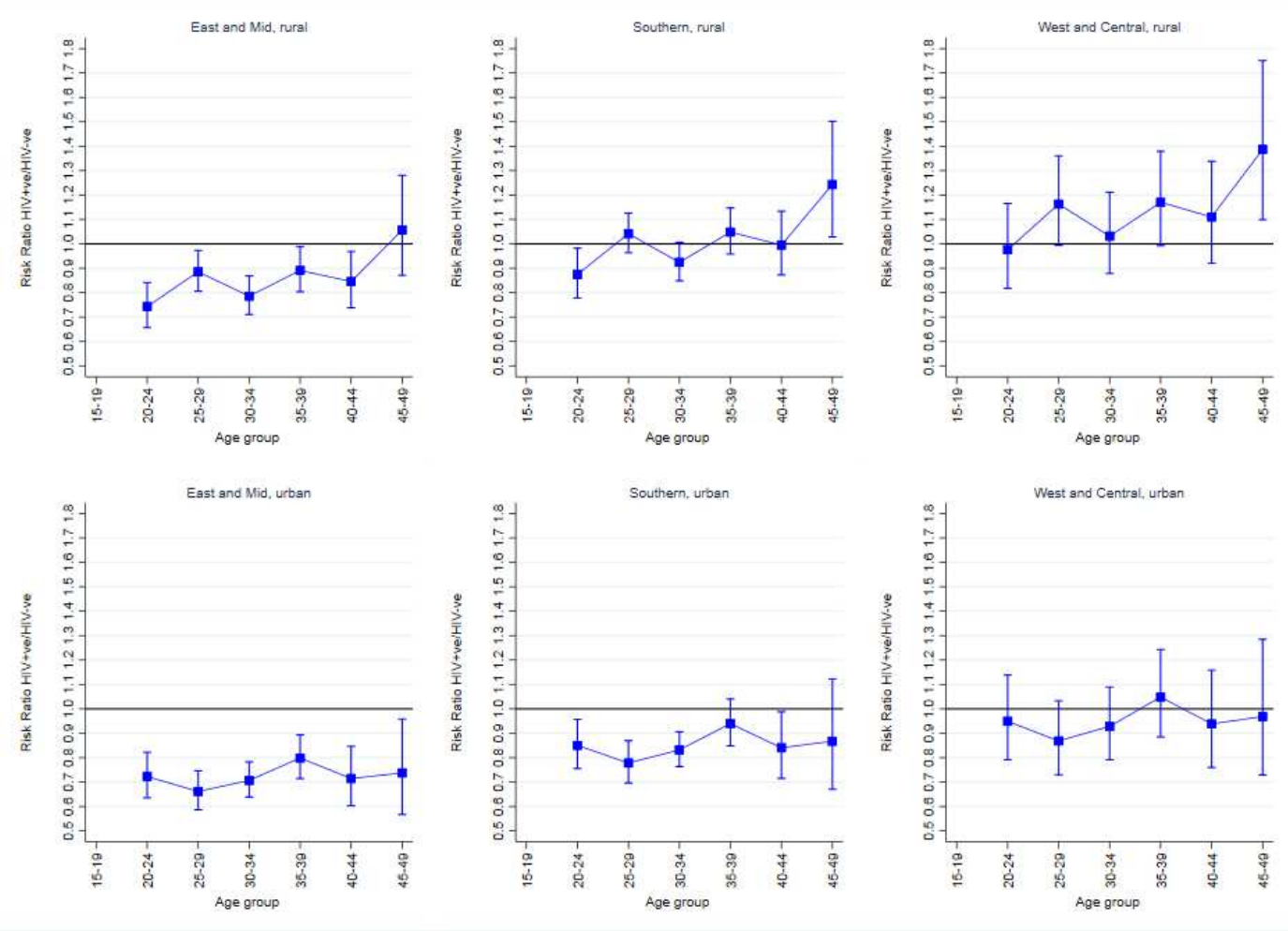


Figure 8.13: Adjusted Risk ratio for exposure to pregnancy, comparing HIV positive women to negative women with Fertility rate ratio for married women

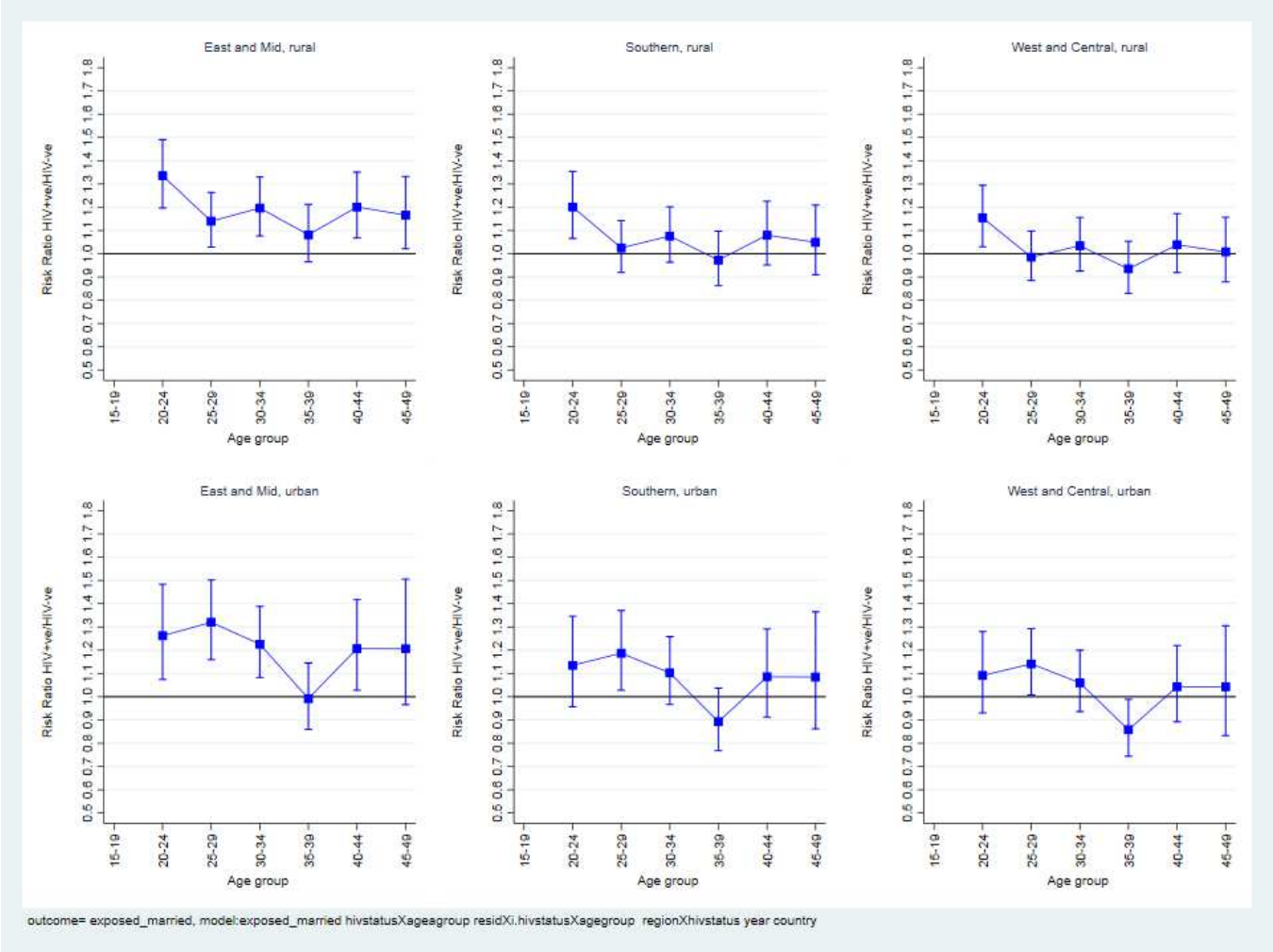
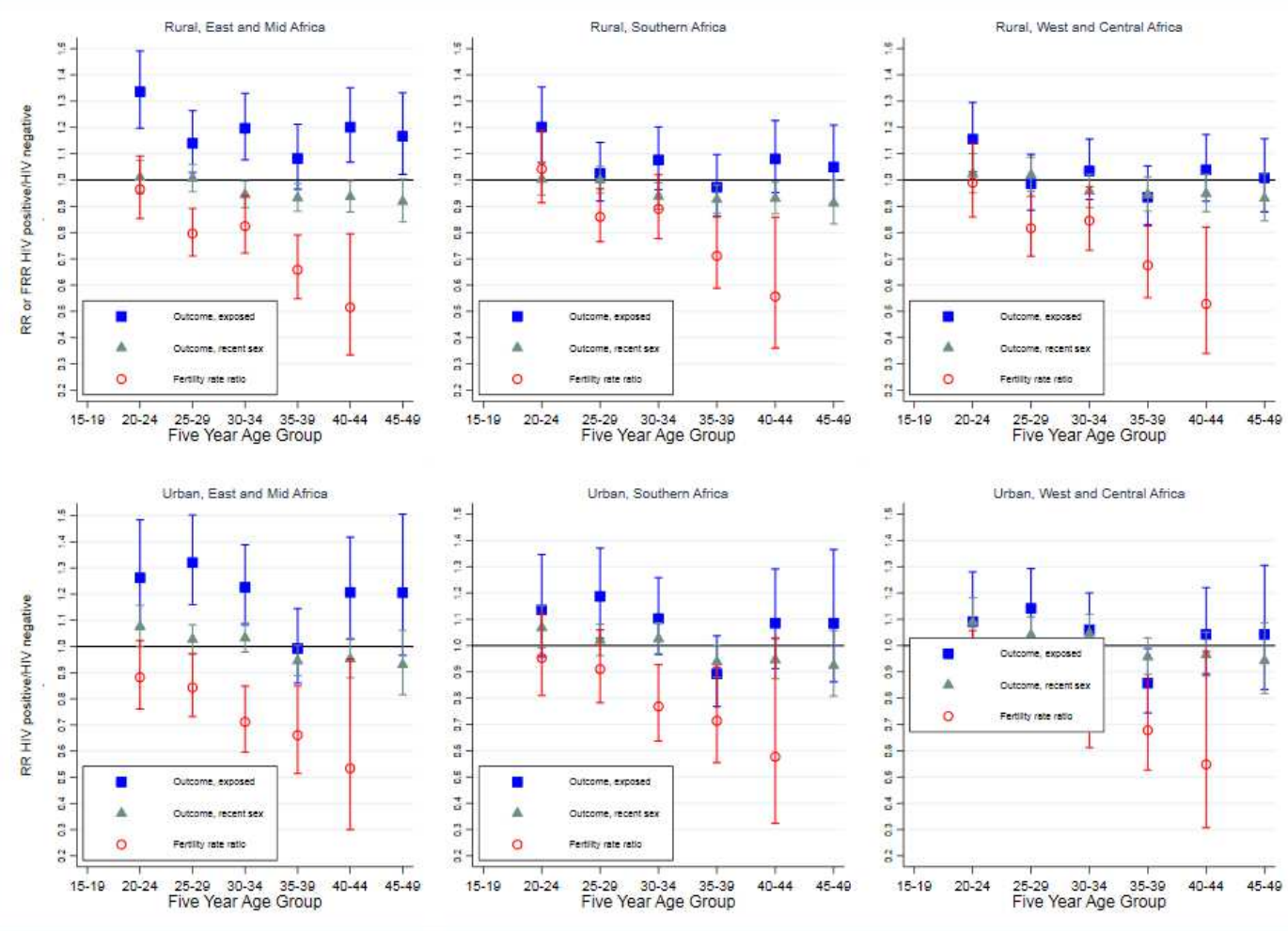


Figure 8.14: Adjusted Risk ratio for recent sex and exposure to a live birth, comparing HIV positive women to negative women with Fertility rate ratio for married women



model: hivstatusXageagroup residXi.hivstatusXagegroup regionXhivstatus year country

Figure 8.15: Adjusted Fertility rate ratio (FRR/RR) for married women

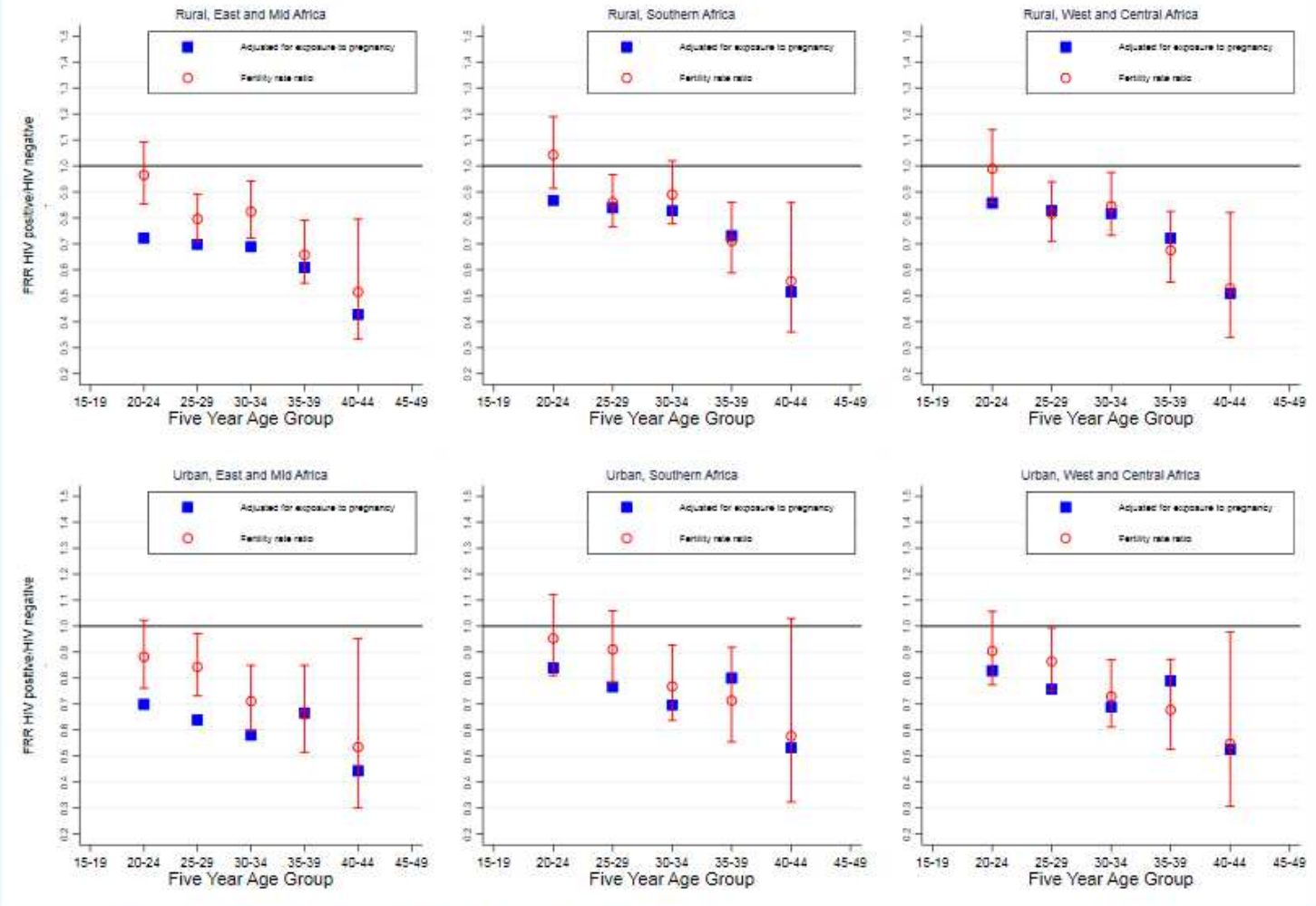
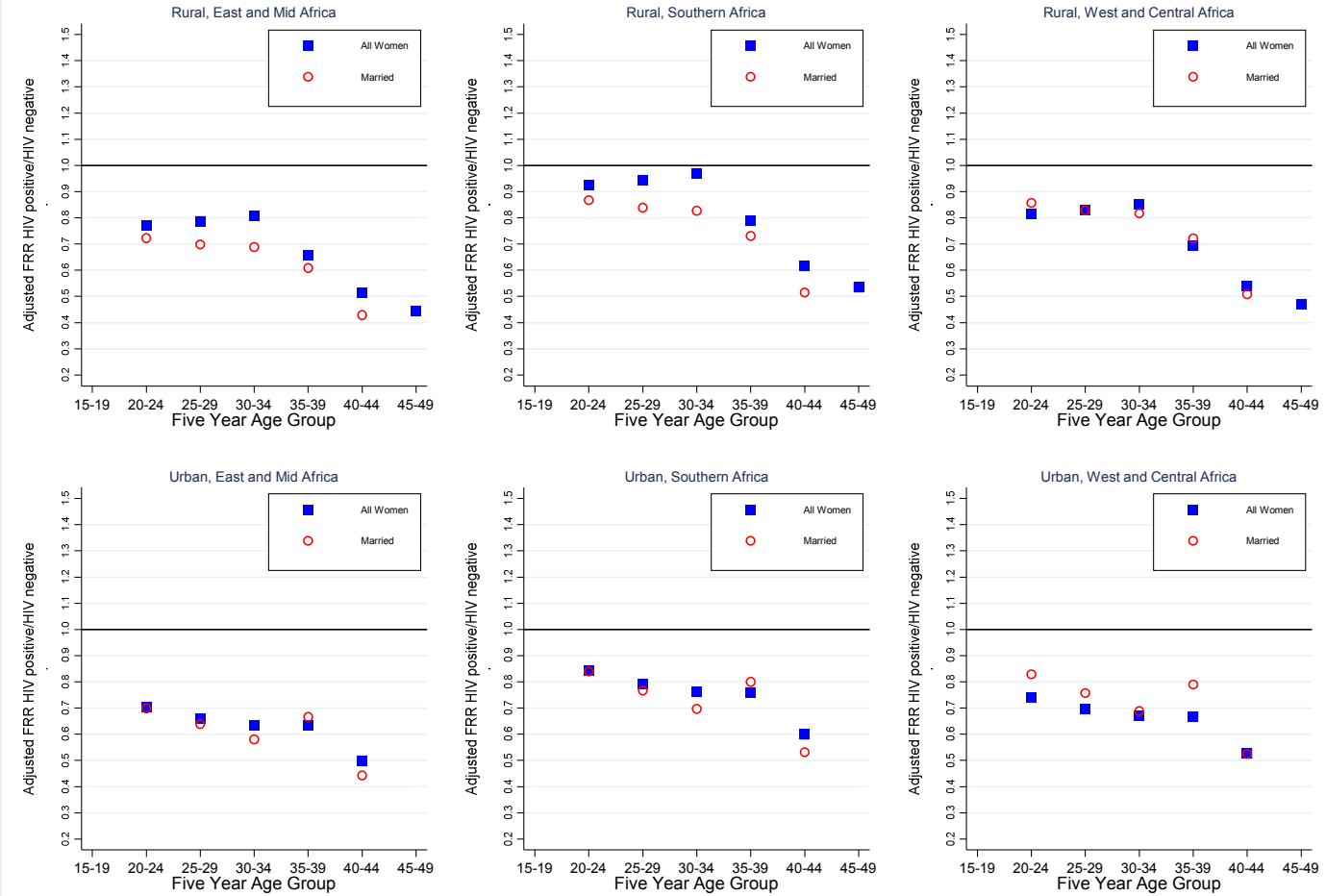


Figure 8.16: Comparing fertility rate ratios adjusted for exposure to pregnancy for all women to married women



model: hivstatusXageagroup residXi.hivstatusXagegroup regionXhivstatus year country

9 Final Discussion

The overall aim of this PhD was to improve empirical evidence to inform estimates of Paediatric HIV. This discussion is divided into three sections on the three distinct topics of this PhD. First paediatric survival from HIV, second the acquisition of HIV in pregnancy and third the impact of HIV on fertility. Each section summarises the key findings, discusses the implications of these findings and make recommendations for future research. The final section is an overall summary. Table 9.1 at the end of this section gives an overview of the main findings from each paper long with how it has influenced estimates of paediatric HIV.

9.1 Paediatric HIV survival

9.1.1 Summary of findings

- Children infected perinatally with HIV have a much higher risk of dying than those infected through breastfeeding
- Differences seen in the survival of children infected perinatally with HIV and through breastfeeding cannot be explained by differences in background mortality, which is much higher in the neonatal period.
- The use of four variants to describe net survival by timing of HIV infection (perinatal and at different breastfeeding durations) improves the realism of child survival when modeling the HIV epidemic.

9.1.2 How has this informed estimates of Paediatric HIV

The work contained in this PhD on Paediatric survival (chapter 3) has been incorporated into models to estimate paediatric HIV, including the Spectrum model used by UNAIDS.

9.1.3 Discussion

Since ART is now widely available, no new data has or will become available on the survival of children infected from HIV in the absence of ART. This means that the study presented in the PhD is the final evidence on the natural history of paediatric survival with HIV.

Limitations of the final estimated double Weibull function are that the survival of children after 2 years old is based on young adult survival patterns. Section 3.3 investigated how changing these assumptions based on data from a European cohort showing more favourable survival in 10-14 year olds compared to 15-19 year olds might change the

paediatric estimates. It concluded that the main effect was to lower AIDS deaths in the 10-14 year olds and increase them in the 15-19 year olds. Matching the resulting estimated prevalence from Spectrum with these new assumptions did not improve its fit to empirical estimates using data from national surveys. After some discussion at the UNAIDS reference group on estimates, projections and modelling as to whether the data from the European cohort (which at young ages was based on Haemophiliacs) should be used to represent African populations it was decided to keep the estimates that were presented in Paper A and section 3.2.

9.2 HIV incidence in pregnancy

9.2.1 Summary of findings

At a population level, pregnancy is protective for the acquisition of HIV compared to non-pregnant and non-postpartum periods. There is no evidence for a difference in the acquisition of HIV in the postpartum period and in non-pregnant periods.

9.2.2 How has this informed estimates of Paediatric HIV

There was a concern that if HIV acquisition in pregnancy had been higher than in non-pregnant women, then estimates of vertical transmission would need to be re-evaluated as in the period immediately after infection viral load is initially high, implying that mother to child transmission is more likely. With evidence from the work presented in this PhD showing that at a population level pregnancy appeared to be protective against HIV acquisition it was decided that a higher rate of incidence among pregnant women should not be assumed in Spectrum.

9.2.3 Discussion

HIV acquisition in pregnancy has continued to be a concern and area of investigation. Shortly after the paper presented in this PhD was published a systematic review was prepared by Drake et al[70]. The authors found five studies that looked at HIV acquisition in pregnancy[56, 57, 59, 176, 177] compared to non-pregnant time; two showed evidence of an increased risk[57, 177] and three showed no evidence of a difference[56, 59, 176]. Based on the meta-analysis of these studies, there was no evidence that pregnancy increased the risk of HIV acquisition (pooled hazard ratio=1.3, 95% CI: 0.5-1.6). However the authors failed to consider the radically different populations these studies were implemented in, which would affect the interpretation of the hazard ratio. Of the two studies that showed evidence for an increased risk in pregnancy one was from a study of serodiscordant couples[57] in which there is an increased risk of the woman's exposure to HIV. The other studies were studies of HIV negative sexually active women, some of whom were at

moderate or high risk of HIV but were not identified as specifically having an HIV positive partner. Therefore these should not have been put into a meta-analysis together. In the study presented in this PhD (not included in Drake at al due to similar publication timing) the population at risk is all HIV negative women in the population regardless of risk of HIV.

Most recently a study of serodiscordant couples by Thomson et al[178] gives evidence of an increased risk of HIV per condomless coital act during pregnancy compared to non-pregnant periods, this study included data from the previous serodiscordant study[57]. This led to a commentary piece in the same journal[71] which finishes with the statement:

"These data serve to emphasize that HIV-seronegative pregnant and postpartum women in HIV-endemic areas need to be considered key populations at high risk for HIV acquisition, requiring urgent attention to the development of interventions to detect HIV seroconversion and initiate ART to prevent transmission to their infants and sexual partners, and even more critically, to maintain their HIV-seronegative status." – Mofenson, 2018, Journal of Infectious diseases.

While it is indeed important to prevent mother to child transmission and help a woman retain her seronegative status it is also important to put this study in the context of the general population where only a small proportion of couples are serodiscordant. It is possible that women who are pregnant (especially those who have been pregnant before) are more likely to be concordant with their partner as they are likely to have had a fairly long sexual history with the father of their child, increasing the risk of HIV transmission prior to the current pregnancy. The study presented in this PhD (Paper B) gave evidence that on a population level pregnancy was actually protective, with the likely explanation that couples were more likely to be concordant during pregnancy. Further work to estimate the number of serodiscordant couples during pregnancy compared to non-pregnant time would enable us to connect up the findings from Thomson et al and the work presented in this PhD to help policy makers understand where best to allocate resources for prevention of HIV infection and mother to child transmission.

9.3 The impact of HIV on fertility

9.3.1 Summary of findings

Key findings from this PhD that inform the differential in fertility among HIV positive and HIV negative women

- Differences in fertility rate comparing HIV positive to HIV negative women at younger ages may be less than previously thought
- There are regional variations in HIV associated subfertility
- Duration of infection is independent of age in its impact on fertility
- Differences in sexual activity and exposure to pregnancy largely explain the steep gradient seen by age in the fertility rate ratios comparing HIV positive to HIV negative women
- After accounting for differences in exposure to pregnancy (defined as recent sexual intercourse without use of contraception), HIV positive women under the age of 30 in urban areas and under 25 in rural areas have a much lower fertility rate than their HIV negative counterparts than previously seen when this exposure was not considered.
- Scale up of ART does not appear to have caused HIV positive women to attain fertility levels similar to HIV negative women.
- Scale up of ART does not appear to have changed the relative differences in exposure to pregnancy between HIV positive and negative women

9.3.2 How has this informed estimates of Paediatric HIV

Work on the impact of HIV on fertility is still being evaluated, however in the last few years the new assumptions about the fertility level discount applied to HIV positive women and the impact of ART on fertility have been implemented in UNAIDS models. The following paragraphs discuss the progress made in improving assumptions about HIV and fertility and include recommendations for further work.

Estimates of fertility rate ratios comparing HIV positive to HIV negative women

Previously the fertility rate ratios used in Spectrum for estimating fertility reduction in HIV positive women came from Chen and Walker[41]. Work from this PhD has re-evaluated these estimates, both their magnitude and how they are implemented in Spectrum. There was concern that the Chen and Walker analysis, based on retrospective data, could be biased due to both misclassification of HIV status and survivorship bias, whereby women who die in the analysis period cannot report on their fertility (and are more likely to be HIV positive and have lower fertility due to illness). General population cohort data such as ALPHA data should be free of these biases and therefore may be

seen as a gold standard. However these data can also be prone to different biases due to missed early infant deaths: a birth and infant death that occur between DSS rounds (typically 6 to 12 months apart in ALPHA sites) may be missed by surveys, and since these are more likely to occur to HIV positive women this would increase the apparent HIV subfertility. Work done in parallel to paper D in this PhD (section 6) calculated age-specific fertility rate ratios using ALPHA network data from four sites. These estimates were then used in later versions of Spectrum from 2017. This initially caused a problem with the estimates which suggested fewer women in need of PMTCT than observed. Therefore, in the light of evidence of heterogeneity by region (seen in Paper D and initial work presented in Paper E, Section 7) a fitting tool was incorporated into the procedure, allowing a scaling of the fertility rate ratios to fit to the number of directly observed pregnant women at ANC when assessing the need for PMTCT.

Following this, paper E of this PhD (Section 7) updated the work of Chen and Walker using 49 DHS and AIS from sub Saharan Africa. This work confirmed that estimates of fertility using the DHS were biased when using data further than one year prior to the survey. The direction of the bias resulted in a higher level of HIV subfertility in younger women and lower level in older women. The analysis in paper E showed that differences in fertility at the population level between HIV positive and HIV negative women at younger ages are small and in some regions negligible, importantly it also showed that there were regional and urban and rural differences in levels of HIV subfertility which had also been noted in paper D, using ALPHA data. The new estimates from paper E were slightly at odds with the fertility rate ratios newly implemented in Spectrum from ALPHA data showing much less HIV subfertility at younger ages. The work expanding on the appendix for paper E in this PhD explored whether biases in either data source could explain the differences and concluded that the number of infant deaths required to be missed in the DSS to explain the differences between the estimates was not plausible. Since it has been demonstrated that there are regional differences one possible explanation is that it is regional differences that explain the differences between DHS data and ALPHA data; the sites used from ALPHA were predominately from rural East Africa which showed the greatest sub fertility. In addition, ALPHA study sites are not nationally representative and may be located in areas that have even higher subfertility.

In the light of this work it was agreed that the regional specific fertility rate ratios derived from Paper E will be used in the next update of Spectrum.

Paper F in this PhD (section 8) demonstrated that the patterns of HIV subfertility change when considering sexual exposure. Adjusting for behavioural exposure to pregnancy risk

increased HIV subfertility at younger ages and decreased it at older ages, thereby removing the steep gradient seen in typical patterns of HIV subfertility by age. The resulting differences in fertility after adjusting for exposure to pregnancy may be attributable to direct biological impacts of HIV if we assume there are no other residual confounders.

If this were the case there are two main things to note, firstly the immediate discount in fertility at young ages occur at a time when the women are likely to be more recently infected; secondly the differences in the levels of fertility impacts over regions. Ross et al[108] found a reduction in fertility from the earliest asymptomatic stage of infection when controlling for age, frequency of sexual intercourse (although not contraceptive use) along with other factors, which corresponds to the findings in Paper F. This could imply the HIV virus itself causes an immediate reduction in fertility. But another biological effect may be due to other Sexually Transmitted Infections (STI), since HIV positive women are more likely to have or have had another STI[179] they could be infertile or sterile from previous or repeated infections. STIs are often more prevalent in younger age groups[180].

The impact STIs might have on the lower fertility of HIV positive women depends on both the prevalence of STIs in the population and differences in STI prevalence between HIV positive and HIV negative women, these two factors may not be correlated. In populations where an STI is very prevalent the differences by HIV status may be lower than in a population with lower prevalence where HIV transmission and STI infection is more strongly associated with higher behavioural risk groups. Published data showing STI prevalence by HIV status in general populations is sparse, and there is very little data on the overall prevalence of STIs in general populations in Sub Saharan Africa. Most data on STI prevalence comes from antenatal clinic settings and studies of pregnant women[180-183]. Data that compare STI prevalence in HIV positive and negative women in antenatal clinics would underestimate the population differences in STI prevalence by HIV for STIs such as Gonorrhoea and Chlamydia which cause infertility leading to fewer women with these infections being found at ANC.

Overall prevalence of STIs in populations varies widely by region[180, 182] which could partly explain differences in the estimated subfertility when accounting for exposure to pregnancy by region, and in urban and rural settings. It would be a useful exercise to try to model the impact of fertility with different levels and differentials in STI prevalence between HIV negative and HIV positive women to see if these could have a significant impact on fertility differentials by HIV status. Recently a study assessed the prevalence of STIs in young people in South Africa[184]. The study was nested in a demographic

surveillance site that is also part of the ALPHA Network. The authors suggested that this proof of concept for population based STI surveillance could be conducted in other similar study sites such as those from the ALPHA network. Since the sites that are part of the ALPHA network have rich longitudinal data on sexual behaviour, HIV status and fertility, nesting STI surveillance within them would not only inform STI prevalence but also enrich studies looking at the impact of STIs on HIV and fertility.

A women's ability to become pregnant also depends on the fertility of her partner. In the absence of ART there is evidence of lower fertility in HIV positive men[95-97], therefore for young HIV positive women with concordant partners this may also impact on their fertility.

The impact of duration of infection

Following evidence that duration of infection has an impact on fertility independent of age it was agreed that parameters for subfertility by stage of infection be incorporated in the Spectrum model. This was in order to take into account the changing composition of duration of infection in each age group as the epidemic matures.

The impact of ART on fertility

Discussions still continue on the impact of ART on fertility, this is a key factor in the current estimates of paediatric HIV and in the future as ART is further scaled up. With most countries now adopting option B+[76] a large proportion of HIV positive women will be on ART therefore the impact of assumptions about their fertility will have a larger impact on Paediatric HIV estimates. In the current version of Spectrum (V5.63) it is assumed that after 6 months an HIV positive women's fertility is the same as HIV negative fertility, this is then scaled up or down to match directly observed ANC data where available. Evidence from this PhD in papers C and E (sections 5 and 7) show that on a population level although there may be a slight narrowing of the differences in fertility between HIV positive and HIV negative women this is not as large as would be expected if it were assumed that HIV positive women on ART have fertility equivalent to their HIV negative counterparts. This is consistent with the systematic review by Yeatman et al[73] concluding that the evidence indicated that fertility increases after the first year on ART but remains lower than in HIV negative women of the same age.

There are many reasons to explain why there is little evidence to support the current assumption that women on ART have the same fertility as HIV negative women. First, there are other biological factors that ART does not influence, such as coinfection with STIs or sterility due to past infection. Secondly a women's ability to become pregnant also depends on the fertility of her partner. In the absence of ART there is evidence of

lower fertility in HIV positive men. ART coverage is higher in women than men so even if a women was on ART her partner may not be. There is evidence that HIV positive men have lower fertility due to lower quality semen that HIV negative men[81]. Thirdly, different drug regimes may also effect fertility in different ways and these have changed over time, for example one of the current recommended first line treatments include Efavirenz[185] for which there is evidence that it can lessen contraceptive efficacy of hormonal implants[186] and may decrease fertility in men[104].

Paper F (section 8) shows no evidence of a change in exposure to pregnancy between HIV positive and HIV negative women with higher national ART coverage indicating that the behavioural component of HIV-associated subfertility has not changed. Paper F found no evidence of a change in the differences in marriage between HIV positive and HIV negative women with increased national ART coverage. There is lower coverage of ART in men compared to women, implying that widowhood would not necessarily be reduced as much as might be expected from overall national ART coverage levels. Separation and divorce may not necessarily change, particularly if the women's partner is HIV negative. HIV positive women who attend CTC may be more likely to have access to family planning due to being in contact with a health facility, and to being counselled about family planning. So it is possible that even if HIV positive women's fecundity improves on ART this is counteracted by more widespread use of contraceptives. However Paper F found no evidence for a change in the relative difference between HIV positive and HIV negative women in modern contraceptive use for those who had reported recent sex

Since around 2005 when ART began to be scaled up in sub Saharan Africa the underlying population on ART has changed and so have recommended drug regimes. Along with this the proportion of HIV positive women with knowledge of their HIV status is increasing. All these changes cause problems when trying to estimate paediatric HIV as estimation of the impact of ART on fertility itself appears to be a moving target.

For estimating the number of children born to HIV positive mothers on or off ART, there are three groups of HIV positive women, those who have not attended CTC, those in CTC but not on ART and finally those on ART. Since there are major selection effects when considering women on ART we also need to consider the women in the general population who are not on treatment. These women could be healthy and possibly not aware of their HIV status, they could be ill and not have been able to seek treatment, or they could be less fertile or sterile due to HIV and STI co infections and thus not have been referred through ANC. Therefore in estimating fertility differences, assuming an

increase in the fertility of HIV positive women on ART may imply a need to decrease it for infected women who are not on ART. An ideal place to compare these three groups of HIV positive women along with HIV negative women is to use data from the ALPHA network: two of these study sites have already looked at this[77, 80] and found no evidence of a difference between fertility of HIV positive women on ART compared to those not on treatment. Increasing the number of sites and follow up time would help us understand the fertility in the different populations and enable us to investigate the inherent biases in these analyses.

The composition of the population on ART could vary in a number of ways over time. Initially as ART is introduced it is likely that there is a high proportion of women on ART who initiated treatment at an advanced stage of disease because they are identified as in need of treatment due to illness. The other important group will be women who are referred from ANC and found to have a CD4 count below the WHO cut off at the time. As scale up of ART continues, the composition will change: firstly because women not coming via ANC referral will have a larger range of disease stages at ART initiation due to increased coverage of VCT. As WHO guidelines change with the introduction of option B+ pregnant women who initiate ART will initially present at a wide range of ages and parities. This will increase the proportion of healthier women on ART, and possibly the proportions of younger, lower parity women who would have been above the CD4 cut-off under options A and B. After option B+ has been in operation over a longer period, the composition of women of child bearing ages on ART should gradually stabilise, although there may be changes in the number of referrals through VCT of infertile women and those prior to child bearing, which could change the age composition. Understanding the composition of women on ART, by age, CD4 count, pregnancy status at initiation, how they were referred at initiation, and how these factors change over time could help us understand reasons for the fertility differences (or lack of difference) between women on and off ART. It would also help us infer how the population not at CTC clinics might be changing. Networks such as the IeDEA network (International Epidemiology Databases to Evaluate AIDS) [187] which is an international network of care and treatment clinics including Sub Saharan Africa, are ideally placed to look at such data.

Table 9.1: Summary of main findings and how there have informed estimates of paediatric HIV.

	Paper Title	Main finding	How has this informed estimates of paediatric HIV?
A	Net survival of perinatally and postnatally HIV-infected children: A pooled analysis of individual data from sub-Saharan Africa	Those children infected perinatally had a much higher risk of dying than those infected through breastfeeding, even allowing for background mortality. The final fitted double Weibul curves gave 75% survival at five months after infection for perinatally-infected, and 1.1 years for postnatally-infected children. An estimated 25% of the early infected children would still be alive at 10.6 years compared to 16.9 years for those infected through breastfeeding.	For modelling of paediatric HIV, the increase in available data has enabled separation of child mortality patterns by timing of infection allowing improvement and more flexibility in modelling of paediatric HIV infection and survival. This work has been incorporated into models to estimate paediatric HIV, including the Spectrum model used by UNAIDS. Previously the single curve used to describe survival post infection of children assumed they would all die before the age of 15. These curves reduced the HIV mortality in the 10-14 year olds and cause a large increase in the proportion of HIV positive women in the 15-24 year old age groups who were infected through mother to child transmission.
	Research (report for UNAIDS) an update to the paediatric curve	Changing the assumption of child survival from HIV where there is no empirical data available deferred AIDS deaths to older ages.	This paper demonstrated possible ways in which the paediatric survival from HIV used in HIV modelling could be changed. The current decision is that, in the absence of more empirical evidence the original estimates from paper A should continue to be used.
B	"Is the risk of HIV acquisition increased during and immediately after pregnancy? A secondary analysis of pooled HIV community-based studies from the ALPHA network".	Although there may be immunological reasons for increased risk of HIV acquisition during pregnancy, at a population level this study indicates a lower risk of HIV acquisition for pregnant women and a similar risk in the first year post partum.	For modelling of Paediatric HIV, this suggests that is no need to increase the proportion of HIV positive women who are considered an incident infection. When planning policies relating to higher transmission of HIV in pregnancy and the postpartum period, the population level should be considered to estimate how many women may be at risk and whether targeting them is the most cost effect way of preventing MTCT.
C	"Measuring the Impact of antiretroviral therapy roll-out on population level fertility in three African countries"	Differences in fertility between HIV positive and HIV negative women are narrowing over time as ART becomes more widely available in these communities.	This provides evidence that routine adjustment of ANC data for estimating national HIV prevalence will need to allow for the impact of treatment.

Table 9.1: continued

	Paper Title	Main finding	How has this informed estimates of paediatric HIV?
D	"The effects of HIV on fertility by infection duration: evidence from African population cohorts before ART availability"	Longer duration of infection is associated with greater relative fertility reduction for HIV-positive women.	This should be considered when creating estimates for HIV prevalence among pregnant women and PMTCT need over the course of the HIV epidemic and ART scale-up. Duration of infection has now been incorporated into the Spectrum model used by UNAIDS.
E	"The relationship between HIV and fertility in the era of antiretroviral therapy in sub Saharan Africa – Evidence from 49 Demographic & Health Surveys"	Significant regional differences exist in HIV and fertility relationships, with less HIV-associated subfertility in Southern Africa. Age patterns of relative fertility are similar. HIV impact on fertility is weaker in urban than rural areas. For women below age 30, regional and urban/rural differences are largely explained by differences in age at sexual debut. Higher levels of national ART coverage appear to slightly attenuate the relationship between HIV and fertility.	Regional differences in HIV-associated subfertility and urban/rural differences in age patterns of relative fertility should be accounted for when predicting need for and coverage of PMTCT services at national and subnational level. Although HIV impacts on fertility are somewhat reduced at higher levels of national ART coverage, differences in fertility between HIV positive and negative remain, and fertility of women on ART should not be assumed to be the same as HIV-negative women. The new estimates from this paper about the fertility level discount applied to HIV positive women and the impact of ART on fertility have been implemented in UNAIDS models.
F	"Relative patterns of sexual activity and fertility among HIV positive and negative women – evidence from 46 DHS"	Exposure to pregnancy differs significantly between HIV positive and negative women by age, modified by region. Younger HIV positive women have a higher exposure to pregnancy that HIV negative women and the opposite is true at older ages. The switch occurs at 25-29 for rural women and 30-34 for urban women. The direct effects of HIV on fertility are broadly similar across ages, while the dramatic age gradient that has frequently been observed is largely attributable to variation in relative sexual exposure by age.	For modelling of the epidemic, consideration should be given to possible changes in sexual activity in the era of ART that may change the differences in fertility in HIV positive women compared to HIV negative women. Also there is some evidence that the discount in HIV positive women's fertility may be seen start after infection when accounting for sexual activity, this could suggest that some of the subfertility seen in HIV positive women may be due to other factors such as STIs or a reduction in their partners fertility if they are HIV positive. Since ART in women cannot improve these determinants of lower fertility, it is possible that we will not see a large improvement at a population level of the fertility in HIV positive women with increased ART roll out.

9.4 Key strengths and weaknesses of data sources

This PhD uses data from a number of sources, clinical cohort studies, cross sectional nationally representative surveys with retrospective reporting and community based demographic and HIV surveillance sites. Each has its strengths and weaknesses in relation to the analyses in this PhD which are discussed in the individual chapters, the key issues are discussed below.

The clinical cohort studies used in this PhD (section 3) have significant strength in being able to accurately identify the timing of HIV infection in infants born to HIV positive mothers using frequent testing from birth, this enabled me to look at survival post infection by timing of infection. One of the weaknesses of these studies is that the follow up time is very short, and there is only follow up to around 2.5 years post infection for perinatally infected children and only 1.5 years for those infected during breastfeeding. Another weakness with clinical cohort studies is the increase the participants may have in contact with medical services compared to if they were not part of the trial. Indeed some of the studies explicitly stated that they provided medical care to the participants[16]. This may mean that they do not reflect the experience of the general population. I calculated the net survival to remove this bias, as it takes into account the lower background mortality experienced by trial participants, however if treatment averts the death of an HIV positive child with a condition that an HIV negative child would have survived from, the bias may persist and cause an underestimate in paediatric survival from HIV.

There is great strength in community based demographic and HIV surveillance sites such as those from the ALPHA network[9] as they represent the experience of a general population. The longitudinal nature of the data allows for knowledge of timing of events such as HIV acquisition and births. There are a number of weaknesses using this data when analysing pregnancy or birth data, these vary across the study sites depending on data collection methods. One is that for many of the studies either since inception or for significant time periods, demographic data has only been collected annually[9] which means that it is possible events are missed such as early infant deaths as they are born and die in the inter census period. This could cause an underestimation of fertility. Some studies use village informers to capture inter census events at the time of the event to go some way to minimise this problem[25]. Often proxy respondents are used to answer questions on pregnancies in the household which may mean underreporting. Another issue is that the source of HIV test data from surveillance rounds may be two or three years apart[9] giving long sero-conversion intervals. Thus, for the analysis of HIV acquisition in pregnancy we only know that a woman was pregnant at some point during

the interval but do not know if the sero-conversion occurred before, during, or immediately after, the pregnancy. However the imputation method I used enabled me to allow for this uncertainty and to generate confidence intervals to reflect this.

Demographic and health surveys offer nationally representative data and the core questionnaire has been standardised to ensure comparability across populations and over time[36]. There are a number of limitations this data has for the analyses in this PhD, one major limitation in the analysis of HIV and fertility is the cross sectional nature of the survey. In these analysis we use retrospective reporting of births, therefore the time period is prior to the survey. We know HIV status at the time of the survey but do not know when the women sero-converted, therefore we must make an assumption of a women's HIV status prior to the survey. An HIV negative women will be HIV negative but an HIV positive women will only have been positive since sero-conversion which is an unknown time point. Therefore the more person years we go back prior to the survey assuming an HIV positive women was still positive the more there will be wrongly attributed negative person years contributing to this group. Analysis of this bias concluded that going further than one year prior to the survey biased the data enough that it should not be included (section 7.2).

For two of the studies (Papers E and F) in the absence of any other information I used estimates of ART coverage in adult women from UNAIDS estimates[167]. Therefore the national ART coverage used is an ecological variable. It does not measure individual exposure to treatment, and hence we have to be cautious about attributing causality, for example countries with better roll out of ART may also have other things in common such as good health systems, with better provision of family planning services. One benefit of an ecological measure is has the potential to include the indirect effects of ART on HIV positive women in the ART era that individual ART usage will not. For example it may be possible that knowledge of ART availability may increase the desire to have another child even if the women is not on treatment.

9.5 Conclusions

The work in this PhD has informed estimates of paediatric HIV through providing empirical evidence upon which assumptions can be based. It has provided:

- estimates of paediatric HIV survival in the absence of ART,
- evidence that at the population level there is no indication of an increased risk of HIV acquisition during pregnancy and the postpartum period that is seen in studies of selected populations such as serodiscordant couples,
- improved estimates of age specific subfertility due to accounting for bias in the data,
- evidence that there are regional and urban rural differentials in HIV subfertility
- added to the body of evidence that although the fertility differentials between HIV positive and HIV negative women appear to be narrowing slightly in the era of ART this is not enough to assume that an HIV positive women on ART's fertility returns to that of her HIV negative counterparts.

Empirical evidence is essential to validate estimates of paediatric HIV. Understanding the underlying mechanisms of population effects of HIV on fertility is essential in order to understand what might happen as ART is scaled up in populations. This PhD work provides evidence that sexual activity, which is highly age-dependant, plays a large part in HIV subfertility and may mask biological impacts that vary relatively little by age.

Along with the importance of informing paediatric HIV estimates, this work also highlights the need for more data on STIs and family planning that need to be collected in general population studies in order to understand more the role of behavioural factors such as family planning and sexual activity and bio-medical factors such as the role of co-infection with other STIs and the direct impact of HIV infection on fertility.

10 References

1. UNAIDS, *Global Plan Towards the Elimination of New HIV Infections Among Children by 2015 and Keeping Mothers Alive*, J.U.N.P.o.H.A. (UNAIDS);, Editor. 2011, Joint United Nations Programme on HIV/AIDS (UNAIDS): Geneva.
2. UNAIDS, *On the fast-track to an AIDS free generation*, UNAIDS, Editor. 2016: Geneva.
3. Stover, J., et al., *Updates to the Spectrum/Estimations and Projections Package model for estimating trends and current values for key HIV indicators.* AIDS, 2017. **31 Suppl 1**: p. S5-S11.
4. Health, A. *Spectrum* 2018 [cited 2018 3/1/2018]; Available from: http://www.avenirhealth.org/software-spectrum.php.
5. Marston, M., et al., *Estimating 'net' HIV-related mortality and the importance of background mortality rates.* AIDS, 2007. **21 Suppl 6**: p. S65-71.
6. Marston, M., et al., *Estimating the net effect of HIV on child mortality in African populations affected by generalized HIV epidemics.* J Acquir Immune Defic Syndr, 2005. **38**(2): p. 219-27.
7. Todd, J., et al., *Time from HIV seroconversion to death: a collaborative analysis of eight studies in six low and middle-income countries before highly active antiretroviral therapy.* Aids, 2007. **21 Suppl 6**: p. S55-63.
8. UNAIDS reference group on estimates, m.a.p. *UNAIDS reference group on estimates, modelling and projections*. 2018 [cited 2018 09/03/18]; Available from: http://www.epidem.org/.
9. Reniers, G., et al., *Data Resource Profile: Network for Analysing Longitudinal Population-based HIV/AIDS data on Africa (ALPHA Network).* Int J Epidemiol, 2016.
10. Marston, M., K. Harriss, and E. Slaymaker, *Non-response bias in estimates of HIV prevalence due to the mobility of absentees in national population-based surveys: a study of nine national surveys.* Sex Transm Infect, 2008. **84 Suppl 1**: p. i71-i77.
11. Marston, M., et al., *Trends in marriage and time spent single in sub-Saharan Africa: a comparative analysis of six population-based cohort studies and nine Demographic and Health Surveys.* Sex Transm Infect, 2009. **85 Suppl 1**: p. i64-71.
12. Becquet, R., et al., *Survival of Children HIV-Infected Perinatally or through Breastfeeding. A pooled analysis of individual data from sub-saharan Africa*, in *The 17th Conference on Retroviruses and Opportunistic Infections* 2010: San Francisco, USA.
13. Marston, M., et al., *Net survival of perinatally and postnatally HIV-infected children: a pooled analysis of individual data from sub-Saharan Africa.* Int J Epidemiol, 2011. **40**(2): p. 385-96.
14. Coovadia, H.M., et al., *Mother-to-child transmission of HIV-1 infection during exclusive breastfeeding in the first 6 months of life: an intervention cohort study.* Lancet, 2007. **369**(9567): p. 1107-16.
15. Dabis, F., et al., *18-Month mortality and perinatal exposure to zidovudine in West Africa.* AIDS, 2001. **15**(6): p. 771-9.
16. Humphrey, J.H., et al., *Effects of a single large dose of vitamin A, given during the postpartum period to HIV-positive women and their infants, on child HIV infection, HIV-free survival, and mortality.* J Infect Dis, 2006. **193**(6): p. 860-71.
17. Jackson, D.J., et al., *Operational effectiveness and 36 week HIV-free survival in the South African programme to prevent mother-to-child transmission of HIV-1.* AIDS, 2007. **21**(4): p. 509-16.
18. Kilewo, C., et al., *Prevention of mother-to-child transmission of HIV-1 through breastfeeding by treating mothers with triple antiretroviral therapy in Dar es Salaam, Tanzania: the Mitra Plus study.* J Acquir Immune Defic Syndr, 2009. **52**(3): p. 406-16.

19. Petra Study Team, *Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial.* Lancet, 2002. **359**(9313): p. 1178-86.
20. Thior, I., et al., *Breastfeeding plus infant zidovudine prophylaxis for 6 months vs formula feeding plus infant zidovudine for 1 month to reduce mother-to-child HIV transmission in Botswana: a randomized trial: the Mashi Study.* JAMA, 2006. **296**(7): p. 794-805.
21. Becquet, R., et al., *Two-year morbidity-mortality and alternatives to prolonged breast-feeding among children born to HIV-infected mothers in Cote d'Ivoire.* PLoS Med, 2007. **4**(1): p. e17.
22. Wiktor, S.Z., et al., *Short-course oral zidovudine for prevention of mother-to-child transmission of HIV-1 in Abidjan, Cote d'Ivoire: a randomised trial.* Lancet, 1999. **353**(9155): p. 781-5.
23. Coutsoudis, A., et al., *Randomized trial testing the effect of vitamin A supplementation on pregnancy outcomes and early mother-to-child HIV-1 transmission in Durban, South Africa. South African Vitamin A Study Group.* AIDS, 1999. **13**(12): p. 1517-24.
24. Mandelbrot, L., et al., *15 Month follow up of African children following vaginal cleansing with benzalkonium chloride of their HIV infected mothers during late pregnancy and delivery.* Sex Transm Infect, 2002. **78**(4): p. 267-70.
25. Crampin, A.C., et al., *Profile: the Karonga Health and Demographic Surveillance System.* Int J Epidemiol, 2012. **41**(3): p. 676-85.
26. Floyd, S., et al., *Underestimation of HIV prevalence in surveys when some people already know their status, and ways to reduce the bias.* Aids, 2013. **27**(2): p. 233-42.
27. Mwaluko, G., et al., *Trends in HIV and sexual behaviour in a longitudinal study in a rural population in Tanzania, 1994-2000.* AIDS, 2003. **17**(18): p. 2645-51.
28. Gregson, et al., *HIV decline associated with behavior change in Eastern Zimbabwe.* Science, 2006. **311**(5761): p. 664-666.
29. Lopman, B., et al., *HIV incidence and poverty in Manicaland, Zimbabwe: is HIV becoming a disease of the poor?* AIDS, 2007. **21 Suppl 7**: p. S57-66.
30. Asiki, G., et al., *The general population cohort in rural south-western Uganda: a platform for communicable and non-communicable disease studies.* Int J Epidemiol, 2013. **42**(1): p. 129-41.
31. Biraro, S., et al., *The role of vertical transmission and health care-related factors in HIV infection of children: a community study in rural Uganda.* J Acquir Immune Defic Syndr, 2007. **44**(2): p. 222-8.
32. Shafer, L.A., et al., *HIV prevalence and incidence are no longer falling in southwest Uganda: evidence from a rural population cohort 1989-2005.* AIDS, 2008. **22**(13): p. 1641-9.
33. Wawer, M.J., et al., *Declines in HIV Prevalence in Uganda: Not as Simple as ABC*, in *12th Conference on Retroviruses and Opportunistic Infections*. 2005: Boston.
34. Tanser, F., et al., *Cohort Profile: Africa Centre Demographic Information System (ACDIS) and population-based HIV survey.* Int J Epidemiol, 2008. **37**(5): p. 956-62.
35. Tanser, F., et al., *High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa.* Science, 2013. **339**(6122): p. 966-71.
36. Corsi, D.J., et al., *Demographic and health surveys: a profile.* Int J Epidemiol, 2012. **41**(6): p. 1602-13.
37. Mishra, V., et al., *HIV testing in national population-based surveys: experience from the Demographic and Health Surveys.* Bull World Health Organ, 2006. **84**(7): p. 537-45.

38. Downs, A.M., G. Salamina, and R.A. Ancelle Park, *Incubation period of vertically acquired AIDS in Europe before widespread use of prophylactic therapies.* J Acquir Immune Defic Syndr Hum Retrovirol, 1995. **9**(3): p. 297-304.
39. Marshall, A., et al., *Combining estimates of interest in prognostic modelling studies after multiple imputation: current practice and guidelines.* BMC Med Res Methodol, 2009. **9**: p. 57.
40. ICF International. *The DHS Program*. [cited 2017; Available from: http://dhsprogram.com/.
41. Chen, W.J. and N. Walker, *Fertility of HIV-infected women: insights from Demographic and Health Surveys.* Sex Transm Infect, 2010. **86 Suppl 2**: p. ii22-7.
42. Rutstein, S.R., G., *Guide to DHS statistics*. 2006, Calverton, Maryland Demographic and Health Surveys, ORC Macro.
43. Marston, M., et al., *The effects of HIV on fertility by infection duration: evidence from African population cohorts before ART availability: Fertility by duration of HIV infection.* AIDS, 2016.
44. Zou, G., *A modified poisson regression approach to prospective studies with binary data.* Am J Epidemiol, 2004. **159**(7): p. 702-6.
45. Marston, M., B. Zaba, and J.W. Eaton, *The relationship between HIV and fertility in the era of antiretroviral therapy in sub-Saharan Africa: evidence from 49 Demographic and Health Surveys.* Trop Med Int Health, 2017. **22**(12): p. 1542-1550.
46. Petersen, M.R. and J.A. Deddens, *A comparison of two methods for estimating prevalence ratios.* BMC Med Res Methodol, 2008. **8**: p. 9.
47. Schwartlander, B., et al., *Country-specific estimates and models of HIV and AIDS: methods and limitations.* AIDS, 1999. **13**(17): p. 2445-58.
48. Mahy, M., et al., *Improving estimates of children living with HIV from the Spectrum AIDS Impact Model.* AIDS, 2017. **31 Suppl 1**: p. S13-S22.
49. Nicoll, A., et al., *Infant feeding and HIV-1 infection.* AIDS, 2000. **14 Suppl 3**: p. S57-74.
50. The UNAIDS Reference Group on Estimates Modelling and Projections, *Improved methods and assumptions for estimation of the HIV/AIDS epidemic and its impact: Recommendations of the UNAIDS Reference Group on Estimates, Modelling and Projections.* AIDS, 2002. **16**: p. W1-W14.
51. Newell, M.L., et al., *Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis.* Lancet, 2004. **364**(9441): p. 1236-43.
52. Stover, J., T. Brown, and M. Marston, *Updates to the Spectrum/Estimation and Projection Package (EPP) model to estimate HIV trends for adults and children.* Sex Transm Infect, 2012. **88 Suppl 2**: p. i11-6.
53. Machiyama, K., *A Re-examination of Recent Fertility Declines in Sub-Saharan Africa*, in *DHS Working Papers No. 68*. 2010, ICF Macro: Calverton, Maryland, USA.
54. Gray, R.H., et al., *Increased risk of incident HIV during pregnancy in Rakai, Uganda: a prospective study.* Lancet, 2005. **366**(9492): p. 1182-8.
55. Leroy, V., et al., *Seroincidence of HIV-1 infection in African women of reproductive age: a prospective cohort study in Kigali, Rwanda, 1988-1992.* AIDS, 1994. **8**(7): p. 983-6.
56. Morrison, C.S., et al., *Pregnancy and the risk of HIV-1 acquisition among women in Uganda and Zimbabwe.* AIDS, 2007. **21**(8): p. 1027-34.
57. Mugo, N.R., et al., *Increased risk of HIV-1 transmission in pregnancy: a prospective study among African HIV-1-serodiscordant couples.* AIDS, 2011. **25**(15): p. 1887-95.
58. Munjoma, M.W., et al., *The incidence of HIV among women recruited during late pregnancy and followed up for six years after childbirth in Zimbabwe.* BMC Public Health, 2010. **10**: p. 668.

59. Reid, S.E., et al., *Pregnancy, contraceptive use, and HIV acquisition in HPTN 039: relevance for HIV prevention trials among African women.* J Acquir Immune Defic Syndr, 2010. **53**(5): p. 606-13.
60. Taha, T.E., et al., *Trends of HIV-1 and sexually transmitted diseases among pregnant and postpartum women in urban Malawi.* AIDS, 1998. **12**(2): p. 197-203.
61. Garcia, P.M., et al., *Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. Women and Infants Transmission Study Group.* N Engl J Med, 1999. **341**(6): p. 394-402.
62. Black, V., et al., *High HIV incidence or poor test performance?* AIDS, 2009. **23**(16): p. 2234-5; author reply 2235-6.
63. Mbizvo, M.T., et al., *HIV-1 seroconversion incidence following pregnancy and delivery among women seronegative at recruitment in Harare, Zimbabwe.* Cent Afr J Med, 2001. **47**(5): p. 115-8.
64. Moodley, D., et al., *High HIV incidence during pregnancy: compelling reason for repeat HIV testing.* AIDS, 2009. **23**(10): p. 1255-9.
65. Mepham, S., *Primary HIV in Pregnancy in Northern KwaZulu-Natal, South Africa, and its impact on mother-to-child transmission*. 2011, University of Aberdeen.
66. Rice, B.D., et al., *Population and antenatal-based HIV prevalence estimates in a high contracepting female population in rural South Africa.* BMC Public Health, 2007. **7**: p. 160.
67. Humphrey, J.H., et al., *HIV incidence among post-partum women in Zimbabwe: risk factors and the effect of vitamin A supplementation.* AIDS, 2006. **20**(10): p. 1437-46.
68. Marston, M., et al., *Is the risk of HIV acquisition increased during and immediately after pregnancy? A secondary analysis of pooled HIV community-based studies from the ALPHA network.* PLoS One, 2013. **8**(12): p. e82219.
69. Chetty, T., et al., *Incident HIV during pregnancy and early postpartum period: a population-based cohort study in a rural area in KwaZulu-Natal, South Africa.* BMC Pregnancy Childbirth, 2017. **17**(1): p. 248.
70. Drake, A.L., et al., *Incident HIV during pregnancy and postpartum and risk of mother-to-child HIV transmission: a systematic review and meta-analysis.* PLoS Med, 2014. **11**(2): p. e1001608.
71. Mofenson, L.M., *Risk of HIV Acquisition during Pregnancy and Postpartum: A Call for Action.* J Infect Dis, 2018.
72. Lewis, J.J., et al., *The population impact of HIV on fertility in sub-Saharan Africa.* AIDS, 2004. **18 Suppl 2**: p. S35-43.
73. Yeatman, S., et al., *Impact of ART on the fertility of HIV-positive women in sub-Saharan Africa.* Trop Med Int Health, 2016.
74. Elul, B., et al., *Untangling the Relationship Between Antiretroviral Therapy Use and Incident Pregnancy: A Marginal Structural Model Analysis Using Data From 47,313 HIV-Positive Women in East Africa.* J Acquir Immune Defic Syndr, 2016. **72**(3): p. 324-32.
75. (WHO), W.H.O., *Programmatic Update: Use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants*, W.H.O. (WHO), Editor. 2012, World Health Organization (WHO): Switzerland.
76. (WHO), W.H.O., *Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV*, WHO, Editor. 2015: Switzerland.
77. Gregson, S., et al., *Do HIV prevalence trends in antenatal clinic surveillance represent trends in the general population in the antiretroviral therapy era? The case of Manicaland, East Zimbabwe.* AIDS, 2015. **29**(14): p. 1845-53.
78. Marston, M., et al., *Measuring the Impact of Antiretroviral Therapy Roll-Out on Population Level Fertility in Three African Countries.* PLoS One, 2016. **11**(3): p. e0151877.
79. Souza, E. and T. Moultrie, *Estimating the effect of HIV/AIDS on fertility among Malawian women using demographic and health survey data.* African Journal of AIDS Research, 2015. **14**(4): p. 315-321.

80. McLean, E., et al., *Changes in Fertility at the Population Level in the Era of ART in Rural Malawi.* J Acquir Immune Defic Syndr, 2017. **75**(4): p. 391-398.
81. Kushnir, V.A. and W. Lewis, *Human immunodeficiency virus/acquired immunodeficiency syndrome and infertility: emerging problems in the era of highly active antiretrovirals.* Fertil Steril, 2011. **96**(3): p. 546-53.
82. Garolla, A., et al., *Sperm viral infection and male infertility: focus on HBV, HCV, HIV, HPV, HSV, HCMV, and AAV.* J Reprod Immunol, 2013. **100**(1): p. 20-9.
83. Kojic, E.M., C.C. Wang, and S. Cu-Uvin, *HIV and menopause: a review.* J Womens Health (Larchmt), 2007. **16**(10): p. 1402-11.
84. Imai, K., et al., *HIV and Menopause: A Systematic Review of the Effects of HIV Infection on Age at Menopause and the Effects of Menopause on Response to Antiretroviral Therapy.* Obstet Gynecol Int, 2013. **2013**: p. 340309.
85. Tsevat, D.G., et al., *Sexually transmitted diseases and infertility.* Am J Obstet Gynecol, 2017. **216**(1): p. 1-9.
86. Brocklehurst, P. and R. French, *The association between maternal HIV infection and perinatal outcome: a systematic review of the literature and meta-analysis.* Br J Obstet Gynaecol, 1998. **105**(8): p. 836-48.
87. Wedi, C.O., et al., *Perinatal outcomes associated with maternal HIV infection: a systematic review and meta-analysis.* Lancet HIV, 2016. **3**(1): p. e33-48.
88. Bulterys, M., et al., *Maternal human immunodeficiency virus 1 infection and intrauterine growth: a prospective cohort study in Butare, Rwanda.* Pediatr Infect Dis J, 1994. **13**(2): p. 94-100.
89. Ladner, J., et al., *Chorioamnionitis and pregnancy outcome in HIV-infected African women. Pregnancy and HIV Study Group.* J Acquir Immune Defic Syndr Hum Retrovirol, 1998. **18**(3): p. 293-8.
90. Selwyn, P.A., et al., *Prospective study of human immunodeficiency virus infection and pregnancy outcomes in intravenous drug users.* JAMA, 1989. **261**(9): p. 1289-94.
91. Gomez, G.B., et al., *Untreated maternal syphilis and adverse outcomes of pregnancy: a systematic review and meta-analysis.* Bull World Health Organ, 2013. **91**(3): p. 217-26.
92. Chen, J.Y., et al., *Highly active antiretroviral therapy and adverse birth outcomes among HIV-infected women in Botswana.* J Infect Dis, 2012. **206**(11): p. 1695-705.
93. Moodley, D., et al., *A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1.* J Infect Dis, 2003. **187**(5): p. 725-35.
94. Zash, R., et al., *Comparative Safety of Antiretroviral Treatment Regimens in Pregnancy.* JAMA Pediatr, 2017. **171**(10): p. e172222.
95. Dondero, F., et al., *Semen analysis in HIV seropositive men and in subjects at high risk for HIV infection.* Hum Reprod, 1996. **11**(4): p. 765-8.
96. Muller, C.H., R.W. Coombs, and J.N. Krieger, *Effects of clinical stage and immunological status on semen analysis results in human immunodeficiency virus type 1-seropositive men.* Andrologia, 1998. **30 Suppl 1**: p. 15-22.
97. Nicopoullos, J.D., et al., *The effect of human immunodeficiency virus on sperm parameters and the outcome of intrauterine insemination following sperm washing.* Hum Reprod, 2004. **19**(10): p. 2289-97.
98. Dulioust, E., et al., *Semen alterations in HIV-1 infected men.* Hum Reprod, 2002. **17**(8): p. 2112-8.
99. Politch, J.A., et al., *The effects of disease progression and zidovudine therapy on semen quality in human immunodeficiency virus type 1 seropositive men.* Fertil Steril, 1994. **61**(5): p. 922-8.
100. Lambert-Niclot, S., et al., *Effect of antiretroviral drugs on the quality of semen.* J Med Virol, 2011. **83**(8): p. 1391-4.

101. Pilatz, A., et al., *Semen quality in HIV patients under stable antiretroviral therapy is impaired compared to WHO 2010 reference values and on sperm proteome level.* AIDS, 2014. **28**(6): p. 875-80.
102. Robbins, W.A., et al., *Antiretroviral therapy effects on genetic and morphologic end points in lymphocytes and sperm of men with human immunodeficiency virus infection.* J Infect Dis, 2001. **184**(2): p. 127-35.
103. van Leeuwen, E., et al., *Effects of antiretroviral therapy on semen quality.* AIDS, 2008. **22**(5): p. 637-42.
104. Frapsauce, C., et al., *Impaired sperm motility in HIV-infected men: an unexpected adverse effect of efavirenz?* Hum Reprod, 2015. **30**(8): p. 1797-806.
105. Cooper, T.G., et al., *World Health Organization reference values for human semen characteristics.* Hum Reprod Update, 2010. **16**(3): p. 231-45.
106. Porter, L., et al., *HIV status and union dissolution in sub-Saharan Africa: the case of Rakai, Uganda.* Demography, 2004. **41**(3): p. 465-82.
107. Terceira, N., et al., *The contribution of HIV to fertility decline in rural Zimbabwe, 1985-2000.* Popul Stud (Camb), 2003. **57**(2): p. 149-64.
108. Ross, A., et al., *HIV-1 disease progression and fertility: the incidence of recognized pregnancy and pregnancy outcome in Uganda.* AIDS, 2004. **18**(5): p. 799-804.
109. Dube, A.L., et al., *Fertility intentions and use of contraception among monogamous couples in northern Malawi in the context of HIV testing: a cross-sectional analysis.* PLoS One, 2012. **7**(12): p. e51861.
110. Johnson, K.B., et al., *Fertility preferences and the need for contraception among women living with HIV: the basis for a joint action agenda.* AIDS, 2009. **23 Suppl 1**: p. S7-S17.
111. Kimani, J., et al., *Family planning use and fertility desires among women living with HIV in Kenya.* BMC Public Health, 2015. **15**: p. 909.
112. Peltzer, K., L.W. Chao, and P. Dana, *Family planning among HIV positive and negative prevention of mother to child transmission (PMTCT) clients in a resource poor setting in South Africa.* AIDS Behav, 2009. **13**(5): p. 973-9.
113. Taulo, F., et al., *Fertility intentions of HIV-1 infected and uninfected women in Malawi: a longitudinal study.* AIDS Behav, 2009. **13 Suppl 1**: p. 20-7.
114. Kaida, A., et al., *Childbearing intentions of HIV-positive women of reproductive age in Soweto, South Africa: the influence of expanding access to HAART in an HIV hyperendemic setting.* Am J Public Health, 2011. **101**(2): p. 350-8.
115. Nattabi, B., et al., *A systematic review of factors influencing fertility desires and intentions among people living with HIV/AIDS: implications for policy and service delivery.* AIDS Behav, 2009. **13**(5): p. 949-68.
116. Maier, M., et al., *Antiretroviral therapy is associated with increased fertility desire, but not pregnancy or live birth, among HIV+ women in an early HIV treatment program in rural Uganda.* AIDS Behav, 2009. **13 Suppl 1**: p. 28-37.
117. Myer, L., C. Morroni, and K. Rebe, *Prevalence and determinants of fertility intentions of HIV-infected women and men receiving antiretroviral therapy in South Africa.* AIDS Patient Care STDS, 2007. **21**(4): p. 278-85.
118. Litwin, L.E., et al., *Impact of Availability and Use of ART/PMTCT Services on Fertility Desires of Previously Pregnant Women in Rakai, Uganda: A Retrospective Cohort Study.* J Acquir Immune Defic Syndr, 2015. **69**(3): p. 377-84.
119. Nguyen, R.H., et al., *Reduced fertility among HIV-infected women associated with viral load in Rakai district, Uganda.* Int J STD AIDS, 2006. **17**(12): p. 842-6.
120. Sedgh, G., et al., *HIV-1 disease progression and fertility in Dar es Salaam, Tanzania.* J Acquir Immune Defic Syndr, 2005. **39**(4): p. 439-45.
121. Myer, L., et al., *Impact of antiretroviral therapy on incidence of pregnancy among HIV-infected women in Sub-Saharan Africa: a cohort study.* PLoS Med, 2010. **7**(2): p. e1000229.
122. Ntozi, J.P., *Widowhood, remarriage and migration during the HIV/AIDS epidemic in Uganda.* Health Transit Rev, 1997. **7 Suppl**: p. 125-44.

123. Stover, J., et al., *Projecting the demographic impact of AIDS and the number of people in need of treatment: updates to the Spectrum projection package.* Sex Transm Infect, 2006. **82 Suppl 3**: p. iii45-50.
124. Nduati, R., et al., *Effect of breastfeeding and formula feeding on transmission of HIV-1: a randomized clinical trial.* JAMA, 2000. **283**(9): p. 1167-74.
125. CASCADE, *Time from HIV-1 seroconversion to AIDS and death before widespread use of highly-active antiretroviral therapy: a collaborative re-analysis. Collaborative Group on AIDS Incubation and HIV Survival including the CASCADE EU Concerted Action. Concerted Action on SeroConversion to AIDS and Death in Europe.* Lancet, 2000. **355**(9210): p. 1131-7.
126. WHO Collaborative Study Team on the Role of Breastfeeding on the Prevention of Infant Mortality, *Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries: a pooled analysis. WHO Collaborative Study Team on the Role of Breastfeeding on the Prevention of Infant Mortality.* Lancet, 2000. **355**(9202): p. 451-5.
127. Demographic and Health Surveys. *MEASURE DHS*. 1984-present Jan 10, 2009 [cited 2009 Jan 10, 2009]; Available from: http://www.measuredhs.com.
128. Brahmbhatt, H. *Maternal HIV and Child Survival in Rakai, Uganda*. in *Demographic Impact of HIV*. 2003. Durban.
129. Berhane, R., et al., *Growth failure as a prognostic indicator of mortality in pediatric HIV infection.* Pediatrics, 1997. **100**(1): p. E7.
130. Stover, J., et al., *The Spectrum projection package: improvements in estimating incidence by age and sex, mother-to-child transmission, HIV progression in children and double orphans.* Sex Transm Infect, 2010. **86 Suppl 2**: p. ii16-21.
131. Darby, S.C., et al., *Importance of age at infection with HIV-1 for survival and development of AIDS in UK haemophilia population. UK Haemophilia Centre Directors' Organisation.* Lancet, 1996. **347**(9015): p. 1573-9.
132. Program, T.D. *The DHS Program*. 2018 [cited 2018 14/03/18]; Available from: https://dhsprogram.com/.
133. Wambura, M., et al., *HIV prevalence and incidence in rural Tanzania: results from 10 years of follow-up in an open-cohort study.* J Acquir Immune Defic Syndr, 2007. **46**(5): p. 616-23.
134. Gregson, S., et al., *HIV decline associated with behavior change in eastern Zimbabwe.* Science, 2006. **311**(5761): p. 664-6.
135. Barnighausen, T., et al., *HIV status and participation in HIV surveillance in the era of antiretroviral treatment: a study of linked population-based and clinical data in rural South Africa.* Trop Med Int Health, 2012. **17**(8): p. e103-10.
136. Reniers, G. and J. Eaton, *Refusal bias in HIV prevalence estimates from nationally representative seroprevalence surveys.* AIDS, 2009. **23**(5): p. 621-9.
137. Cleland, J.G., M.M. Ali, and V. Capo-Chichi, *Post-partum sexual abstinence in West Africa: implications for AIDS-control and family planning programmes.* Aids, 1999. **13**(1): p. 125-31.
138. Lurie, M.N., et al., *The impact of migration on HIV-1 transmission in South Africa: a study of migrant and nonmigrant men and their partners.* Sex Transm Dis, 2003. **30**(2): p. 149-56.
139. Auvert, B., et al., *Ecological and individual level analysis of risk factors for HIV infection in four urban populations in sub-Saharan Africa with different levels of HIV infection.* Aids, 2001. **15 Suppl 4**: p. S15-30.
140. WHO, U., *Global update on HIV treatment 2013: results, impact and opportunities*. 2013, World Health Organization: Geneva.
141. Baggaley, R., et al., *From caution to urgency: the evolution of HIV testing and counselling in Africa.* Bull World Health Organ, 2012. **90**(9): p. 652-658B.
142. UNAIDS/WHO working group on Global HIV/AIDS and STI surveillance, *Guidelines for conducting HIV sentinal serosurveys among pregnant women and other groups.* 2003: New York.
143. Marsh, K., et al., *Assessing and adjusting for differences between HIV prevalence estimates derived from national population-based surveys and antenatal care*

surveillance, with applications for Spectrum 2013. AIDS, 2014. **28 Suppl 4**: p. S497-505.
144. Zaba, B. and S. Gregson, *Measuring the impact of HIV on fertility in Africa.* AIDS, 1998. **12 Suppl 1**: p. S41-50.
145. Homsy, J., et al., *Reproductive intentions and outcomes among women on antiretroviral therapy in rural Uganda: a prospective cohort study.* PLoS One, 2009. **4**(1): p. e4149.
146. Maher, D., et al., *Translating global health research aims into action: the example of the ALPHA network.* Trop Med Int Health, 2010. **15**(3): p. 321-8.
147. Tanser, F., et al., *Cohort profile: Africa Centre Demographic Information System (ACDIS) and population-based HIV survey.* International Journal of Epidemiology, 2008. **37**(5): p. 956-962.
148. Wawer, M.J., et al., *A randomized, community trial of intensive sexually transmitted disease control for AIDS prevention, Rakai, Uganda.* AIDS, 1998. **12**(10): p. 1211-25.
149. Wawer, M.J., et al., *Control of sexually transmitted diseases for AIDS prevention in Uganda: a randomised community trial. Rakai Project Study Group.* Lancet, 1999. **353**(9152): p. 525-35.
150. Houlihan, C.F., et al., *Cohort Profile: Hlabisa HIV Treatment and Care Programme.* International Journal of Epidemiology, 2011. **40**(2): p. 318-326.
151. Kasamba, I., et al., *The impact of antiretroviral treatment on mortality trends of HIV-positive adults in rural Uganda: a longitudinal population-based study, 1999–2009.* Tropical Medicine & International Health, 2012. **17**(8): p. e66-e73.
152. Makumbi, F.E., et al., *Associations between HIV Antiretroviral Therapy and the Prevalence and Incidence of Pregnancy in Rakai, Uganda.* AIDS Res Treat, 2011. **2011**: p. 519492.
153. Wringe, A., et al., *Antiretroviral therapy uptake and coverage in four HIV community cohort studies in sub-Saharan Africa.* Tropical Medicine & International Health, 2012. **17**(8): p. e38-e48.
154. Lee, L.M., et al., *Duration of human immunodeficiency virus infection and likelihood of giving birth in a Medicaid population in Maryland.* Am J Epidemiol, 2000. **151**(10): p. 1020-8.
155. Porter, L., et al., *HIV status and union dissolution in sub-Saharan Africa: the case of Rakai, Uganda.* Demography, 2004. **41**(3): p. 465-82.
156. Gray, R.H., et al., *Population-based study of fertility in women with HIV-1 infection in Uganda.* Lancet, 1998. **351**(9096): p. 98-103.
157. Gregson, S., et al., *Study of bias in antenatal clinic HIV-1 surveillance data in a high contraceptive prevalence population in sub-Saharan Africa.* AIDS, 2002. **16**(4): p. 643-52.
158. Anderson, R.M., et al., *The spread of HIV-1 in Africa: sexual contact patterns and the predicted demographic impact of AIDS.* Nature, 1991. **352**(6336): p. 581-9.
159. Gregson, S., et al., *Critique of early models of the demographic impact of HIV/AIDS in sub-Saharan Africa based on contemporary empirical data from Zimbabwe.* Proc Natl Acad Sci U S A, 2007. **104**(37): p. 14586-91.
160. Gouws, E., V. Mishra, and T.B. Fowler, *Comparison of adult HIV prevalence from national population-based surveys and antenatal clinic surveillance in countries with generalised epidemics: implications for calibrating surveillance data.* Sex Transm Infect, 2008. **84 Suppl 1**: p. i17-i23.
161. Carpenter, L., et al., *Estimates of the impact of HIV-1 infection on fertility in a rural Ugandan population cohort.* Health Transition Review 1997. **7**: p. 113-126.
162. Program, T.D. *StatComplier*. 2016 [cited 2016 30/09/2016]; Available from: http://www.statcompiler.com/en/.
163. Case, K.K., et al., *Editorial: methodological developments in the Joint United Nations Programme on HIV/AIDS estimates.* AIDS, 2017. **31 Suppl 1**: p. S1-S4.
164. Glynn, J.R., et al., *Decreased fertility among HIV-1-infected women attending antenatal clinics in three African cities.* J Acquir Immune Defic Syndr, 2000. **25**(4): p. 345-52.

165. Desgrees du Lou, A., et al., *Impaired fertility in HIV-1-infected pregnant women: a clinic-based survey in Abidjan, Cote d'Ivoire, 1997.* AIDS, 1999. **13**(4): p. 517-21.
166. UNAIDS, *Global AIDS Update 2016*, J.U. Nations and P.o. HIV/AIDS, Editors. 2016, UNAIDS: Geneva, Switzerland.
167. UNAIDS. *AIDSinfo*. [cited 2016 17/12/2016]; Available from: http://aidsinfo.unaids.org/.
168. Doyle, A.M., et al., *The sexual behaviour of adolescents in sub-Saharan Africa: patterns and trends from national surveys.* Trop Med Int Health, 2012. **17**(7): p. 796-807.
169. Marston, M., et al., *The impact of antiretroviral therapy on adult mortality in rural Tanzania.* Tropical Medicine & International Health, 2012. **17**(8): p. e58-e65.
170. Mumah, J.N., A.K. Ziraba, and E.M. Sidze, *Effect of HIV status on fertility intention and contraceptive use among women in nine sub-Saharan African countries: evidence from Demographic and Health Surveys.* Glob Health Action, 2014. **7**(1): p. 25579.
171. Gregson, S., B. Zaba, and G.P. Garnett, *Low fertility in women with HIV and the impact of the epidemic on orphanhood and early childhood mortality in sub-Saharan Africa.* AIDS, 1999. **13 Suppl A**: p. S249-57.
172. Gray, R.H., et al., *Population-based study of fertility in women with HIV-1 infection in Uganda.* Lancet, 1998. **351**(9096): p. 98-103.
173. Mayaud, P., *The role of reproductive tract infections*, in *Women and infertility in sub-Saharan Africa: A multi-disciplinary perspective*, J.T. Boerma and Z. Mgalla, Editors. 2001, KIT publishers: Amsterdam. p. 71-108.
174. Ross, A., et al., *Reduced fertility associated with HIV: the contribution of pre-existing subfertility.* AIDS, 1999. **13**(15): p. 2133-41.
175. Mayaud, P., *Sexually Transmitted infections*, in *Principles of Medicine in Africa*, D. Maybe, Editor. 2013, Cambridge University Press: Cambridge. p. 279-307.
176. Braunstein, S.L., et al., *High human immunodeficiency virus incidence in a cohort of Rwandan female sex workers.* Sex Transm Dis, 2011. **38**(5): p. 385-94.
177. Wand, H. and G. Ramjee, *Combined impact of sexual risk behaviors for HIV seroconversion among women in Durban, South Africa: implications for prevention policy and planning.* AIDS Behav, 2011. **15**(2): p. 479-86.
178. Thomson, K.A., et al., *Increased Risk of Female HIV-1 Acquisition Throughout Pregnancy and Postpartum: A Prospective Per-coital Act Analysis Among Women with HIV-1 Infected Partners.* J Infect Dis, 2018.
179. Hayes, R., et al., *Treatment of sexually transmitted infections for HIV prevention: end of the road or new beginning?* AIDS, 2010. **24 Suppl 4**: p. S15-26.
180. Torrone, E.A., et al., *Prevalence of sexually transmitted infections and bacterial vaginosis among women in sub-Saharan Africa: An individual participant data meta-analysis of 18 HIV prevention studies.* PLoS Med, 2018. **15**(2): p. e1002511.
181. Chico, R.M., et al., *Prevalence of malaria and sexually transmitted and reproductive tract infections in pregnancy in sub-Saharan Africa: a systematic review.* JAMA, 2012. **307**(19): p. 2079-86.
182. Joseph Davey, D.L., et al., *Prevalence of Curable Sexually Transmitted Infections in Pregnant Women in Low- and Middle-Income Countries From 2010 to 2015: A Systematic Review.* Sex Transm Dis, 2016. **43**(7): p. 450-8.
183. Kalichman, S.C., J. Pellowski, and C. Turner, *Prevalence of sexually transmitted co-infections in people living with HIV/AIDS: systematic review with implications for using HIV treatments for prevention.* Sex Transm Infect, 2011. **87**(3): p. 183-90.
184. Francis, S.C., et al., *Prevalence of sexually transmitted infections among young people in South Africa: A nested survey in a health and demographic surveillance site.* PLoS Med, 2018. **15**(2): p. e1002512.
185. (WHO), W.H.O., *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV*

infection: recommendations for a public health approach – 2nd ed, W.H.O. (WHO), Editor. 2012, World Health Organization (WHO): Switzerland.
186. Patel, R.C., et al., *Pregnancy rates in HIV-positive women using contraceptives and efavirenz-based or nevirapine-based antiretroviral therapy in Kenya: a retrospective cohort study.* Lancet HIV, 2015. **2**(11): p. e474-82.
187. McGowan, C.C., et al., *Cohort Profile: Caribbean, Central and South America Network for HIV research (CCASAnet) collaboration within the International Epidemiologic Databases to Evaluate AIDS (IeDEA) programme.* Int J Epidemiol, 2007. **36**(5): p. 969-76.

11 APPENDICES

11.1 APPENDIX 1 - ALPHA data specifications

ALPHA data specifications

Data Specifications for participants in ALPHA fertility writing workshop

Preparation before the workshop

Variables have been included if they are pertinent to the key research questions and are available for more than one study centre. Any variables that are not available at your study centre, or which you cannot derive by transforming existing data, can be marked "not available" (coded "." in Stata) in your dataset.

For site-specific analyses, additional variables may be useful, and these can also be included in the datasets that you bring to the workshop, although we cannot guarantee that we will have the time to help you explore them fully during the workshop. For example, if in your site it is common practice to produce all results broken down by educational attainment, you may like to include highest educational attainment, or educational attainment by a fixed age, or educational attainment at entry into study as a variable to be included in your analysis.

Please prepare your data as a STATA data set – there will be limited expertise at the workshop to help people convert data from other formats. You will probably have to write queries or programming procedures to extract and convert data from existing project data sets into the format required for the workshop. Please save the queries and procedures (these may be Stata do files or procedures in database management systems) so they can become part of the documentation for moving data from your site-specific storage to ALPHA data collections in the future.

Variable names, categories and coding

The variable names used in the data specification below will be used in the STATA do-files written for the workshop. We recommend that you use the same variable names in your study centre's dataset (renaming existing variables where necessary). However, it is also possible for each study centre to modify the do-files that we provide so they work with their own existing variable names.

Categories and coding given in the data specification tables should be followed as far as possible, but if it is not appropriate to your study centre then you can use a categorisation that is better suited to your data. During the workshop we will discuss ways of forming common category codes in pooled datasets.

Personal identifiers

Unique individual identifiers are used to index all the data tables and link across them when we merge the data ready for analysis, and at a later stage, for pooling data for a meta-analysis. All study centres have their own conventions for identifying study members, but we do not encourage the use of these identifiers for data sets used during the workshops which may be pooled with data from other study centres. Please create new, numeric identifiers for the data set to be used in the workshop to prevent anyone from outside your study centre cross linking back to your original data. These identifiers should fit in a Stata long integer field, i.e. they must be less than 2,147,483,620. You should save a copy of your original personal identifiers mapped onto the ones created for the workshop, so you can re-create the ALPHA data set on future occasions.

Data specification 6

Data spec 6.1 is for all study centres, and will be used to compute person-year denominators for age-specific rates. We expect to see **one record per residence episode** for each individual in the data set. Individuals who have been resident continuously in the same household between first and last date of observation will have only one residence episode record each.

Individuals who have moved household within the DSS area, or have left and returned to the DSS area since the time they were first seen, will have two or more records, depending on the number of periods of absence from the study area and the number of times they have moved household. In this case, entry and exit dates and types in the classification below refer to the start and end of an episode of residence rather than to the first and last encounter with the individual in the study throughout the whole of his/her life.

For records relating to consecutive residence episodes, where an individual moves within the study area, the (household) exit date of the earlier episode should be equal to the (household) entry date of the later episode. For records relating to individuals who moved out of the study area and then moved back in, the entry date of the later episode must be strictly greater than the exit date of the earlier episode.

6.1 Essential data for each residence episode – one record per episode, include children

Variable name	Description	Coding	Notes
idno	Person ID number	site specific	Numeric IDs long integer format, unique for an individual
study_name	Name of your study field site	site specific	Character – please be consistent across data sets
sex	Male or female	1 Male 2 Female	
dob	Date of birth- best estimate	in STATA format (days since 1st Jan 1960).	If actual month and day are not known it is OK to impute, e.g. assign to middle of the month or mid-year
residence	Type of area within DSS	site-specific grouping, expect 2 to 4 categories	Aim to distinguish urban / rural, or among rural areas distinguish remote / roadside, or by dominant industry
entry_date	Date of start of residence episode	in STATA format	This date should be known quite accurately – it could be the date of a household interview or in between two recent interviews
entry_type	Type of entry	1 baseline recruitment 2 birth 3 in-migration	
exit_date	Date of end of residence episode	in STATA format	For individuals remaining resident in the study area this will be date of last household interview
exit_type	Type of exit	1 present in study site 2 death 3 out-migration 4 lost to follow-up	Code 1 refers to those alive and still resident in study area – they will be treated as censored at last interview date when known to be in study population

Data specs 6.2a or 6.2b are for ALPHA study centres only – i.e. for those study sites where all the adults in the whole community have been tested for HIV. These tables supply the extra information required to classify individuals by HIV status and track how this has changed over the course of the study. Please note that spec 6.2a is a summary that can be produced from spec 6.2b. Spec 6.2a is sufficient for all the cross-site analyses planned for this workshop. However, any site that can bring an up-to-date version of spec 6.2b, will be able to compare relatives' reports concerning HIV diagnosis of the deceased person with the study record of whether the deceased had received HIV counselling and testing.

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6.2a HIV status: alternative (a) – summary HIV test data – one record per individual who has ever tested

Variable name	Description	Coding	Notes
idno	Person ID number	site specific	Numeric IDs long integer format, unique for an individual
study_name	Name of your study field site	site specific	Character – please be consistent across data sets
frst_neg_date	Date of first negative HIV test	in STATA format	coded not available "." for those whose first HIV test was positive
last_neg_date	Date of last negative HIV test	in STATA format	coded not available "." for those whose first HIV test was positive, may be equal to first negative date for those with only one negative test
frst_pos_date	Date of first positive HIV test	in STATA format	coded not available "." for those who have never tested positive
last_pos_date	Date of last positive HIV test	in STATA format	coded not available "." for those who have never tested positive, may be equal to first positive date for those with only one positive test
sero_conv_date	Estimated sero-conversion date	in STATA format	Only necessary to include this if your site estimates sero-conversion date in a way other than the mid-point between last negative and first positive HIV test

6.2b HIV status: alternative (b) – one record for every test recorded or reported in the study

Variable name	Description	Coding	Notes
idno	Person ID number	site specific	Numeric IDs long integer format, unique for an individual
study_name	Name of your study field site	site specific	Character – please be consistent across data sets
hiv_test_date	date of HIV test	in STATA format	If test carried out in survey or study clinic date will be known exactly, if retrospectively reported by respondent may be approximated to mid-month or mid-year
hiv_test_result	HIV test result	0 negative 1 positive 2 indeterminate 3 not reported	indeterminate means test was part of study, but results were inconclusive; not reported means that participant said they had an HIV test outside of study setting but did not disclose result in interview
informed_of_result	whether or not the participant was informed of test result	0 no 1 yes	no codes typical for anonymised tests in sero-surveys; yes codes typical for VCT
location_of_test	whether test was carried out in study area and recorded as part of research record	1 part of community survey 2 study clinic or test centre 3 reported by participant, not part of study	to distinguish between routine tests in surveys, extra tests in study clinics with results recorded in study data base, and outside tests retrospectively reported by participant

Data specification 7

Data specs 7.1, 7.2 and 7.3 are for all study centres. No HIV test information is required. The information supplied in these tables will be used to estimate the completeness of pregnancy reporting in the DSS, to compare pregnancy-related deaths identified in the DSS with pregnancy-related and maternal deaths identified in VA reports, and to derive person-year denominators for calculating age-specific rates for pregnancy-related and maternal deaths.

Each table heading specifies the number of records expected per individual. Please note carefully as this differs from table to table.

7.1 Mother and father identifiers, one record for each individual in DSS

Variable name	Description	Coding	Notes
idno	Person ID number	site specific	Numeric IDs long integer format, unique for an individual
study_name	Name of your study field site	site specific	Character – please be consistent across data sets
mother_id	Unique ID number of mother	site specific	numeric IDs long integer format
father_id	Unique ID number of father	site specific	numeric IDs long integer format

7.2 Reported births, females only, one record for each birth reported by all mothers in DSS

Variable name	Description	Coding	Notes
idno	Person ID number	site specific	Numeric IDs long integer format, unique for an individual
study_name	Name of your study field site	site specific	Character – please be consistent across data sets
m_delivery_date	Date of reported birth	in STATA format	This may be an imputed value or actual date if reported
m_delivery_date_imp	Whether date of birth was imputed	0 no 1 yes	e.g. halfway between interviews if no information available
m_child_id	Child's unique ID if collected		
m_delivery_loc	Place of delivery	0 Home 1 Heath Centre 2 Hospital	If more codes please add to end of list
m_parity	Parity of birth		If live birth
m_stillborn	Was it a still birth?	0 no 1 yes	

7.3 Pregnancy and background characteristics, females only, one record for each DSS interview

Variable name	Description	Coding	Notes
idno	Unique ID number	Site specific	numeric IDs preferred, unique for an individual
study_name	name of your study site	site specific	character – please be consistent
date_int	Date of interview	In Stata format	
survey_name	Which survey interview was part of	site specific	For example round1, round2, sero1, sero2
pregnant	Currently pregnant	0 no 1 yes 88 Don't know 99 Question not asked	
marital_status		0 "Never married/cohabited" 1 "Currently married mono" 2 "Currently married Poly" 3 "Currently married" 4 "Currently cohabiting" 5 "Widowed" 6 "Separated/divorced" 7 "Married but living apart" 8 "Widowed/divorced/separated" 9 "Unclear/missing" 88 Don't know 99 Question not asked	The categories here are to enable all the sites to contribute as much detail as possible. For example if you know the person is married but not if they are monogamous or polygamous you can use category 3, if you distinguish between monogamous and polygamous you can use categories 1 and 2 accordingly.
education_level	Highest education level	Site Specific	

		88 Don't know 99 Question not asked	
family_planning	Currently using family planning?	0 no 1 yes 88 Don't know 99 Question not asked	
family_planning_method	Main type of method currently used	1 Hormonal pill 2 Hormonal injection 3 Hormonal implant 4 Hormonal unspecified 5 IUD 6 Diaphragm 7 Sterilisation/Vasectomy 8 Condom male or female 9 Traditional withdrawal 10 Traditional Calendar 11 Traditional herbal or charms 12 Traditional unspecified 88 Don't know 99 Question not Asked	Note that if the woman reports dual use (condom and another modern method) please code the other modern method in this section, not the condom. The next question asks specifically about condom use, and gives you a chance to record dual protection if your site collects this information. If condom use is mentioned as well as withdrawal and calendar methods it is OK to code only condom use for this question.
Current_condom_use_with_partner	Currently using a condom with partner	0 no 1 yes 88 Don't know 99 Question not Asked	This can be taken from anywhere in your site's questionnaire. For example if they answered dual use in the family planning method question, or they answered that they used a condom during last sex with their partner in a section on sexual behaviour.

11.2 APPENDIX 2 - Ethical approval

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Ms Milly Marston
LSHTM

13 April 2017

Dear Milly

Study Title: HIV and fertility in sub Saharan Africa, has it changed in the era of antiretroviral therapy? – Evidence using 48 Demographic health surveys

LSHTM Ethics Ref: 14098

Thank you for your application for the above research project which has now been considered by the Observational Committee via Chair's Action.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved is as follows:

Document Type	File Name	Date	Version
Investigator CV	CV Milly Marston 2017_04_10_for_ethics	10/04/2017	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

At the end of the study, the CI or delegate must notify the committee using the End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk.

Further information is available at: www.lshtm.ac.uk/ethics.

Yours sincerely,

[redacted]

Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Ms. Milly Marston,
LSHTM

2 May 2017

Dear Ms. Milly Marston,

Study Title: Changes in exposure to unprotected sex in Sub Saharan Africa

LSHTM Ethics Ref: 14102

Thank you for your application for the above research project which has now been considered by the Observational Committee via Chair's Action.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved is as follows:

Document Type	File Name	Date	Version
Investigator CV	CV Milly Marston 2017_04_10_for_ethics	25/04/2017	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

At the end of the study, the CI or delegate must notify the committee using the End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk.

Further information is available at: www.lshtm.ac.uk/ethics.

Yours sincerely,

[redacted]

Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636
www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Basia Zaba
DPH / EPH
LSHTM

23 August 2013

Dear Professor Zaba,

Study Title: **Deaths among HIV infected adults in African populations since the introduction of Antiretroviral Treatment**
LSHTM ethics ref: **6467**

Thank you for your email of 21 August 2013, responding to the Observational Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
LSHTM ethics application	n/a	
Protocol		

After ethical review

Any subsequent changes to the application must be submitted to the Committee via an E2 amendment form. All studies are also required to notify the ethics committee of any serious adverse events which occur during the project via form E4. At the end of the study, please notify the committee via form E5.

Yours sincerely,

[redacted]

Professor John DH Porter
Chair
ethics@lshtm.ac.uk
http://intra.lshtm.ac.uk/management/committees/ethics/

11.3 APPENDIX 3 - copyright for Figure 3.6

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Mar 15, 2018

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