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The Impact of Antiretroviral Treatment Exposure on Incident Pregnancy Among HIV-infected
Women in sub-Saharan Africa:

Findings from Four Population-based HIV Impact Assessment Surveys, 2015-2017

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Abstract

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Research has shown that HIV infection is associated with a reduced incidence of pregnancy in sub-Saharan Africa. As recommendations for universal treatment take precedence, further research is needed to understand the association between antiretroviral therapy (ART) and pregnancy incidence among women living with HIV. The Population-based HIV Impact Assessment (PHIA) Project has collected HIV-focused, cross-sectional, nationally representative data to measure the global impact of HIV. This study analyzed data from four countries where PHIA reports are publicly available: Zambia, Malawi, Tanzania, and Eswatini. Time-varying exposure and event categories were defined according to the HIV status, ART status, and pregnancy status of each observation at multiple points in a forty-five-month time series. Time to pregnancy was then modeled using Cox proportional hazards regressions, with follow-up censored at the pregnancy start date for women with a live birth in the last three years and at the survey date for women without a live birth. There were two primary models assessed, 1: comparing HIV-negative women to HIV-positive women not on ART and HIV-positive women on ART; 2: comparing HIV-positive women not on ART to HIV-positive women on ART <1 year and HIV-positive women on ART >1 year. In this analysis, we found that pregnancy incidence rates were lower in HIV-positive women not on ART and HIV-positive women on ART compared to HIV-negative women. These findings were consistent for all four countries, except for Eswatini, where pregnancy incidence was higher for HIV-positive women not on ART compared to HIV-negative women. Additionally, we concluded that HIV-positive women on ART >1 year were overall less likely to report a recent pregnancy than HIV-positive women not on ART in all countries except Malawi. Further, HIV-positive women on ART <1 year were overall more likely to report a recent pregnancy than HIV-positive women not on ART in all countries except for Tanzania. Our findings suggest that fertility differs by the duration of antiretroviral therapy with further qualitative and quantitative data needed to expand upon the biological, behavioral, and social effects of HIV and ART on pregnancy incidence in sub-Saharan Africa.

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Introduction

HIV Among Women of Reproductive Age in sub-Saharan Africa

Human immunodeficiency deficiency virus (HIV) disproportionately affects women in sub-Saharan Africa, with women and girls accounting for 59% of all new HIV infections in 2019 [1]. According to UNAIDS, young women aged 15-24 years were twice as likely to be living with HIV in 2019 compared to men in in this region [1]. Recent prevalence estimates by the Population-based HIV Impact Assessment (PHIA) Project demonstrate that this region continues to report a disproportionate burden of global HIV infection. Example prevalence estimates reported among women aged 15 years and older by the PHIA Project include: 14.9% in Zambia [2], 12.8% in Malawi [3], 6.5% Tanzania [4], and 32.5% in Eswatini [5]. The high prevalence of HIV among women of reproductive age in sub-Saharan Africa has been largely measured through routine testing at antenatal clinics (ANC) and prevention of mother to child transmission (PMTCT) programs, which allow us to study rates of transmission among pregnant women and mothers.

The transmission of HIV from a mother to child during pregnancy is a significant public health and women's health issue as transmission rates can range from 15% to 45% without effective interventions [6]. The data collected through PMTCT programs not only set standards for HIV prevention, treatment, and care for pregnant women, new mothers, and infants but also drive global health policy with trends among pregnant women informing estimates of national and sub-national HIV prevalence. These data, however, have been historically adjusted for the reduced fertility of HIV-positive women and, therefore, may be outdated given increased access to care and treatment for women living with HIV (WLHIV) [7]. Because HIV continues to significantly impact women of reproductive age, it is important that we assess the impact of the rapid scale-up

of antiretroviral therapy (ART) in sub-Saharan Africa on the pregnancy outcomes of WLHIV to determine trends of infection among pregnant women and the general population.

Expanding Access of Antiretrovirals for HIV-Positive Women

As recommendations for universal treatment and access to antiretroviral therapy take precedence, sub-Saharan Africa has become the leading target for global progress in HIV with more than 7.5 million people receiving ART at the end of 2012 [8]. The rapid scale-up of ART has been specifically targeted towards pregnant and breastfeeding women through ANC and PMTCT services, with ART coverage for this population now far exceeding that for non-pregnant women [8]. Research has shown that ART is an adequate and appropriate treatment strategy for pregnant women, with little to no increased risk of virologic failure associated with pregnancy at ART initiation [9]. Approximately two thirds of pregnant women living with HIV in sub-Saharan Africa were receiving ART at the end of 2014, demonstrating immense progress in access to ART among this key vulnerable population [6].

The differing prevalence of HIV in sub-Saharan Africa must be understood before evaluating the impact of HIV and ART on pregnancy outcomes and fertility desires. The prevalence of HIV among pregnant women, men, and women in the general population were first compared in parallel studies in east Zimbabwe, with data collected from both a population-level survey and local ANC surveillance methods [10]. In this study, Gregson *et al.* analyzed trends in HIV prevalence between 1998 and 2011 over the time of ART scale-up to determine if trends in ANC continued to mirror that of the general population. It was concluded that in the late 1990s and early 2000s, ANC surveillance data provided reasonable estimates of HIV prevalence for men and women in the general population. HIV prevalence declined more rapidly in later years among

pregnant ANC attendees, especially after the expanding access of ART in sub-Saharan Africa. Although the decline in prevalence in the general population was greater in men compared to women, the decline was much steeper in pregnant women compared to all women and compared to all men and women combined [10]. This finding is consistent with an earlier study on the prevalence of HIV in 13 sub-Saharan countries, which discovered that HIV prevalence declined by 19% in pregnant women between 2008 and 2013 [11]. The decline of HIV infection observed among pregnant woman in ANC surveillance data is not representative of the HIV epidemic in the wider female population; therefore, this data can no longer inform national estimates of HIV prevalence. Future prevalence estimates should account for the effects of HIV and ART on the pregnancy outcomes and fertility desires of WLWH when interpreting trends in prevalence [11].

Comparing the Fertility of HIV-Positive and HIV-Negative Women

Analyses on the fertility desires and outcomes of both pregnant and non-pregnant women living with HIV have suggested that HIV serostatus is associated with biological, behavioral, and social factors that influence pregnancy prevalence and incidence. After reviewing evidence on the impact of HIV on fertility in Africa in 1998, Zaba and Gregson determined that the fertility of HIV-positive women was lower than that of HIV-negative women in all but the youngest age category [12]. This difference in fertility was attributed to the direct biological effects of infection on fecundity and indirect changes in behavior in the general population. According to data later collected from four community-based demographic and HIV surveillance sites in sub-Saharan Africa, these fertility differences were sustained throughout the pre-ART era but narrowed over time with the scale-up of ART [13]. Researchers in this study concluded that differences in fertility between HIV-positive and HIV-negative women would continue to diminish over time as ART

becomes more widely available in sub-Saharan Africa. Additional researchers have hypothesized that rates of pregnancy among women living with HIV will begin to increase in sub-Saharan Africa due to a variety of factors including changes to subjective health status, prevention of mother-to-child transmission (PMTCT) programs, availability of social support, and, most significantly, access to antiretroviral therapies (ART).

Another study analyzing data from a longitudinal population survey administered at antenatal clinics in Zimbabwe between 1998 and 2011 concluded that HIV-positive women continued to have lower fertility and pregnancy prevalence compared to HIV-negative women, regardless of ART use [10]. It is important to note that almost half of the women living with HIV in this study were not on ART; therefore, substantial changes in fertility may not have translated due to the biological sub-fertility previously seen in untreated women. This study demonstrates the need to collect data on the use of antiretroviral therapy among women living with HIV in sub-Saharan Africa. Recent research has supported the closing gap in fertility in the post-ART period not only due to declining rates of pregnancy among HIV-negative women but also due to the increasing rates of pregnancy among HIV-positive women.

Fertility Desires and Pregnancy Outcomes of HIV-Positive Women on ART

Early studies determined that HIV was associated with a 25–40% decrease in fertility among HIV-positive women in sub-Saharan Africa [12]. In the pre-ART era, this reduction in pregnancy outcomes was primarily due to increased fetal loss, reduced conception, and excess mortality among HIV-positive women [12]. However, with expanding global access to treatment, there has been growing interest in whether ART is associated with positive changes in fertility among HIV-positive women. According to a cross-sectional study among HIV-positive women in

Uganda in 2013, researchers hypothesized that ART would increase fertility through improved quality and length of life, improved health status, strengthened biological ability to conceive and carry to term, increased number of sexual partners, and increased likelihood to engage in unprotected sex [14]. This analysis, however, only suggested that ART use increased the desire to have more children but did not yet increase the odds of pregnancy or live birth among women living with HIV. This study suggests that the introduction of ART in Uganda failed to reverse the impact of HIV on fertility and translate sufficiently to adjusted health outcomes.

Analyzing data from HIV-positive women enrolled at 26 HIV clinics in Kenya and Uganda between 2001 and 2009, researchers discovered that ART initiation was not associated with incident pregnancy among women enrolling in HIV care [15]. Although there was no evidence that incident pregnancy resulted from ART initiation, this study was able to determine that treatment was associated with prevalent pregnancy at baseline. The higher pregnancy prevalence observed at baseline suggests that many factors predispose women to both ART initiation and conception such as the receipt of PMTCT services prior to enrollment in care. These findings stress the importance of adjusting for prevalent pregnancy in future research analyzing the association between ART initiation and fertility. Another study in Uganda assessing the association between HIV, ART, and pregnancy expanded its scope to account for changes in immunological and virological status in relation to fertility [16]. Researchers determined that prevalent pregnancy, defined as pregnancies detected at or within two-weeks of entry into care, was significantly reduced among women with lower CD4 counts in the program. Incident pregnancy, defined as those detected more than two weeks after entry into care, was found to be significantly higher after ART initiation. The higher incidence of pregnancy observed among HIV-positive women on ART was hypothesized to result from improved immune status or reduced HIV viral load [16].

Additional evidence has examined the difference in fertility between HIV-positive women on antiretrovirals and HIV-positive women not on antiretrovirals. According to data collected in seven African countries from the Mother-to-Child Transmission-Plus (MTCT-Plus) Initiative, the rate of incident pregnancy was significantly higher among women receiving ART (9.0/100 PY) compared to women not receiving ART (6.5/100 PY) [7]. According to MTCT-Plus, the likelihood of becoming pregnant increased over time in the ART group to almost 80% greater than the pre-ART group, while remaining low and constant before treatment initiation [7]. Johnson *et al.* reaffirmed these findings in a recent study published in June 2020 comparing HIV-positive women on antiretrovirals and HIV-positive women not on antiretrovirals to HIV-negative women in South Africa between 2007 and 2017. This analysis determined that pregnancy incidence rates in South Africa were highest among HIV-positive women on ART, lower among HIV-negative women, and lowest among HIV-positive women not on ART [17].

There has been mixed evidence as to why ART is linked to higher fertility desires and outcomes among women living with HIV. Myer *et al.* hypothesized that the rapid improvements in health and quality of life observed after ART initiation led to increased sexual activity or new partner acquisition [7]. In this study, ART was thought to reverse the biological effects of infection and advanced disease by improving immunological function and thereby improving female fecundity [7]. Additional studies have focused specifically on the evolving fertility desires of women living with HIV and receiving ART. Maeir *et al.* suggested that ART was associated with increased fertility desires among HIV-infected women due to increased hopes and planning for the future [14]. These findings were consistent with those from a qualitative study exploring the fertility desires, intentions, and fertility decision-making of WLWH in India [18]. A study conducted in Nigeria also concluded that improvements in health status after ART initiation

allowed women to reassess fertility desires [19] while a study in Kenya demonstrated that increased fertility desires resulted from increased child mortality and reduced breastfeeding [20]. There continues to be a lack of clarity on why ART restores fertility among women living with HIV, with further research needed to determine the direct and indirect factors influencing fertility desires and outcomes in sub-Saharan Africa.

ART Duration, Fertility Desires, and Pregnancy Outcomes Among HIV-Positive Women

Although evidence in African countries has suggested an association between fertility and antiretroviral use, less is known about fertility and the duration of antiretroviral therapy. A retrospective cohort study among women in an urban ART clinic in Malawi between 2007 and 2010 found that pregnancy incidence increased among all age groups, with the fertility rates of women living with HIV mirroring that of the general population after the first 6 months on ART [21]. This study demonstrated that ART was a strong predictor of pregnancy incidence with results indicating that women on ART for more than 6 months were three times as likely to become pregnant compared to those on ART for shorter time periods [21]. Another study discovered that pregnancy occurrence increased significantly after ART initiation among HIV-positive women living in the West African region. Incident pregnancy appeared to increase proportionally to the duration of ART exposure with the highest pregnancy rates observed at year four of the study [22]. These studies suggest a positive effect of ART on fertility throughout years in care.

Additional research from the Uganda AIDS Rural Treatment Outcomes (UARTO) cohort concluded that nearly one-third of women living with HIV became pregnant within 3 years of ART initiation [23]. At years one, two, and three after ART initiation, the cumulative probability of pregnancy was measured at 12%, 20%, and 28%, respectively. Incident pregnancy within this

population increased after treatment initiation and varied by time on ART. First incident pregnancy peaked between 6 to 12 months while recurrent pregnancy peaked between 24 and 30 months and again at 48+ months after ART initiation [23]. Researchers determined that incident pregnancy was lowest during times distal to ART initiation with first and recurrent pregnancy declining between 12 and 18 months, peaking again between 18 and 30 months, and then sharply declining between 30 and 48+ months after ART initiation.

According to a systematic review conducted in 2016, current research suggests that fertility increases among women living with HIV approximately 1 year after ART initiation; this evidence, however, was insufficient to confidently assert the conclusion that longer duration of ART is positively associated with pregnancy [24]. Further research is needed to determine the association between fertility and the duration of ART. Additionally, further research should assess the biological and behavioral impacts of HIV and ART on pregnancy incidence over time.

Research Gaps

Research trends suggest that fertility desires and outcomes among HIV-positive women have evolved during the post-ART era. Incident pregnancy appears to have increased among HIV-positive women on ART over time, however, these findings are supported by inconsistent and insufficient evidence. There is a demonstrated need for further research given the recent and rapid scale-up of antiretroviral therapies in sub-Saharan Africa. Research focusing on nationally representative biomarker and self-report data has been recommended to analyze the impact of antiretrovirals and duration of ART exposure on fertility.

Research Question and Aim

The proposed study will utilize data produced from the Population-based HIV Impact Assessment (PHIA) Project to determine the association between the duration of antiretroviral therapy and pregnancy incidence among women living with HIV in Zambia, Malawi, Tanzania, and Eswatini. The PHIA Project has administered HIV-focused, cross-sectional, nationally representative surveys through the Ministries of Health in 13 countries most affected by the HIV epidemic [25]. The data produced from the PHIA Project provides a unique opportunity to describe and compare fertility desires and outcomes among women in sub-Saharan Africa as well as address the research questions and aims of interest to the analysis:

Research Question 1: *What is the effect of antiretroviral therapy on pregnancy incidence among HIV-infected women in Zambia, Malawi, Tanzania, and Eswatini?*

Research Question 2: *What is the effect of the duration of antiretroviral therapy on pregnancy incidence among HIV-infected women in Zambia, Malawi, Tanzania, and Eswatini?*

Research Aim 1: *Determine whether pregnancy incidence increases after antiretroviral initiation among HIV-positive women in Zambia, Malawi, Tanzania, and Eswatini.*

Research Aim 2: *Determine whether pregnancy incidence increases with longer duration of antiretroviral therapy among HIV-positive women in Zambia, Malawi, Tanzania, and Eswatini.*

Methods

Data Sources and Definitions

The Population-based HIV Impact Assessment (PHIA) surveys are HIV-focused, cross-sectional, nationally representative household-based surveys, designed to measure the impact of HIV programs [25]. The analysis utilized data from the four countries where final PHIA reports were currently available: Zambia, Malawi, Tanzania, and Eswatini. The PHIA Project collected data in Zambia from March 2016 to August 2016, in Malawi from November 2015 to August 2016, in Tanzania from November 2016 to June 2017, and in Eswatini from August 2016 to March 2017 [25]. The data were collected through household interviews, individual interviews, and HIV diagnostic testing administered by trained staff via computer-assisted personal interviews (CAPI).

The PHIA Project utilized a stratified multistage survey sampling design, with strata defined by sub-national geographic divisions and census enumeration areas (EAs) randomly selected [25]. Households were then randomly sampled within each selected EAs and consenting households were administered a household survey. Additional individual interviews were administered within selected households based on an assessment of eligibility criteria. All participation in the PHIA Project was voluntary with eligible participants required to provide informed consent before data collection [2-5]. All women and men aged 18 years and older living in the selected households, and all visitors who slept in the household prior to the survey, who were able and willing to provide written/verbal consent were eligible to participate in the survey [2-5]. Additionally, all persons aged 10-17 years living in the selected households, and all visitors who slept in the household prior to the survey, who were able and willing to provide written/verbal assent and who were able to acquire written/verbal consent from a parent or guardian were eligible to participate in the survey [2-5]. All children aged 0-9 years living in the selected households, and

all child visitors who slept in the household prior to the survey, who were provided written/verbal consent from a parent or guardian were also eligible to participate in the survey [2-5].

After providing informed consent, all participants answered survey questions related to sociodemographic characteristics and HIV-related risk factors before receiving home-based HIV testing and counseling. The PHIA surveys included questions from the following modules: Respondent Background; Marriage; Reproduction; Children; Male Circumcision; Sexual Activity; HIV/AIDS Knowledge and Attitudes (Eswatini N/A); HIV Testing; HIV Status, Care, and Treatment; Tuberculosis and Other Health Issues; Alcohol Use; Gender Norms; and Violence (Appendix D). HIV rapid testing was then conducted at the household level using the current national HIV testing algorithm in each country (Appendix E-H). Those samples with a reactive or indeterminate rapid test received confirmatory testing using the Geenius HIV 1/2 Supplemental Assay (Bio-Tad, Hercules, California, United States) in each country (Appendix E-H). All participants who were confirmed positive for HIV through Geenius underwent additional testing related to antiretroviral (ARV) detection, HIV viral load, drug resistance, and HIV subtyping. All interview and biomarker data have been made publicly available through ICAP at Columbia University with support and funding from the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and the U.S. Centers for Disease Control and Prevention (CDC).

Eligibility Criteria for the Analysis

The analysis was restricted to women of reproductive age (15-49 years) who participated in the individual interview and biomarker test and yielded a valid HIV test result. The analysis was further limited to women with a valid response for the outcome of interest, *delivered3years*. This variable indicates whether a mother has given birth in the last three years prior to the survey (i.e.,

births occurring during 2012–2017, depending on the date of the survey) with valid interview responses defined as follows: 1 - Gave birth 3 years preceding survey; 2 - Did not give birth 3 years preceding survey; 3 - Missing (mothers missing data on last delivery); 99 - N/A (men and non-mothers). Additional exclusions were then defined and outlined in the assessment of time to pregnancy to account for missing HIV, ARV, and pregnancy-related data (Appendix I-L).

Analysis of Time to Pregnancy

To determine time to pregnancy among women of reproductive age, we analyzed both pre-existing date variables collected by the PHIA Project and new date variables created as part of the analysis. The PHIA Project collected date variables including, but not limited to, birth dates, first HIV positive test dates, first ARV use dates, last ARV use dates, and survey dates. These date variables were collected through interview responses, which allowed participants to provide partial dates for the relevant day, month, and/or year for each date variable of interest. All final date variables were created by cleaning and combining partial date variables into final date variables with valid responses for the day, month, and year. All participants with missing month variables were assigned a month at random and all participants with a missing year variable were assigned a missing final date variable. All date variables without a recorded day variable were assigned to the first day of the recorded month.

The date for the first HIV positive test combined variables for the month (*hivtspasm*) and year (*hivtspasy*) of the participants first HIV positive test result. The date for ARV first use combined variables for the month (*arvftm*) and year (*arvfty*) when participants first started taking ARVs while the date for ARV last use combined variables for the month (*arvltm*) and year (*arvlty*)

when participants last received ARVs. Additional dates variables were created for this analysis by calculating new date variables from pre-existing PHIA date variables.

The pregnancy start date was a new variable calculated by subtracting the average gestational period of nine months from the birth date of the most recent live birth. This variable approximates time of conception and allows us to determine HIV status and ARV use at the pregnancy start. The start date for person-time contributions was another new variable calculated by subtracting forty-five months from the survey date of each participant. This variable represents the time start for all participants whose pregnancy events and exposures were considered in the survival analyses. The start date allows us to backdate all pregnancies that resulted in a live birth in the last three years by subtracting three years plus the average gestation period of nine months from the recorded survey date.

All eligible women of reproductive age included in the analysis were stratified into three categories of exposure: HIV-negative women, HIV-positive women not on ART, and HIV-positive women on ART. These time-varying exposure categories were determined based on the HIV status and ARV status of each observation at multiple points in the time series. This allowed the person time contributions for all women to be partitioned into intervals, each defined by a “start” and “stop” date, over the potential person time contribution of forty-five months. Additionally, time-varying event variables were defined alongside the exposure categories to determine whether a pregnancy event occurred during the relevant interval in the time series. A sequence of exposure and event variables were defined per observation and a new data set was established with multiple rows for each observation. The person time contribution for each observation was first calculated in days, by subtracting the “start” date from the “stop” date, and then converted into years.

Statistical Analysis

Rates of pregnancy incidence in each country were calculated as pregnancies per 1000 person years and compared among the three primary categories of HIV exposure: HIV-negative women, HIV-positive women not on ART, and HIV-positive women on ART. Additional categories of exposure were analyzed to distinguish the duration of ART and defined as follows: HIV-positive women on ART <6 months, HIV-positive women on ART between 6 and 12 months, HIV-positive women on ART between 12 months and 18 months, and HIV-positive women on ART >18 months. All rates of pregnancy incidence accounted for blood test base and replicate weights, which were provided through the PHIA Project. The blood test base weights were based on the individual base weights and calculated by the PHIA Project after adjusting for nonresponse. Meanwhile, the replicate weights were created through jackknife variation estimation with variance estimates reflecting nonresponse and poststratification adjustments. The JK coefficients were set to 1 and the degrees of freedom (df) were set to 25 in all four country-level analyses utilizing replicate weights [25].

After determining weighted pregnancy incidence rates, we then assessed time to pregnancy using Cox proportional hazards models. The survival analyses censored follow-up at the pregnancy start date for women with a live birth in the last three years and at the survey date for women without a live birth in the last three years. The event of interest was defined as pregnancy conception and coded as a binary variable 1: event (failure), 0: no event (i.e., right censored). There were two survival analyses conducted in this study:

Model 1: Comparing HIV-negative women (reference) to HIV-positive women not on ART and HIV-positive women on ART;

Model 2: Comparing HIV-positive women not on ART (reference) to HIV-positive women on ART <1 year and HIV-positive women on ART >1 year.

An additional exploratory analysis was conducted to further assess differences in pregnancy incidence among HIV-positive women on ART. There was one proportional hazards model analyzed in the exploratory study:

Model 3: Comparing HIV-positive women not on ART (reference) to HIV-positive women on ART <6 months, HIV-positive women on ART between 6 and 12 months, HIV-positive women on ART between 12 months and 18 months, and HIV-positive women on ART >18 months.

The proportional hazards assumption was assessed for each model utilizing log-log survival curves, goodness of fit tests, and time-dependent covariates. All models were first run without replicate weights to generate estimates of survival through Kaplan-Meier curves. The three Cox proportional hazards models were then run with replicate weights applied to determine hazards ratios and 95% Confidence Intervals. All statistical analyses were performed using SAS (version 9.4; SAS Institute).

Ethics Statement

This analysis was undertaken as part of a Master of Public Health thesis, approved by the Epidemiology Department within the Rollins School of Public Health at Emory University. The

data was collected through cross-sectional, nationally representative surveys and anonymized before publication through ICAP at Columbia University; therefore, informed consent was not required to conduct this analysis. All PHIA survey protocols were reviewed and approved by the CDC Institutional Review Board (IRB), the Columbia University Medical Center IRB, and the IRB in each country with informed consent obtained prior to participation in PHIA surveys.

Results

Eswatini

The analysis reported 1,029 unweighted pregnancy events in the last three years among women of reproductive age in Eswatini (Appendix B). Of these pregnancy events, 77.6% occurred among HIV-negative women, 5.9% occurred among HIV-positive women not on ART, and 16.5% occurred among HIV-positive women on ART. Of the 170 pregnancy events that occurred among HIV Positive women on ART, 13.5% occurred among those on ART less than 6 months, 17.1% occurred among those on ART between 6 and 12 months, 8.8% occurred among those on ART between 12 and 18 months, and 60.6% occurred among those on ART more than 18 months.

Pregnancy incidence rates were calculated for each category of HIV and ART exposure and reported as births per 1000 person years (Appendix C). HIV-positive women on ART between 6 and 12 months reported the highest pregnancy incidence rate at 130.9 (95% CI: 86.2, 175.7) births per 1000 person years followed by HIV-positive women on ART less than 6 months (Rate: 95.2, 95% CI: 54.5, 135.9) and HIV-positive women not on ART (Rate: 90.2, 95% CI: 65.3, 115.0). HIV-negative women reported a pregnancy incidence rate at 69.0 (95% CI: 64.4, 73.7) births per 1000 person years. Lastly, HIV-positive women on ART between 12 and 18 months reported a pregnancy incidence rate of 64.2 (95% CI: 30.2, 98.2) births per 1000 person years

while HIV-positive women on ART more than 18 months reported 52.0 (95% CI: 41.1, 63.0) births per 1000 person years.

Model 1 determined that the hazard of pregnancy for HIV-positive women not on ART (HR: 1.22; 95% CI: 0.92, 1.61; p=0.16) and HIV-positive women on ART (HR: 0.9; 95% CI: 0.74, 1.09; p=0.26) did not differ than that of HIV-negative women. Assessing the association between time to pregnancy and time on ART, Model 2 determined that the pregnancy incidence rate for HIV-positive women on ART <1 year (HR: 1.28; 95% CI: 0.8, 2.05; p=0.28) did not differ than that of HIV-positive women not on ART. The hazard of pregnancy did significantly differ, however, among HIV-positive women on ART >1 year (HR: 0.63; 95% CI: 0.44, 0.9; p=0.01). According to the survival analysis, HIV-positive women on ART >1 year were 37% less likely to have a recent pregnancy than HIV-positive women not on ART.

Malawi

There were 3,001 pregnancy events reported in the last three years among women of reproductive age in the unweighted analysis for Malawi (Appendix B). Approximately 95.4% of these pregnancy events occurred among HIV-negative women, 0.7% occurred among HIV-positive women not on ART, and 3.9% occurred among HIV-positive women on ART. Of the 116 pregnancy events that occurred among HIV-positive women on ART, 13.8% occurred among those on ART less than 6 months, 11.2% occurred among those on ART between 6 and 12 months, 5.2% occurred among those on ART between 12 and 18 months, and 69.8% occurred among those on ART more than 18 months.

HIV-positive women on ART less than 6 months reported the highest pregnancy incidence rate at 126.7 (95% CI: 59.7, 193.6) births per 1000 person years followed by HIV-negative women

(Rate: 125.6, 95% CI: 120.1, 131.2) and HIV-positive women on ART between 6 and 12 months (Rate: 106.5, 95% CI: 30.1, 182.9). HIV-positive women not on ART reported a pregnancy incidence rate of 67.0 (95% CI: 13.9, 120.1) births per 1000 person years while HIV Positive women on ART more than 18 months reported a rate of 70.0 (95% CI: 53.2, 86.9) births per 1000 person years. Reported rates for pregnancy incidence were lowest for HIV-positive women on ART between 12 and 18 months (Rate: 66.7, 95% CI: 3.9, 129.6).

The hazard of pregnancy among HIV-positive women not on ART (HR: 0.36; 95% CI: 0.21, 0.61; p=0.0006) in Malawi was 64% less than the corresponding hazard among HIV-negative women, according to Model 1. Meanwhile, HIV-positive women on ART (HR: 0.6; 95% CI: 0.47, 0.76; p=0.0002) were only 40% less likely to report an incident pregnancy compared to HIV-negative women. According to the Model 2, there was no significant association between pregnancy and ART duration for HIV-positive women on ART >1 year (HR: 1.61; 95% CI: 0.85, 3.02; p=0.14) when compared to HIV-positive women not on ART. Rates of pregnancy incidence did differ for HIV-positive women on ART <1 year (HR: 2.65; 95% CI: 1.19, 5.89; p=0.02), with this population of women being 2.65 times more likely to report a recent pregnancy compared to HIV-positive women not on ART.

Tanzania

The analysis reported 5,586 pregnancy events in the last three years among women of reproductive age in the unweighted analysis for Tanzania (Appendix B). Of these pregnancy events, 98.2% occurred among HIV-negative women, 0.6% occurred among HIV-positive women not on ART, and 1.3% occurred among HIV-positive women on ART. Of the 72 pregnancy events that occurred among HIV-positive women on ART, 13.9% occurred among those on ART less

than 6 months, 15.3% occurred among those on ART between 6 and 12 months, 9.7% occurred among those on ART between 12 and 18 months, and 61.1% occurred among those on ART more than 18 months.

The highest pregnancy incidence rates observed in Tanzania were for HIV-positive women on ART less than 6 months (Rate: 156.0, 95% CI: 24.3, 287.8) and HIV-negative women (Rate: 127.4, 95% CI: 122.2, 132.7). HIV-positive women on ART between 12 and 18 months (Rate: 124.0, 95% CI: 9.0, 239.0) and HIV-positive women not on ART (Rate: 109.5, 95% CI: 67.3, 151.6) also reported relatively high pregnancy rates. Meanwhile, HIV-positive women on ART between 12 and 18 months (Rate: 65.9, 95% CI: 13.0, 118.8) and HIV-positive women on ART more than 18 months (Rate: 62.1, 95% CI: 40.2, 84.0) reported low pregnancy incidence rates.

According to Model 1, the hazard of pregnancy for HIV-positive women not on ART (HR: 0.85; 95% CI: 0.57, 1.25; $p=0.38$) was not significantly different than that for HIV-negative women. The hazard of pregnancy for HIV-positive women on ART (HR: 0.66; 95% CI: 0.47, 0.93; $p=0.02$), however, was 34% less than the hazard for HIV-negative women. There were no differences observed in the association between time to pregnancy and time on ART for either HIV-positive women on ART <1 year (HR: 0.67; 95% CI: 0.28, 1.59; $p=0.35$) or HIV-positive women on ART >1 year (HR: 0.64; 95% CI: 0.39, 1.04; $p=0.07$).

Zambia

According to the reported unweighted data, 3,595 recent pregnancy events were identified among women of reproductive age in Zambia (Appendix B). Of these pregnancy events, 96.4% occurred among HIV-negative women, 1.0% occurred among HIV-positive women not on ART, and 2.6% occurred among HIV-positive women on ART. Of the 94 pregnancy events that occurred

among HIV-positive women on ART, 19.1% occurred among those on ART less than 6 months, 16.0% occurred among those on ART between 6 and 12 months, 6.4% occurred among those on ART between 12 and 18 months, and 58.5% occurred among those on ART more than 18 months.

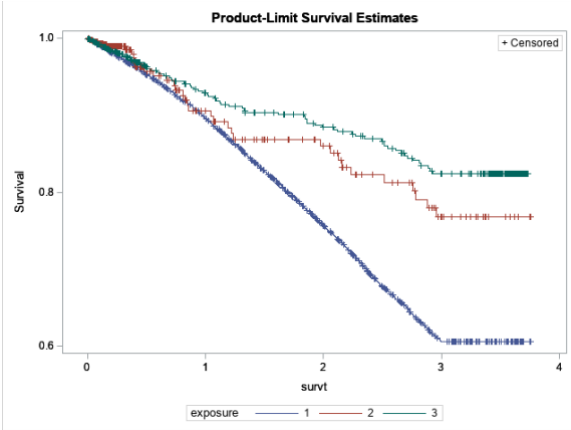
HIV-positive women on ART less than 6 months reported the highest pregnancy incidence rate at 139.8 (95% CI: 70.9, 208.6) births per 1000 person years. HIV-positive women on ART between 6 and 12 months (Rate: 135.8, 95% CI: 66.9, 204.8) and HIV-negative women (Rate: 130.5, 95% CI: 124.8, 136.3) also reported high rates of pregnancy. The lowest rates of pregnancy incidence were reported for HIV-positive women not on ART (Rate: 74.8, 95% CI: 48.4, 101.2), HIV-positive women on ART between 12 and 18 months (Rate: 68.2, 95% CI: 13.3, 123.1), and HIV-positive women on ART > 18 months (Rate: 48.3, 95% CI: 35.1, 61.6), respectively.

Model 1 determined that the hazard of pregnancy among HIV-positive women not on ART (HR: 0.6; 95% CI: 0.41, 0.87; p=0.01) was 40% less than the corresponding hazard among HIV-negative women in Zambia. Additionally, the hazard of pregnancy incidence for HIV-positive women on ART (HR: 0.51; 95% CI: 0.41, 0.64; p<0.0001) was 49% less than that for HIV-negative women. After assessing the association between survival time and ART duration, we determined that there was a significant difference in the hazard of pregnancy for HIV Positive Women on ART <1 Year (HR: 2.24; 95% CI: 1.17, 4.31; p=0.02) compared to HIV-positive women not on ART. HIV Positive Women on ART <1 Year were 2.24 times more likely to report a recent pregnancy than women not on ART. There was no difference observed in the association between time to pregnancy and duration of ART for HIV-positive women on ART >1 year (HR: 0.64; 95% CI: 0.41, 1.02; p=0.06).

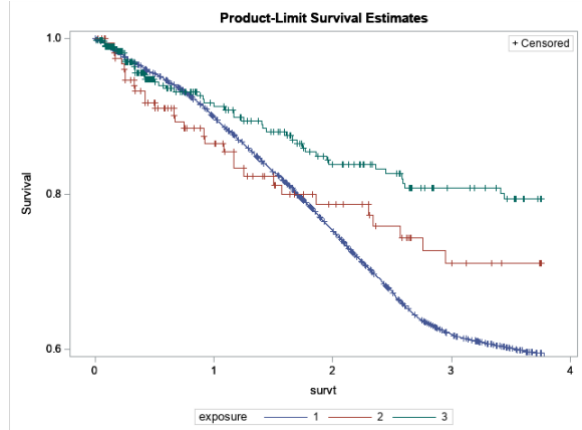
Table 4a. Cox Proportional Hazards Model to Determine Predictors of Time to Next Pregnancy: HIV-negative Women (Reference) Compared to HIV-positive Women not on ART and HIV-positive Women on ART				
	Zambia	Malawi	Eswatini	Tanzania
HIV-negative Women				
Pregnancy Events	3465	2863	5483	798
Person Time in Years	25616.3	23068.96	39409.82	11503.89
Hazard Ratio	1.0	1.0	1.0	1.0
95% Confidence Interval	-	-	-	-
HIV-positive Women Not on ART				
Pregnancy Events	36	22	31	61
Person Time in Years	485.79	380.57	218.76	645.7
Hazard Ratio	0.6	0.36	1.22	0.85
95% Confidence Interval	(0.41, 0.87)	(0.21, 0.61)	(0.92, 1.61)	(0.57, 1.25)
HIV-positive Women on ART				
Pregnancy Events	94	116	72	170
Person Time in Years	1520.19	1609.38	884.28	2581.84
Hazard Ratio	0.51	0.6	0.9	0.66
95% Confidence Interval	(0.41, 0.64)	(0.47, 0.76)	(0.74, 1.09)	(0.47, 0.93)

Figure 1: Kaplan-Meier Curves of Time to Pregnancy: Comparing HIV-negative Women, HIV-positive Women not on ART, and HIV-positive Women on ART in sub-Saharan Africa, 2012-2017

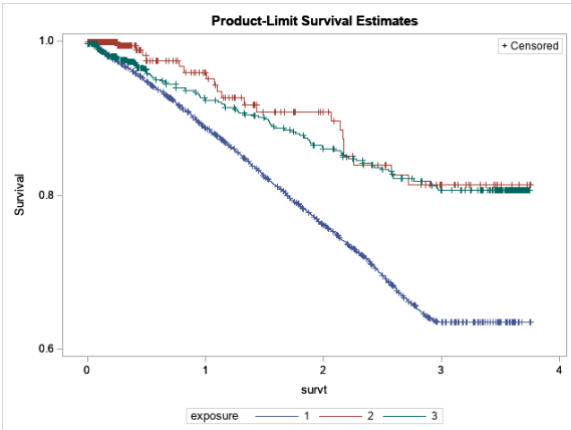
Zambia



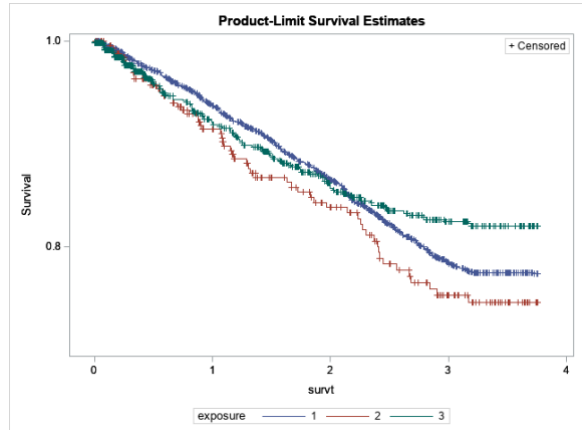
Tanzania



Malawi



Eswatini



Legend

Survvt: Time in Years

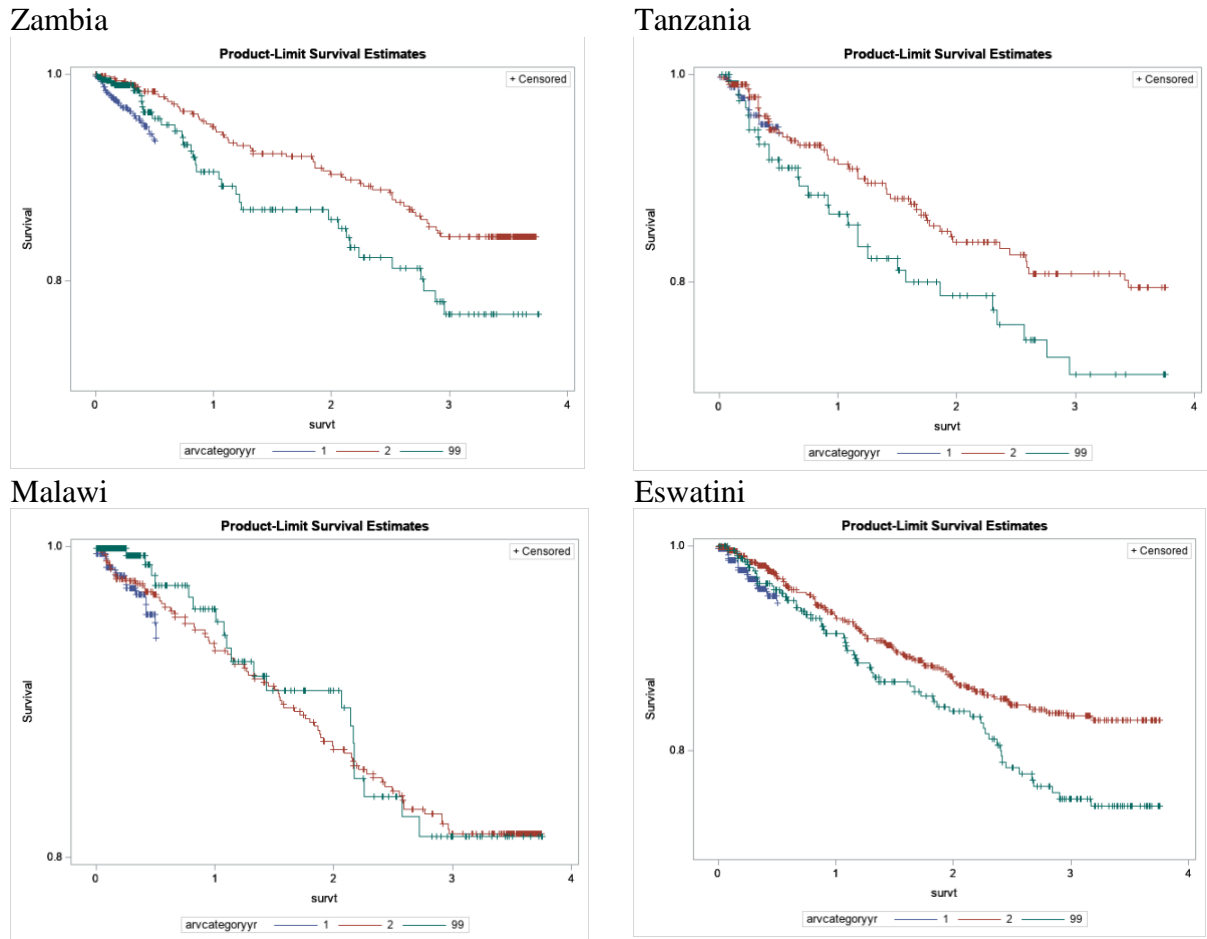
Exposure 1: HIV-negative Women

Exposure 2: HIV-positive Women not on ART

Exposure 3: HIV-positive Women on ART

Table 4b. Cox Proportional Hazards Model to Determine Predictors of Time to Next Pregnancy: HIV-positive Women not on ART (Reference) Compared to HIV-positive Women on ART, with 1 Year ART Duration Categories				
	Zambia	Malawi	Eswatini	Tanzania
HIV-positive Women Not on ART				
Pregnancy Events	36	22	31	61
Person Time in Years	485.79	380.57	218.76	645.7
Hazard Ratio	1.0	1.0	1.0	1.0
95% Confidence Interval	-	-	-	-
HIV-positive Women on ART < 1 Year				
Pregnancy Events	33	29	21	52
Person Time in Years	246.79	251.55	179.29	456.75
Hazard Ratio	2.24	2.65	1.28	0.67
95% Confidence Interval	(1.17, 4.31)	(1.19, 5.89)	(0.8, 2.05)	(0.28, 1.59)
HIV-positive Women on ART > 1 Year				
Pregnancy Events	61	87	51	118
Person Time in Years	1273.4	1357.83	704.99	2125.09
Hazard Ratio	0.64	1.61	0.63	0.64
95% Confidence Interval	(0.41, 1.02)	(0.85, 3.02)	(0.44, 0.9)	(0.39, 1.04)

Figure 2: Kaplan-Meier Curves of Time to Pregnancy: Comparing HIV-positive Women not on ART, HIV-positive Women on ART <1 Year, and HIV-positive Women on ART >1 Year in sub-Saharan Africa, 2012-2017



Legend

Survvt: Time in Years
 ART Category 1: HIV-positive Women on ART <1 Year
 ART Category 2: HIV-positive Women on ART >1 Year
 ART Category 99: HIV-positive Women not on ART

Exploratory Analysis

A third proportional hazards model was run to determine more precise differences in pregnancy incidence among HIV-positive women on ART <6 months, on ART between 6 and 12 months, on ART between 12 months and 18 months, and on ART >18 months. The previous analysis reported risk of incident pregnancy at 1 year duration intervals due to the initial findings of the exploratory analysis. These initial findings demonstrated a similar risk of incident pregnancy for women on ART <6 months and on ART between 6 and 12 months. Additionally, the exploratory analysis also suggested a similar fertility risk for women on ART between 12 months and 18 months and on ART >18 months. The former and latter duration categories were therefore merged in the final analysis; however, shorter duration intervals may provide insight for future studies analyzing time to pregnancy and time on ART.

The rate of incident pregnancy among HIV-positive women on ART in Eswatini was not different than the rate among HIV-positive women not on ART for the following 6-month duration categories: on ART <6 months (HR: 1.14; 95% CI: 0.65, 1.99; p=0.64), on ART between 6 and 12 months (HR: 1.56; 95% CI: 0.9, 2.73; p=0.11), and on ART between 12 and 18 months (HR: 0.77; 95% CI: 0.39, 1.52; p=0.44). The hazard of pregnancy among HIV-positive women on ART >18 months (HR: 0.62; 95% CI: 0.43, 0.89; p=0.01), however, was 38% less than the corresponding hazard among HIV-positive women not on ART in Eswatini.

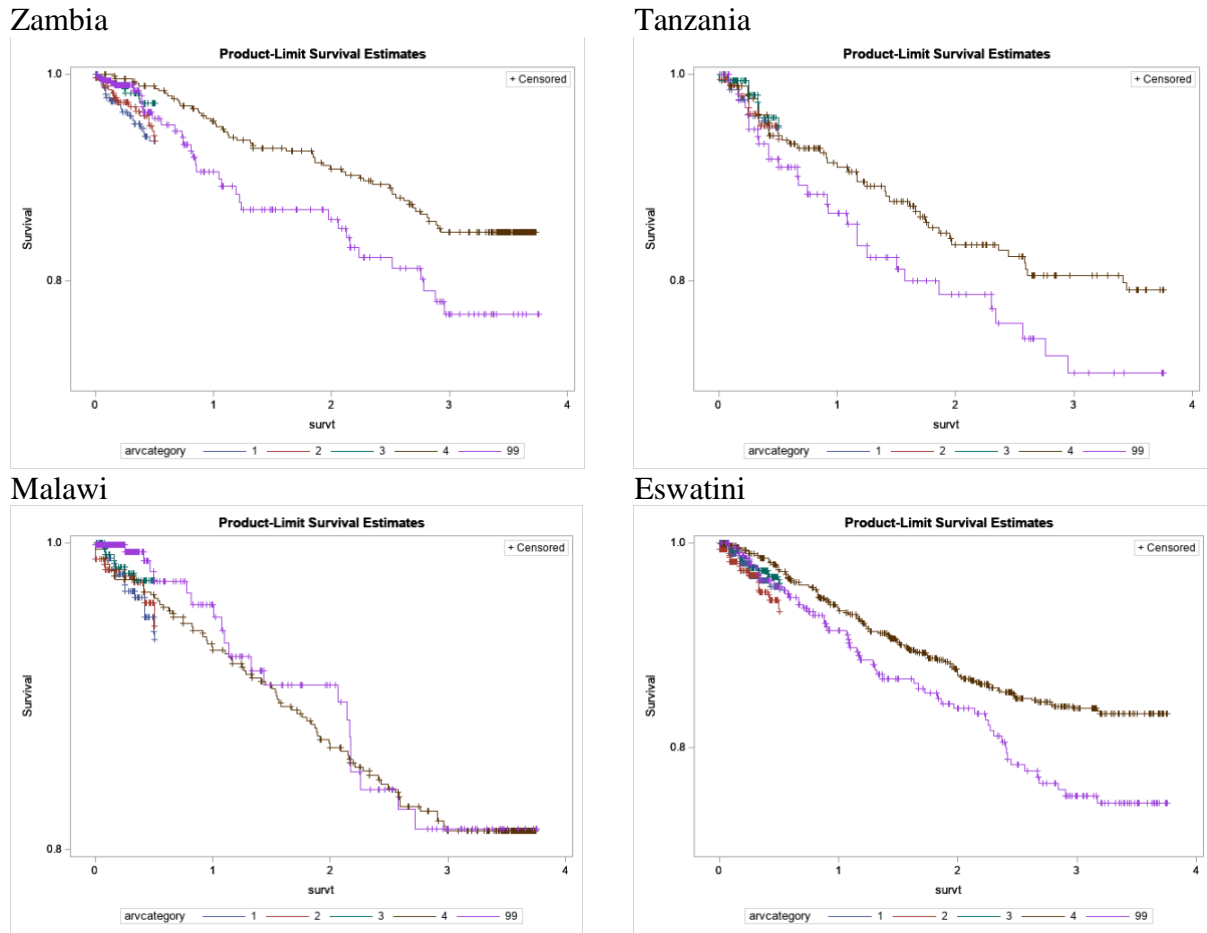
Assessing the association between time to pregnancy and time on ART in Malawi, we determined that the hazard of pregnancy among HIV-positive women on ART <6 months was 2.83 times that of HIV-positive women not on ART (HR: 2.83; 95% CI: 1.30, 6.16; p=0.01). The hazard of pregnancy among HIV-positive women on ART between 6 and 12 months (HR: 2.39; 95% CI: 0.89, 6.46; p=0.08), HIV-positive women on ART between 12 months and 18 months (HR: 1.51;

95% CI: 0.49, 4.66; $p=0.46$), and HIV-positive women on ART >18 months (HR: 1.62; 95% CI: 0.85, 3.09; $p=0.14$) did not differ than that of women not on ART. Additionally, there were no differences observed in the association between time to pregnancy and time on ART for any of the 6-month duration categories in Tanzania, when compared to HIV-positive women not on ART: HIV-positive women on ART <6 months (HR: 0.96; 95% CI: 0.34, 2.73; $p=0.93$), HIV-positive women on ART between 6 and 12 months (HR: 0.40; 95% CI: 0.16, 1.03; $p=0.06$), HIV-positive women on ART between 12 and 18 months (HR: 0.77; 95% CI: 0.26, 2.28); $p=0.62$), and HIV-positive women on ART >18 months (HR: 0.62; 95% CI: 0.37, 1.02; $p=0.06$).

After analyzing survival time in Zambia, we determined that the pregnancy incidence rate for HIV-positive women on ART <6 months (HR 2.59; 95% CI: 1.20, 5.59; $p=0.02$) was 2.59 times that of HIV-positive women not on ART. Additionally, the hazard of pregnancy among HIV-positive women on ART between 6 and 12 months (HR: 2.50; 95% CI: 1.15, 5.47; $p=0.02$) was 2.5 times the corresponding hazard among HIV-positive women not on ART. The pregnancy incidence rate for HIV-positive women on ART >18 months, on the other hand, was 40% less than that of HIV-positive women not on ART (HR: 0.60; 95% CI: 0.37, 0.96; $p=0.03$). There was no difference observed in the association between time to pregnancy and ART duration for HIV-positive women on ART between 12 and 18 months (HR: 1.26; 95% CI: 0.45, 3.51; $p=0.65$).

Table 4c. Cox Proportional Hazards Model to Determine Predictors of Time to Next Pregnancy: HIV-positive Women not on ART (Reference) Compared to HIV-positive Women on ART, with 6 Month ART Duration Categories				
	Zambia	Malawi	Eswatini	Tanzania
HIV-positive Women Not on ART				
Pregnancy Events	36	22	31	61
Person Time in Years	485.79	380.57	218.76	645.7
Hazard Ratio	1.0	1.0	1.0	1.0
95% Confidence Interval	-	-	-	-
HIV-positive Women on ART < 6 Months				
Pregnancy Events	18	16	10	23
Person Time in Years	131.43	129.99	93.73	244.84
Hazard Ratio	2.59	2.83	1.14	0.96
95% Confidence Interval	(1.2, 5.59)	(1.3, 6.16)	(0.65, 1.99)	(0.34, 2.73)
HIV-positive Women on ART 6-12 Months				
Pregnancy Events	15	13	11	29
Person Time in Years	115.36	121.56	85.56	211.91
Hazard Ratio	2.5	2.39	1.56	0.4
95% Confidence Interval	(1.15, 5.47)	(0.89, 6.46)	(0.9, 2.73)	(0.16, 1.03)
HIV-positive Women on ART 12-18 Months				
Pregnancy Events	6	6	7	15
Person Time in Years	103.53	117.43	72.04	189.88
Hazard Ratio	1.26	1.51	0.77	0.77
95% Confidence Interval	(0.45, 3.51)	(0.49, 4.66)	(0.39, 1.52)	(0.26, 2.28)
HIV-positive Women on ART >18 Months				
Pregnancy Events	55	81	44	103
Person Time in Years	1169.87	1240.4	632.95	1935.21
Hazard Ratio	0.6	1.62	0.62	0.62
95% Confidence Interval	(0.37, 0.96)	(0.85, 3.09)	(0.43, 0.89)	(0.37, 1.02)

Figure 3: Kaplan-Meier Curves of Time to Pregnancy: Comparing HIV-positive Women not on ART and HIV-positive Women on ART at 6 Month Duration Intervals in sub-Saharan Africa, 2012-2017



Legend

- Survvt: Time in Years
- ART Category 1: HIV-positive Women on ART <6 Months
- ART Category 2: HIV-positive Women on ART Between 6 and 12 Months
- ART Category 3: HIV-positive Women on ART Between 12 and 18 Months
- ART Category 4: HIV-positive Women on ART >18 Months
- ART Category 99: HIV-positive Women not on ART

Summary of Findings

The analysis determined that the pregnancy incidence rates for HIV-negative women were higher in all four countries, except for Eswatini, when compared to HIV-positive women not on ART. This trend mirrored that of the General Fertility Rates collected by the PHIA Project, with women living with HIV in Eswatini reporting higher fertility than their negative counterparts (Table 5). The General Fertility Rates (GFR) estimate the average annual births per 1000 women of reproductive age in each country. These rates were calculated as the number of weighted births in the last year divided by the number of weighted women of reproductive age with all women assumed to contribute 1 year of person time to the study. The GFRs provide a comparable estimate to the weighted fertility rates calculated as part of this analysis; however, these rates do not differentiate between HIV-positive women on ART and those not on ART. Rates of pregnancy incidence among HIV-negative women in our analysis were also higher than HIV-positive women on ART in all four countries. Additionally, pregnancy incidence was higher among HIV-positive women not ART compared to those on ART in Zambia, Eswatini, and Tanzania. Meanwhile, rates of pregnancy incidence for women not ART were lower than women on ART in Malawi.

Table 5. Comparison of Weighted Pregnancy Incidence Rates					
	GFR: HIV- negative Women	Analysis: HIV- negative Women	GFR: HIV-positive Women, ART N/A	Analysis: HIV-positive Women not on ART	Analysis: HIV-positive Women on ART
Zambia					
Rate per 1000 PYs	147.28	130.53	111.8	74.84	64.4
Malawi					
Rate per 1000 PYs	132.69	125.66	115.5	66.98	77.15
Tanzania					
Rate per 1000 PYs	150.37	127.43	127.17	109.46	76.1
Eswatini					
Rate per 1000 PYs	91.57	69.04	103.95	90.19	63.26

According to the proportional hazards' regressions, pregnancy incidence was significantly less for HIV-positive women not on ART compared to HIV-negative women in both Malawi and Zambia. Rates of pregnancy incidence for HIV-positive women on ART were also significantly less than HIV-negative women in Malawi, Zambia, and Tanzania. Analyzing the duration of antiretroviral therapy, HIV-positive women on ART <1 year were determined to have significantly higher pregnancy incidence than HIV-positive women not on ART in both Malawi and Zambia. Meanwhile, HIV-positive women on ART >1 year were found to have significantly lower pregnancy incidence compared to HIV-positive women not on ART; however, this finding was only significant in Eswatini. The analysis determined that there was no significant difference in pregnancy incidence for the following hazards comparisons:

- HIV-positive women not on ART and HIV-negative women in Eswatini
- HIV-positive women on ART and HIV-negative women in Eswatini
- HIV-positive women on ART <1 year and HIV-positive women not on ART in Eswatini
- HIV-positive women on ART >1 year and HIV-positive women not on ART in Malawi
- HIV-positive women not on ART and HIV-negative women in Tanzania
- HIV-positive women on ART <1 year and HIV-positive women not on ART in Tanzania
- HIV-positive women on ART >1 year and HIV-positive women not on ART in Tanzania
- HIV-positive women on ART >1 year and HIV-positive women not on ART in Zambia

Discussion

ART and Fertility

In this analysis, we found that pregnancy incidence was lower among HIV-positive women not on ART and HIV-positive women on ART compared to HIV-negative women. These findings were consistent for all four countries, except for Eswatini, where pregnancy incidence was higher for HIV-positive women not on ART compared to HIV-negative women. This analysis supports the preliminary conclusions of Yeatman *et al.*, who suggested that the fertility of women on ART was similar to women not yet on ART but still lower than that of HIV-negative women [24]. These findings, however, contradict more recent conclusions suggesting that pregnancy incidence rates are highest among women on ART, low among HIV-negative women, and lowest among HIV-positive women not on ART [12]. Johnson *et al.* determined that the receipt of ART was associated with high rates of second pregnancy in this analysis; therefore, these results may not be comparable to our study, which did not account for time from first to second pregnancy. There is conflicting evidence in the available literature comparing the fertility of HIV-negative women, HIV-positive women on ART, and HIV-positive women not yet on ART. Few studies have directly compared pregnancy incidence rates between HIV-positive women on ART and HIV-negative women, although several studies have compared HIV-positive women on ART with those not on ART; these latter analyses, however, have produced inconsistent results.

According to a systematic review analyzing fertility differences by duration of ART, fertility was suggested to increase 1 year after ART initiation among women living with HIV [20]. In our analysis, however, we found that HIV-positive women on ART >1 year were overall less likely to report a recent pregnancy than HIV-positive women not on ART in all countries except Malawi. Further, HIV-positive women on ART <1 year were overall more likely to report a recent

pregnancy than HIV-positive women not on ART in all countries except for Tanzania. Additional differences in fertility were estimated at 6-month duration intervals in the exploratory analysis, which can be evaluated against previous studies examining pregnancy incidence at similar and shorter intervals of treatment duration.

ART and Fertility: Exploratory Analysis

In our exploratory analysis, we concluded that pregnancy incidence was highest for HIV-positive women on ART <6 months in Zambia and Malawi, with consistent decreases in fertility at 6-12 months and 12-18 months duration, respectively. Fertility continued to decrease for HIV-positive women, on ART >18 months in Zambia while fertility increased slightly between 12-18 months and >18 months duration in Malawi. Similar to Zambia and Malawi, the highest rates of pregnancy incidence in Tanzania were among HIV-positive women on ART <6 months. The trend of fertility in Tanzania declined between 6 and 12 months, representing the lowest hazard of pregnancy compared to HIV-positive women not on ART. Fertility increased at 12-18 months and then decreased again at greater than 18 months duration in Tanzania. In Eswatini, rates of pregnancy were highest among HIV-positive women on ART between 6 and 12 months, followed by those on ART <6 months. Fertility decreased in the latter two duration categories in Eswatini, with HIV-positive women on ART >18 months reporting the lowest fertility rates when compared to HIV-positive women not on ART.

Analyzing pregnancy rates among women in an urban Malawian ART clinic, Tweya and colleagues concluded that women on ART >6 months were three times as likely to report an incident pregnancy compared to those on ART for shorter durations [21]. Researchers concluded

that improved health status among women on ART was strongly associated with increased risk of pregnancy. Fertility rates among women on ART in this study were similar to that of the average urban population after 6 months on treatment for HIV [21]. These findings do not directly reflect the results of our analysis; however, additional research has demonstrated a higher risk of pregnancy with recent initiation of ART. Kaida *et al.* determined that incident pregnancy peaked at 6–12 months after ART initiation, declined and stabilized between 12–36 months, then drastically decreased after 36 months on treatment [23]. Although the duration intervals utilized in this study differ from those applied in our analysis, the trends of decreasing fertility with increased duration of ART mirror the declining hazard of pregnancy incidence observed within our population of women living with HIV.

Biological Impacts of ART on Fertility

Research has historically shown that women living with HIV have experienced sub-fertility due to both biological alterations in the reproductive system that impact fertility outcomes and behavioral or social factors that influence fertility desires. Systemic illness, stress, weight loss, and wasting associated with HIV-infection have overall reduced the reproductive potential of women living with HIV [26]. These women are more likely to experience anovulation and amenorrhea with one study concluding that HIV-positive women were three times more likely than HIV-negative controls to have prolonged amenorrhea [27]. WLWH are also at increased risk of opportunistic infections (OIs) and sexually transmitted infections (STIs), which have both been found to contribute to infertility and declining reproductive health [26].

Although research has demonstrated the negative impacts of HIV infection on fertility, the direct impact of antiretroviral therapy on fertility remains unclear. According to studies conducted

in developed countries, HIV infection is associated with a decline in fertility while ART is associated with both increased survival times and delayed progression to AIDS. Additionally, antiretroviral therapy was found to improve general health and reduce physical stress among women living with HIV, which are factors associated with normal ovulation and regular menstrual cycles [26]. These preliminary findings suggest that ART reverses HIV-related declines in fertility. Further evidence has also shown that those on ART report fewer OIs and increased contact with the health care system, thereby providing increased opportunities for treatment, testing, and prevention of STIs [26]. Additional research is needed to evaluate the direct impact of antiretroviral agents on the biological processes of reproduction to fully understand the changing fertility potential of women living with and being treated for HIV.

Behavioral Impacts of ART on Fertility

Fertility differences among women living with HIV are also rooted in associated changes in sexual behavior and fertility desires after diagnosis. Many women reported a decrease in sexual activity due to feelings of shame, guilt, and fear associated with awareness and stigma of HIV-infection [26]. Previous studies have demonstrated that HIV-positive women avoid pregnancy or prefer to have fewer children after infection. According to a 1998 study in Zimbabwe, women reported that they overall wanted fewer children and delayed births because of the AIDS epidemic [28]. Additionally, respondents felt that women should stop having children after receiving an HIV diagnosis due to risk of vertical transmission and concern about maternal mortality. A recent qualitative study conducted among HIV-positive women in western Kenya concluded that HIV still negatively influences fertility desires [29]. According to this study, initiating ART did not

translate to increased fertility desires with individual socioeconomic factors and societal influences having the greatest influence on future fertility rates of women living with HIV.

Although women living with HIV continue to report reduced fertility desires, studies have suggested that high risk sexual behaviors and unwanted pregnancies remain prevalent within this population [30]. A previous study concluded that women living with HIV continue to exhibit high risk sexual behavior even after infection and, therefore, remain at risk for pregnancy regardless of fertility desire. In response to findings such as these, Prevention of Mother-to-child Transmission of HIV (PMTCT) Programs have directly targeted the prevention of unplanned pregnancies among HIV-infected women [31]. Since a significant distribution of our target population are diagnosed through PMTCT programs, women living with HIV in sub-Saharan Africa may experience lower rates of unintended pregnancy compared those diagnosed and treated through other programs due to this targeted focus on pregnancy prevention.

Limitations

Our analysis had several limitations. Most significantly, women living with HIV but unaware of their serostatus were excluded in the final analysis. This subset of women was lacking a first HIV positive test date, which prevented researchers from generating an accurate timeline for the time-varying exposure categories and related pregnancy events. The analysis also excluded women who were currently pregnant or pregnant before the time start, which was defined as forty-five months before the survey date. There were additional limitations related to partial and missing date variables in each country. Data related to the ARV last treatment date was not available in Eswatini or Tanzania and, therefore, the time-varying exposure categories were not able to account for treatment termination in these countries. There was also no birth month data available for recent

live births in Eswatini and Tanzania, which thereby impacted the calculated pregnancy start date for women in these countries. All women with a recent live birth in Eswatini and Tanzania were assigned a random birth month integer that was then utilized to estimate conception. Lastly, pregnancy start dates in all countries were based on an assumed gestational period of nine months; however, this did not account for potentially altered gestational periods among women living with HIV or on ART and therefore, may have contributed bias to our study design.

Another limitation of our analysis is that we did not account for covariates in our proportional hazard's models due to the restricted timeline for thesis submission. Many previous studies assessed for confounding and interaction by age, CD4 count, and viral load, specifically, which we recommend for future work analyzing the association between antiretroviral therapy and time to pregnancy. Additionally, we did not account for women with expressed fertility desires or women who were actively utilizing methods of pregnancy prevention. These reproductive health factors may indicate a predisposition, or lack thereof, for future pregnancy events. Finally, the sample size of women living with HIV was relatively small in each country analyzed in our study. This was a driving limiting factor in the assessment of potential covariates as well as in the analysis of time to pregnancy for various duration categories. Despite these limitations, our findings reflect comprehensive fertility estimates for women living with HIV and on ART in sub-Saharan Africa while filling a research gap that has not been sufficiently addressed in previous studies and reviews.

Future Research and Recommendations

The results of this analysis indicate that women living with HIV need better access to family planning and HIV counseling services to determine barriers to fertility and assess fertility

desires. Although women living with HIV and receiving ART were less likely to have a recent pregnancy in this study, rates of unintended pregnancy remain high among HIV-positive African women, demonstrating a need for expanded pregnancy prevention in this region. Further research on the association between time to pregnancy and antiretroviral therapy is also needed given the mixed evidence presented in this analysis and in previous studies. First, the methodology utilized for this analysis should be applied to the remaining nine countries where PHIA data are publicly available. Next, an amended methodology should be applied to larger longitudinal data sets to overcome the limitations associated with the small sample size of women living with HIV and on ART in this study. Additional research should also account for age, CD4 count, and viral load as well as other demographic and reproductive health outcomes. Finally, future research should analyze first and subsequent pregnancies over a longer duration of time to determine whether ART contributes to fertility differences with respect to parity.

Conclusion

Fertility differences between HIV-negative women and HIV-positive women are narrowing with the expansion of ART throughout sub-Saharan Africa. Our findings suggest that fertility differs by the duration of antiretroviral therapy with further qualitative and quantitative data needed to expand upon the association between time to pregnancy and time on ART. All women living with HIV should be better informed about the advances in antenatal, prenatal, and postnatal care as well as in the prevention of vertical transmission as they prepare for childbearing. Assessing and managing fertility desires among women living with HIV is a significant gap in care with little focus directed towards family planning and assisted fertility therapy programs for those impacted by HIV/AIDS. Improving access to antiretroviral therapy as well as family

planning services has the potential to decrease the burden of HIV and unwanted pregnancies among women of reproductive age in sub-Saharan Africa. Additionally, these expansion efforts have the potential to reduce maternal mortality, AIDS progression, and co-morbidities related to HIV and unwanted pregnancies. Further studies are needed to address the differential fertility desires and outcomes for WLWH as well as understand the biological, behavioral, and psychosocial effects of HIV and ART on pregnancy incidence in sub-Saharan Africa.

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Appendix

A. Table 1. Baseline Characteristics by Country

Table 1a. Description of Sociodemographic and Clinical Characteristics of HIV-positive Women and HIV-negative Women, 15-49 years of age, in Eswatini, August 2016 to March 2017								
	HIV-positive Women (N=1694)						HIV-negative Women (N=3184)	
	Aware of HIV Status				Unaware of HIV Status			
	On ART, n (%)	95% CI	Not on ART, n (%)	95% CI	ART N/A, n (%)	95% CI	HIV-negative, n (%)	95% CI
Total, N (%)	1342 (100.0%)		190 (100.0%)		158 (100.0%)		3184 (100.0%)	
Age								
15-19 years	45 (3.2%)	(2.3, 4.2)	6 (3.4%)	(0.4, 6.3)	21 (11.5%)	(7.1, 15.9)	959 (27.4%)	(26.7, 28.1)
20-24 years	128 (9.1%)	(7.5, 10.7)	25 (13.5%)	(8.6, 18.4)	43 (27.2%)	(19.6, 34.8)	698 (22.7%)	(21.8, 23.5)
25-29 years	240 (17.8%)	(16.0, 19.6)	44 (20.8%)	(14.9, 26.8)	35 (22.0%)	(14.4, 29.6)	492 (16.2%)	(15.3, 17.0)
30-34 years	317 (22.1%)	(19.7, 24.4)	50 (26.6%)	(20.4, 32.8)	24 (14.8%)	(9.3, 20.4)	350 (11.2%)	(10.2, 12.1)
35-39 years	271 (21.2%)	(18.9, 23.4)	29 (17.0%)	(11.6, 22.4)	19 (12.7%)	(7.2, 18.1)	249 (8.7%)	(7.8, 9.7)
40-44 years	197 (16.5%)	(14.2, 18.9)	16 (8.3%)	(3.9, 12.6)	11 (7.7%)	(3.5, 12.0)	206 (7.1%)	(6.2, 8.0)
45-49 years	144 (10.1%)	(8.7, 11.4)	20 (10.5%)	(6.6, 14.4)	5 (4.0%)	(0.03, 8.04)	230 (6.8%)	(6.2, 7.3)
Region								
Urban	327 (30.0%)	(26.3, 33.7)	50 (30.5%)	(20.1, 40.8)	46 (34.7%)	(25.0, 44.3)	676 (28.1%)	(24.9, 31.3)
Rural	1015 (70.0%)	(66.3, 73.8)	140 (69.6%)	(59.2, 79.9)	112 (65.4%)	(55.7, 75.0)	2508 (71.9%)	(68.7, 75.1)
Education								
Ever Attended School	1277 (95.2%)	(93.9, 96.4)	187 (98.9%)	(97.7, 100.0)	154 (97.7%)	(95.6, 99.8)	3114 (97.9%)	(97.3, 98.4)
Highest Level of Education								
Primary	439 (32.4%)	(29.7, 35.0)	59 (29.4%)	(22.1, 36.7)	36 (20.0%)	(13.5, 26.5)	696 (20.3%)	(18.4, 22.1)
Secondary	477 (37.3%)	(34.5, 40.0)	65 (36.7%)	(29.4, 43.9)	54 (35.4%)	(27.9, 43.0)	1070 (32.2%)	(30.3, 34.1)
High School	293 (24.4%)	(21.6, 27.2)	49 (26.2)	(19.5, 32.9)	51 (34.0%)	(25.3, 42.7)	1003 (34.0%)	(32.2, 35.8)
Tertiary	67 (5.9%)	(4.1, 7.8)	14 (7.8)	(3.3, 12.3)	12 (10.1%)	(3.0, 17.1)	341 (13.4%)	(11.2, 15.6)
Wealth Status								
Lowest Quintile	323 (22.0%)	(19.5, 24.6)	41 (19.6%)	(14.1, 25.2)	28 (15.0%)	(8.9, 21.1)	712 (19.5%)	(17.5, 21.1)
Second Quintile	306 (21.7%)	(18.8, 24.7)	32 (17.9%)	(11.6, 24.3)	31 (18.4%)	(12.1, 24.7)	666 (19.1%)	(17.0, 21.2)
Middle Quintile	286 (20.5%)	(17.9, 23.2)	45 (24.0%)	(17.1, 31.0)	43 (25.7%)	(18.0, 33.3)	754 (22.8%)	(20.1, 25.5)

Forth Quintile	245 (20.6%)	(17.4, 23.8)	41 (23.2%)	(17.1, 29.2)	29 (21.3%)	(14.2, 28.4)	505 (17.7%)	(15.1, 20.3)
Highest Quintile	180 (15.1%)	(12.2, 18.0)	31 (15.2%)	(9.6, 20.8)	27 (19.6%)	(10.8, 28.3)	547 (20.9%)	(16.8, 24.9)
Reproductive History								
Live Birth Ever	1142 (84.8%)	(82.2, 87.4)	161 (83.9%)	(78.3, 89.6)	100 (63.1%)	(55.4, 70.8)	1806 (57.7%)	(55.8, 59.5)
Birth Last 1 Year	147 (10.9%)	(8.9, 12.9)	6 (3.4%)	(0.4, 6.4)	7 (3.9%)	(0.8, 7.0)	276 (8.5%)	(7.5, 9.6)
Birth Last 3 Years	357 (25.8%)	(22.7, 28.9)	34 (18.0%)	(12.3, 23.7)	26 (16.3%)	(10.3, 22.3)	699 (22.0%)	(20.5, 23.5)
Currently Pregnant	60 (4.2%)	(3.2, 5.3)	6 (2.9%)	(0.3, 5.6)	5 (2.7%)	(0.4, 5.0)	120 (3.7%)	(3.0, 4.4)
Currently Avoiding Pregnancy	937 (72.3%)	(69.3, 75.4)	129 (69.7%)	(63.5, 76.0)	89 (58.7%)	(50.2, 67.1)	1533 (51.4%)	(49.5, 53.3)
HIV Biomarkers								
CD4 <100	17 (1.5%)	(0.6, 2.3)	5 (2.3%)	(0.3, 4.3)	4 (2.8%)	(0.0, 6.0)	N/A	N/A
100=<CD4 <200	35 (2.6%)	(1.6, 3.6)	19 (9.8%)	(6.3, 13.3)	13 (9.4%)	(4.4, 14.4)	N/A	N/A
200=<CD4 <350	122 (9.6%)	(7.6, 11.5)	40 (21.1%)	(15.2, 27.0)	35 (22.5%)	(15.3, 29.7)	N/A	N/A
350=<CD4 <500	253 (18.7%)	(16.4, 21.0)	37 (19.2%)	(13.0, 25.4)	36 (21.9%)	(15.3, 28.5)	N/A	N/A
CD4 >=500	915 (67.7%)	(64.5, 70.8)	89 (47.6%)	(40.4, 54.8)	69 (42.9%)	(33.5, 52.3)	N/A	N/A
VLS	1223 (91.4%)	(89.0, 92.8)	23 (12.7%)	(7.5, 17.9)	21 (14.0%)	(6.1, 21.8)	N/A	N/A
Not VLS	119 (8.6%)	(7.2, 10.1)	167 (87.3%)	(82.1, 92.5)	137 (86.0%)	(78.2, 93.9)	N/A	N/A
ART Duration								
>=24 Months	841 (62.6%)	(60.0, 65.3)	N/A	N/A	N/A	N/A	N/A	N/A
12-23 Months	190 (13.6%)	(11.5, 15.8)	N/A	N/A	N/A	N/A	N/A	N/A
<12 Months	236 (17.5%)	(14.9, 20.0)	N/A	N/A	N/A	N/A	N/A	N/A
¹ Sociodemographic and Clinical Characteristics are presented as unweighted frequencies and weighted percent distributions.								
² Abbreviations: HIV, human immunodeficiency virus; ART, antiretroviral therapy								

Table 1b. Description of Sociodemographic and Clinical Characteristics of HIV-positive Women and HIV-negative Women, 15-49 years of age, in Malawi, November 2015 to August 2016								
	HIV-positive Women (N=1327)						HIV-negative Women (N=7622)	
	Aware of HIV Status			Unaware of HIV Status			HIV-negative, n (%)	95% CI
	On ART, n (%)	95% CI	Not on ART, n (%)	95% CI	ART N/A, n (%)	95% CI		
Total, N (%)	971 (100%)		89 (100%)		264 (100%)		7622 (100%)	
Age								
15-19 years	15 (2.3%)	(1.1, 3.5)	1 (2.7%)	(0.0, 7.8)	22 (10.1%)	(4.4, 15.8)	1608 (26.2%)	(25.9, 26.5)

20-24 years	74 (6.0%)	(4.4, 7.7)	11 (11.6%)	(3.4, 19.7)	47 (15.7%)	(10.6, 20.9)	1801 (21.1%)	(20.8, 21.3)
25-29 years	143 (16.4%)	(13.6, 19.3)	19 (26.5%)	(12.5, 40.4)	55 (23.9%)	(17.7, 30.0)	1294 (16.2%)	(15.8, 16.5)
30-34 years	216 (20.1%)	(17.2, 22.9)	17 (15.1%)	(5.8, 24.4)	60 (20.3%)	(14.7, 25.9)	1132 (12.9%)	(12.6, 13.3)
35-39 years	233 (22.0%)	(19.4, 24.7)	21 (20.9%)	(10.6, 31.2)	41 (13.4%)	(8.1, 18.7)	801 (9.8%)	(9.5, 10.2)
40-44 years	176 (19.9%)	(17.1, 22.7)	14 (17.8%)	(5.8, 29.8)	25 (10.3%)	(5.7, 14.8)	569 (7.6%)	(7.2, 7.9)
45-49 years	114 (13.2%)	(10.6, 15.9)	6 (5.4%)	(0.2, 10.6)	14 (6.4%)	(2.5, 10.3)	417 (6.2%)	(5.9, 6.5)
Region								
Urban	464 (26.8%)	(22.0, 31.7)	52 (32.0%)	(20.1, 43.8)	143 (30.8%)	(23.3, 38.2)	2808 (18.4%)	(15.7, 21.2)
Rural	507 (73.2%)	(68.3, 78.0)	37 (68.0%)	(56.2, 80.0)	121 (69.2%)	(61.8, 76.7)	4814 (81.6%)	(78.9, 84.3)
Education								
Ever Attended School	849 (84.2%)	(81.2, 87.0)	77 (83.4%)	(72.7, 94.2)	243 (89.8%)	(84.2, 95.3)	7026 (90.5%)	(89.5, 91.4)
Highest Level of Education								
Primary	587 (76.2%)	(72.9, 79.6)	52 (82.0%)	(72.8, 91.1)	143 (64.1%)	(55.4, 72.9)	4559 (73.2%)	(71.4, 75.1)
Secondary	224 (20.9%)	(17.7, 24.1)	22 (16.9%)	(8.0, 25.8)	90 (33.6%)	(24.9, 42.2)	2143 (24.3%)	(22.6, 26.0)
Higher	38 (2.9%)	(1.7, 4.0)	2 (1.2%)	(0.0, 2.9)	10 (2.3%)	(0.6, 4.0)	321 (2.4%)	(2.0, 2.8)
Wealth Status								
Lowest Quintile	117 (16.7%)	(13.5, 19.8)	8 (18.4%)	(4.8, 31.9)	25 (14.7%)	(8.7, 20.6)	920 (16.5%)	(15.0, 18.1)
Second Quintile	123 (17.6%)	(14.6, 20.6)	9 (15.1%)	(5.6, 24.6)	23 (12.7%)	(7.7, 17.7)	1090 (18.0%)	(16.6, 19.4)
Middle Quintile	131 (17.9%)	(14.9, 20.8)	14 (21.4%)	(10.2, 32.6)	33 (18.4%)	(11.7, 25.1)	1248 (20.4%)	(18.9, 21.9)
Forth Quintile	182 (21.1%)	(17.2, 25.0)	11 (13.5%)	(4.2, 22.8)	47 (17.0%)	(10.6, 23.4)	1575 (21.6%)	(20.0, 23.1)
Highest Quintile	418 (26.8%)	(22.7, 30.8)	47 (31.6%)	(20.1, 43.1)	136 (37.2%)	(28.7, 45.8)	2789 (23.5%)	(21.4, 25.7)
Reproductive History								
Live Birth Ever	915 (94.8%)	(93.0, 96.5)	81 (90.7%)	(83.6, 97.7)	215 (82.6%)	(76.0, 89.2)	5675 (72.5%)	(71.4, 73.6)
Birth Last 1 Year	112 (11.8%)	(9.4, 14.3)	4 (5.5%)	(0.0, 11.3)	14 (5.7%)	(2.1, 9.3)	987 (13.3%)	(12.3, 14.2)
Birth Last 3 Years	306 (32.1%)	(28.4, 35.8)	14 (21.5%)	(8.6, 34.5)	49 (23.7%)	(16.8, 30.7)	2778 (36.9%)	(35.6, 28.3)
Currently Pregnant	37 (4.4%)	(2.8, 6.0)	5 (9.8%)	(0.3, 19.2)	8 (4.1%)	(0.5, 7.6)	512 (6.7%)	(6.0, 7.4)
Currently Avoiding Pregnancy	490 (51.7%)	(47.6, 55.8)	42 (52.8%)	(38.1, 67.5)	112 (43.7%)	(37.0, 50.5)	3889 (53.3%)	(51.7, 54.8)
Currently Wanting Another Child	78 (8.4%)	(6.3, 10.6)	7 (7.4%)	(1.1, 13.7)	46 (14.9%)	(9.6, 20.2)	697 (8.7%)	(7.9, 9.5)

HIV Biomarkers								
CD4 <100	25 (2.2%)	(1.1, 3.3)	9 (7.3%)	(1.6, 12.9)	13 (4.0%)	(1.1, 6.9)	N/A	N/A
100=<CD4 <200	46 (4.2%)	(2.8, 5.7)	17 (22.4%)	(9.4, 35.4)	36 (12.6%)	(7.4, 17.7)	N/A	N/A
200=<CD4 <350	161 (13.7%)	(11.3, 16.0)	23 (21.1%)	(11.5, 30.6)	68 (24.7%)	(18.3, 31.0)	N/A	N/A
350=<CD4 <500	263 (23.6%)	(20.5, 26.7)	23 (24.1%)	(13.3, 34.8)	72 (23.7%)	(17.9, 29.6)	N/A	N/A
CD4 ≥=500	617 (56.1%)	(20.5, 26.7)	28 (25.2%)	(15.6, 34.8)	92 (29.0%)	(22.4, 35.6)	N/A	N/A
VLS	1020 (91.7%)	(89.4, 93.9)	10 (9.7%)	(3.0, 16.5)	57 (20.2%)	(14.9, 25.5)	N/A	N/A
Not VLS	90 (7.9%)	(5.7, 10.0)	90 (90.3%)	(83.5, 97.0)	238 (79.8%)	(74.5, 85.1)	N/A	N/A
ART Duration								
≥=24 Months	723 (64.7%)	(60.9, 68.6)	N/A	N/A	N/A	N/A	N/A	N/A
12-23 Months	129 (11.1%)	(8.8, 13.4)	N/A	N/A	N/A	N/A	N/A	N/A
<12 Months	161 (13.9%)	(11.6, 16.1)	N/A	N/A	N/A	N/A	N/A	N/A
¹ Sociodemographic and Clinical Characteristics are presented as unweighted frequencies and weighted percent distributions.								
² Abbreviations: HIV, human immunodeficiency virus; ART, antiretroviral therapy								

Table 1c. Description of Sociodemographic and Clinical Characteristics of HIV-positive Women and HIV-negative Women, 15-49 years of age, in Tanzania, November 2016 to June 2017								
	HIV-positive Women (N=1040)						HIV-negative Women (N=13589)	
	Aware of HIV Status			Unaware of HIV Status			HIV-negative, n (%)	95% CI
	On ART, n (%)	95% CI	Not on ART, n (%)	95% CI	ART N/A, n (%)	95% CI		
Total, N (%)	608 (100%)		42 (100%)		355 (100%)		13589 (100%)	
Age								
15-19 years	14 (3.5%)	(1.7, 5.3)	1 (0.6%)	(0.0, 1.8)	14 (4.1%)	(1.2, 7.0)	2969 (23.9%)	(23.8, 24.1)
20-24 years	49 (8.5%)	(5.6, 11.4)	5 (12.7%)	(0.3, 25.1)	57 (14.4%)	(10.3, 18.5)	2732 (19.7%)	(19.5, 19.8)
25-29 years	80 (12.4%)	(9.6, 15.3)	11 (29.7%)	(11.0, 48.3)	58 (16.5%)	(11.6, 21.4)	2363 (16.6%)	(16.4, 16.7)
30-34 years	112 (17.4%)	(13.6, 21.1)	7 (19.0%)	(2.6, 36.4)	82 (22.9%)	(17.2, 28.6)	1855 (13.6%)	(13.4, 13.8)
35-39 years	147 (23.8%)	(19.3, 28.2)	8 (20.5%)	(7.6, 33.3)	59 (18.1%)	(12.0, 24.2)	1525 (10.9%)	(10.7, 11.1)
40-44 years	111 (17.8%)	(14.2, 21.3)	7 (13.9%)	(1.2, 26.6)	53 (14.5%)	(9.4, 19.6)	1230 (8.7%)	(8.5, 8.9)
45-49 years	95 (16.7%)	(12.6, 20.7)	3 (3.7%)	(0.0, 8.7)	32 (9.5%)	(5.5, 13.6)	915 (6.7%)	(6.5, 6.9)
Region								
Urban	290 (52.3%)	(45.4, 59.3)	21 (67.6%)	(51.5, 83.6)	146 (45.4%)	(37.6, 53.3)	4703 (39.3%)	(35.5, 43.1)

Rural	318 (47.7%)	(40.7, 54.6)	21 (32.4%)	(16.4, 48.5)	209 (54.6%)	(46.7, 62.4)	8886 (60.7%)	(56.9, 64.5)
Education								
Ever Attended School	510 (85.6%)	(81.4, 89.8)	36 (80.3%)	(67.0, 93.6)	275 (78.7%)	(73.5, 83.9)	11405 (86.4%)	(85.1, 87.6)
Highest Level of Education								
Pre-Primary	2 (0.4%)	(0.0, 1.0)	N/A	N/A	3 (0.8%)	(0.0, 1.9)	63 (0.6%)	(0.4, 0.8)
Primary	437 (84.2%)	(80.1, 88.3)	28 (77.8%)	(59.0, 96.7)	229 (80.4%)	(74.2, 86.7)	7972 (68.1%)	(66.6, 69.6)
Post Primary	4 (1.6%)	(0.0, 3.5)	1 (5.5%)	(0.0, 17.0)	4 (1.2%)	(0.0, 2.6)	139 (1.2%)	(0.9, 1.5)
Secondary (O-Level)	62 (13.2%)	(9.6, 16.8)	5 (11.5%)	(0.0, 25.3)	36 (16.3%)	(10.2, 22.3)	2708 (24.7%)	(23.4, 25.9)
Post-Secondary (O-Level)	4 (0.2%)	(0.0, 0.5)	2 (5.2%)	(0.0, 12.9)	3 (1.3%)	(0.0, 3.0)	312 (3.4%)	(2.9, 3.9)
Secondary (A-Level)	1 (0.3%)	(0.0, 1.0)	N/A	N/A	N/A	N/A	65 (0.7%)	(0.5, 0.9)
Post-Secondary (A-Level)	N/A	N/A	N/A	N/A	N/A	N/A	34 (0.3%)	(0.2, 0.5)
University	N/A	N/A	N/A	N/A	N/A	N/A	107 (1.1%)	(0.8, 1.4)
Wealth Status								
Lowest Quintile	85 (12.9%)	(8.7, 17.0)	5 (5.2%)	(0.0, 11.4)	65 (16.8%)	(11.2, 22.3)	2779 (18.0%)	(15.6, 20.4)
Second Quintile	105 (16.4%)	(12.6, 20.2)	5 (6.2%)	(0.2, 12.1)	64 (15.7%)	(10.5, 20.9)	2768 (19.4%)	(17.7, 21.0)
Middle Quintile	171 (26.4%)	(21.1, 31.6)	9 (20.6%)	(6.5, 34.7)	82 (20.6%)	(15.2, 26.0)	2974 (20.1%)	(18.5, 21.7)
Forth Quintile	144 (24.4%)	(19.9, 29.0)	17 (50.5%)	(31.5, 69.5)	90 (27.7%)	(21.7, 33.7)	2521 (19.8%)	(18.0, 21.7)
Highest Quintile	103 (20.0%)	(15.6, 24.4)	6 (17.6%)	(2.3, 32.9)	54 (19.2%)	(14.0, 24.4)	2542 (22.7%)	(20.5, 24.9)
Reproductive History								
Live Birth Ever	559 (89.2%)	(85.3, 93.0)	37 (84.0%)	(68.7, 99.4)	303 (84.0%)	(78.8, 89.3)	10042 (71.2%)	(70.3, 72.2)
Birth Last 1 Year	81 (12.6%)	(9.1, 16.1)	1 (1.8%)	(0.0, 5.5)	30 (8.1%)	(4.6, 11.6)	2209 (15.0%)	(14.3, 15.8)
Birth Last 3 Years	199 (31.4%)	(26.2, 36.6)	13 (25.8%)	(7.9, 43.6)	91 (23.1%)	(18.1, 28.0)	5666 (39.1%)	(37.9, 40.4)
Currently Pregnant	40 (5.9%)	(3.6, 8.1)	2 (5.1%)	(0.0, 13.6)	22 (5.1%)	(2.4, 7.8)	1228 (8.6%)	(8.0, 9.3)
Currently Avoiding Pregnancy	234 (40.2%)	(34.5, 45.9)	16 (33.2%)	(16.8, 49.6)	101 (27.9%)	(22.1, 33.8)	3976 (32.7%)	(31.4, 34.1)
HIV Biomarkers								
CD4 <100	9 (1.0%)	(0.3, 1.7)	2 (3.1%)	(0.0, 7.8)	9 (3.6%)	(1.2, 6.1)	N/A	N/A
100=<CD4 <200	44 (7.5%)	(4.2, 10.8)	5 (6.3%)	(0.0, 12.9)	45 (14.2%)	(9.2, 19.1)	N/A	N/A
200=<CD4 <350	104 (17.1%)	(13.1, 21.0)	11 (24.4%)	(7.1, 41.8)	77 (19.1%)	(14.0, 24.2)	N/A	N/A

350=<CD4 <500	152 (24.2%)	(20.0, 28.5)	10 (33.6%)	(13.9, 53.3)	73 (21.1%)	(15.0, 27.3)	N/A	N/A
CD4 >=500	297 (50.0%)	(45.1, 54.9)	14 (32.5%)	(13.4, 51.6)	150 (41.7%)	(35.3, 48.1)	N/A	N/A
VLS	532 (88.4%)	(84.7, 92.1)	3 (5.0%)	(0.0, 11.2)	35 (9.8%)	(5.5, 14.1)	N/A	N/A
Not VLS	76 (11.6%)	(7.9, 15.3)	39 (95.0%)	(88.8, 100.0)	320 (90.2%)	(85.9, 94.5)	N/A	N/A
ART Duration								
>=24 Months	303 (50.0%)	(44.7, 55.4)	N/A	N/A	N/A	N/A	N/A	N/A
12-23 Months	65 (10.8%)	(7.7, 13.9)	N/A	N/A	N/A	N/A	N/A	N/A
<12 Months	68 (10.5%)	(7.7, 13.3)	N/A	N/A	N/A	N/A	N/A	N/A
¹ Sociodemographic and Clinical Characteristics are presented as unweighted frequencies and weighted percent distributions.								
² Abbreviations: HIV, human immunodeficiency virus; ART, antiretroviral therapy								

Table 1d. Description of Sociodemographic and Clinical Characteristics of HIV-positive Women and HIV-negative Women, 15-49 years of age, in Zambia, March 2016 to August 2016

	HIV-positive Women (N=1,503)						HIV-negative Women (N=8507)	
	Aware of HIV Status			Unaware of HIV Status			HIV-negative, n (%)	95% CI
	On ART, n (%)	95% CI	Not on ART, n (%)	95% CI	ART N/A, n (%)	95% CI		
Total, N (%)	884 (100%)		144 (100%)		458 (100%)		8507 (100%)	
Age								
15-19 years	19 (2.6%)	(1.4, 3.8)	2 (1.8%)	(0.0, 4.6)	46 (12.1%)	(8.7, 15.5)	2053 (26.5%)	(26.2, 26.8)
20-24 years	58 (7.1%)	(5.3, 9.0)	19 (12.7%)	(7.0, 18.4)	90 (20.6%)	(16.8, 24.3)	1876 (22.0%)	(21.7, 22.4)
25-29 years	125 (15.4%)	(12.8, 18.1)	24 (16.9%)	(10.5, 23.4)	73 (16.4%)	(12.8, 20.0)	1395 (16.8%)	(16.5, 17.2)
30-34 years	169 (19.4%)	(16.6, 22.1)	45 (32.4%)	(23.9, 40.9)	86 (17.7%)	(14.1, 21.4)	1155 (13.3%)	(12.9, 13.6)
35-39 years	191 (21.4%)	(18.8, 24.0)	27 (18.6%)	(11.7, 25.6)	64 (13.2%)	(10.1, 16.2)	873 (9.4%)	(9.1, 9.8)
40-44 years	213 (21.7%)	(19.0, 24.3)	21 (13.1%)	(7.6, 18.7)	57 (10.8%)	(8.0, 13.7)	695 (6.9%)	(6.5, 7.2)
45-49 years	109 (12.4%)	(10.2, 14.5)	6 (4.4%)	(0.6, 8.2)	42 (9.1%)	(6.4, 11.9)	460 (5.0%)	(4.8, 5.3)
Region								
Urban	555 (62.4%)	(57.1, 67.8)	88 (61.0%)	(51.4, 70.5)	256 (55.4%)	(49.3, 61.6)	3729 (44.7%)	(41.2, 48.3)
Rural	329 (37.6%)	(32.2, 42.9)	56 (39.0%)	(29.5, 48.5)	202 (44.6%)	(38.4, 50.7)	4778 (55.3%)	(51.7, 58.2)
Education								
Ever Attended School	838 (94.3%)	(92.7, 95.9)	133 (90.7%)	(84.5, 96.9)	443 (97.1%)	(95.5, 98.7)	7971 (93.5%)	(92.4, 94.5)
Highest Level of Education								

Primary	390 (43.3%)	(39.4, 47.2)	59 (41.2%)	(32.6, 49.8)	207 (46.7%)	(41.6, 51.8)	3886 (45.2%)	(43.1, 47.2)
Secondary	378 (43.0%)	(39.2, 46.9)	62 (41.2%)	(32.8, 49.6)	206 (44.0%)	(38.8, 49.2)	3527 (41.4%)	(39.5, 43.4)
Higher	70 (7.9%)	(5.9, 9.9)	12 (8.3%)	(3.0, 13.6)	30 (6.3%)	(3.9, 8.8)	558 (6.9%)	(5.8, 8.0)
Wealth Status								
Lowest Quintile	73 (8.6%)	(6.3, 10.9)	18 (13.7%)	(6.8, 20.5)	47 (10.5%)	(7.1, 13.9)	1408 (16.6%)	(14.9, 18.4)
Second Quintile	95 (10.8%)	(8.2, 13.4)	14 (10.3%)	(5.0, 15.6)	60 (14.2%)	(10.1, 18.3)	1567 (18.3%)	(16.8, 19.8)
Middle Quintile	193 (21.8%)	(18.2, 25.4)	20 (12.6%)	(6.7, 18.5)	107 (23.1%)	(18.3, 27.8)	1643 (19.0%)	(17.1, 20.9)
Forth Quintile	240 (27.0%)	(23.1, 30.9)	53 (37.9%)	(27.7, 48.1)	136 (27.9%)	(22.7, 33.1)	1821 (21.2%)	(18.9, 23.6)
Highest Quintile	277 (31.7%)	(27.0, 36.5)	39 (25.5%)	(17.4, 33.6)	107 (24.3%)	(19.4, 29.2)	2033 (24.8%)	(22.2, 27.4)
Reproductive History								
Live Birth Ever	813 (91.8%)	(89.7, 93.8)	135 (93.6%)	(89.2, 98.0)	377 (81.5%)	(77.6, 85.3)	5987 (67.8%)	(66.7, 69.0)
Birth Last 1 Year	101 (11.9%)	(9.4, 14.4)	8 (5.0%)	(1.4, 8.5)	33 (8.2%)	(5.2, 11.1)	1269 (14.7%)	(13.9, 15.6)
Birth Last 3 Years	258 (30.4%)	(26.7, 34.2)	42 (29.3%)	(21.8, 36.7)	115 (25.9%)	(21.4, 30.4)	3341 (38.2%)	(36.8, 39.5)
Currently Pregnant	54 (6.2%)	(4.6, 7.9)	5 (3.5%)	(0.3, 6.6)	20 (4.0%)	(2.1, 6.0)	710 (8.5%)	(7.8, 9.3)
Currently Avoiding Pregnancy	316 (35.6%)	(32.2, 38.9)	55 (37.3%)	(29.4, 45.1)	155 (33.6%)	(29.1, 38.2)	3116 (35.3%)	(34.0, 36.6)
Currently Wanting Another Child	223 (24.9%)	(21.3, 28.4)	39 (28.8%)	(20.4, 37.1)	175 (39.1%)	(33.7, 44.4)	3090 (36.1%)	(34.8, 37.5)
HIV Biomarkers								
CD4 <100	22 (2.5%)	(1.3, 3.6)	14 (8.9%)	(3.9, 14.0)	13 (2.8%)	(1.2, 4.4)	N/A	N/A
100=<CD4 <200	55 (6.3%)	(4.6, 8.0)	10 (6.8%)	(2.5, 11.0)	49 (9.7%)	(6.9, 12.4)	N/A	N/A
200=<CD4 <350	142 (16.0%)	(13.3, 18.7)	43 (30.6%)	(22.6, 38.6)	120 (26.2%)	(21.5, 30.8)	N/A	N/A
350=<CD4 <500	249 (27.9%)	(24.7, 31.0)	31 (21.3%)	(13.6, 29.0)	121 (26.0%)	(21.5, 30.6)	N/A	N/A
CD4 >=500	413 (46.9%)	(43.1, 50.8)	45 (31.5%)	(23.5, 39.5)	151 (34.3%)	(29.5, 39.1)	N/A	N/A
VLS	787 (88.9%)	(86.5, 91.2)	12 (8.2%)	(3.4, 13.0)	95 (19.6%)	(16.1, 23.2)	N/A	N/A
Not VLS	97 (11.1%)	(8.8, 13.5)	127 (87.8%)	(81.6, 94.0)	353 (78.2%)	(74.4, 82.1)	N/A	N/A
ART Duration								
>=24 Months	554 (61.3%)	(57.5, 65.0)	N/A	N/A	N/A	N/A	N/A	N/A
12-23 Months	124 (14.6%)	(12.0, 17.4)	N/A	N/A	N/A	N/A	N/A	N/A
<12 Months	158 (18.4%)	(15.5, 21.2)	N/A	N/A	N/A	N/A	N/A	N/A

¹ Sociodemographic and Clinical Characteristics are presented as unweighted frequencies and weighted percent distributions.

² Abbreviations: HIV, human immunodeficiency virus; ART, antiretroviral therapy

B. Table 2. Unweighted Pregnancy Events and Person-Time Contributions by Exposure

Category and Country

Table 2. Unweighted Pregnancy Events and Person-Time Contributions by Exposure Category and Country				
	Zambia	Malawi	Tanzania	Eswatini
HIV-negative Women				
Pregnancy Events	3465	2863	5483	798
Person Time in Years	25616.3	23068.96	39409.82	11503.89
HIV-positive Women, Not on ART				
Pregnancy Events	36	22	31	61
Person Time in Years	485.79	380.57	218.76	645.7
HIV-positive Women, on ART <6 Months				
Pregnancy Events	18	16	10	23
Person Time in Years	131.43	129.99	93.73	244.84
HIV-positive Women, on ART 6-12 Months				
Pregnancy Events	15	13	11	29
Person Time in Years	115.36	121.56	85.56	211.91
HIV-positive Women, on ART 12-18 Months				
Pregnancy Events	6	6	7	15
Person Time in Years	103.53	117.43	72.04	189.88
HIV-positive Women, on ART >18 Months				
Pregnancy Events	55	81	44	103
Person Time in Years	1169.87	1240.4	632.95	1935.21

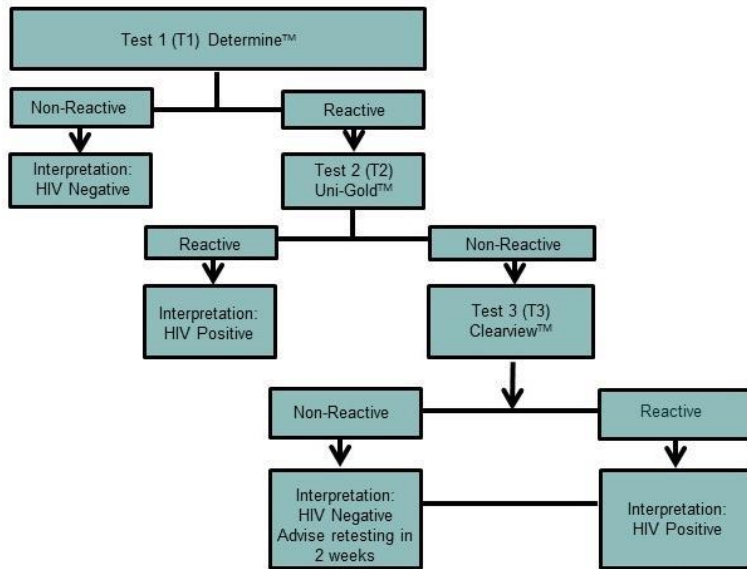
C. Table 3. Weighted Pregnancy Events, Pregnancy Rates, and Person-Time Contributions by Exposure Category and Country

Table 3. Weighted Pregnancy Events, Pregnancy Rates, and Person-Time Contributions by Exposure Category and Country				
	Zambia	Malawi	Tanzania	Eswatini
HIV-negative Women				
Pregnancy Events	1279702.23	1299456.89	4711356.9	54108.05
Person Time in Years	9804282.16	10340974.99	36971131.83	783690.55
Rate per 1000 PYs	130.53	125.66	127.43	69.04
95% CI	(124.8, 136.25)	(120.14, 131.18)	(122.2, 132.67)	(64.37, 73.72)
HIV-positive Women, Not on ART				
Pregnancy Events	12587.87	7458.16	23074.89	4126.02
Person Time in Years	168187.89	111342.81	210810.2	45747.23
Rate per 1000 PYs	74.84	66.98	109.46	90.19
95% CI	(48.44, 101.25)	(13.85, 120.12)	(67.3, 151.62)	(65.36, 115.02)
HIV-positive Women, on ART <6 Months				
Pregnancy Events	6318.31	5916.46	10999.01	1548.92
Person Time in Years	45207.74	46706.09	70492.13	16267.24
Rate per 1000 PYs	139.76	126.67	156.03	95.22
95% CI	(70.91, 208.62)	(59.72, 193.63)	(24.28, 287.79)	(54.53, 135.9)
HIV-positive Women, on ART 6-12 Months				
Pregnancy Events	5320.1	4656.33	4205.54	1835.35
Person Time in Years	39168.47	43731.37	63785.45	14017.23
Rate per 1000 PYs	135.83	106.48	65.93	130.94
95% CI	(66.86, 204.79)	(30.07, 182.88)	(13.02, 118.85)	(86.16, 175.71)
HIV-positive Women, on ART 12-18 Months				
Pregnancy Events	2394.08	2755.77	6905.47	812.06
Person Time in Years	35100.84	41304.44	55693.95	12650.3
Rate per 1000 PYs	68.21	66.72	123.99	64.19
95% CI	(13.31, 123.11)	(3.88, 129.56)	(9.03, 238.95)	(30.17, 98.22)
HIV-positive Women, on ART >18 Months				
Pregnancy Events	19089.32	31183.76	33947.46	6870.6
Person Time in Years	394824.87	445204.74	546613.29	132003.22
Rate per 1000 PYs	48.35	70.04	62.11	52.05
95% CI	(35.1, 61.6)	(53.18, 86.91)	(40.18, 84.03)	(41.07, 63.03)

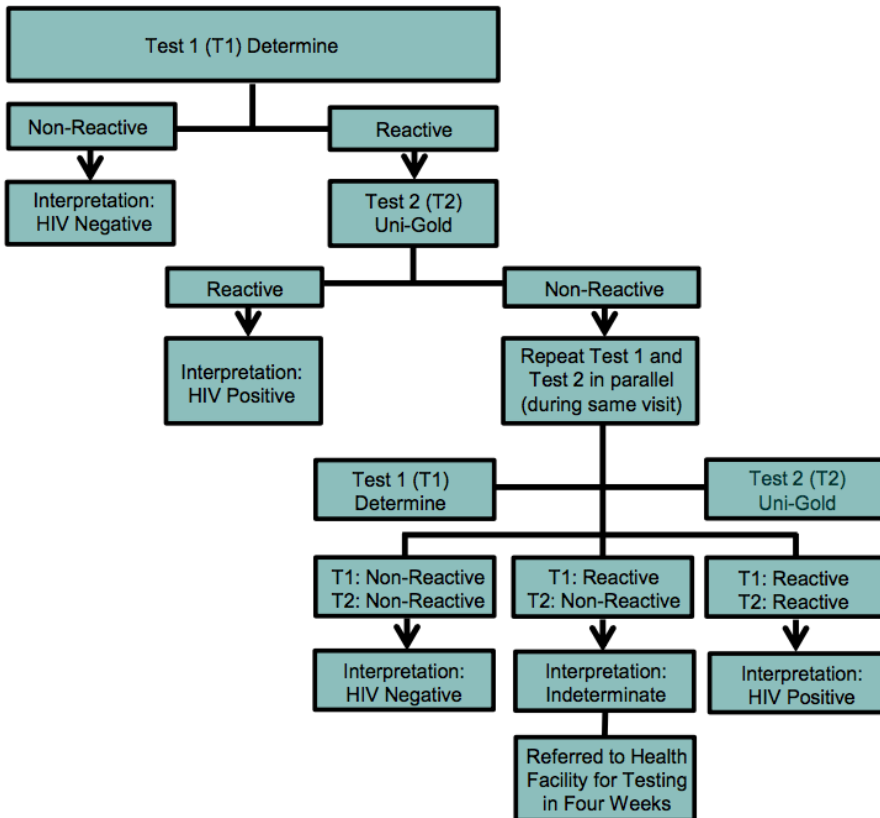
D. Table 6. PHIA Survey Modules

Table 6. PHIA Survey Modules				
Country	Zambia	Malawi	Eswatini	Tanzania
Module Names and Numbers	Module 1: Respondent Background	Module 1: Respondent Background	Module 1: Respondent Background	Module 1: Respondent Background
	Module 2: Marriage	Module 2: Marriage	Module 2: Marriage	Module 2: Marriage
	Module 3: Reproduction	Module 3: Reproduction	Module 3: Reproduction	Module 3: Reproduction
	Module 3A: Children	Module 3A: Children	Module 4: Children	Module 4: Children
	Module 4: Male Circumcision	Module 4: Male Circumcision	Module 5: Male Circumcision	Module 5: Male Circumcision
	Module 5: Sexual Activity	Module 5: Sexual Activity	Module 6: Sexual Activity	Module 6: Sexual Activity
	Module 6: HIV/AIDS Knowledge and Attitudes	Module 6: HIV/AIDS Knowledge and Attitudes	Module 7: HIV Testing	Module B: HIV/AIDS Knowledge and Attitudes
	Module 7: HIV Testing	Module 7: HIV Testing	Module 8: HIV Status, Care, and Treatment	Module 7: HIV Testing
	Module 8: HIV Status, Care, and Treatment	Module 8: HIV Status, Care, and Treatment	Module 9: Tuberculosis and Other Health Issues	Module 8: HIV Status, Care, and Treatment
	Module 9: Tuberculosis and Other Health Issues	Module 9: Tuberculosis and Other Health Issues	Optional Module C: Alcohol Use	Module 9: Tuberculosis and Other Health Issues
	Module 10: Alcohol Use	Module 10: Alcohol Use	Module 10: Gender Norms	Optional Module C: Alcohol Use
	Module 11: Gender Norms	Module 11: Gender Norms	Module 11: Violence	Module 10: Gender Norms
Module 12: Violence	Module 12: Violence		Optional Module D: Violence	

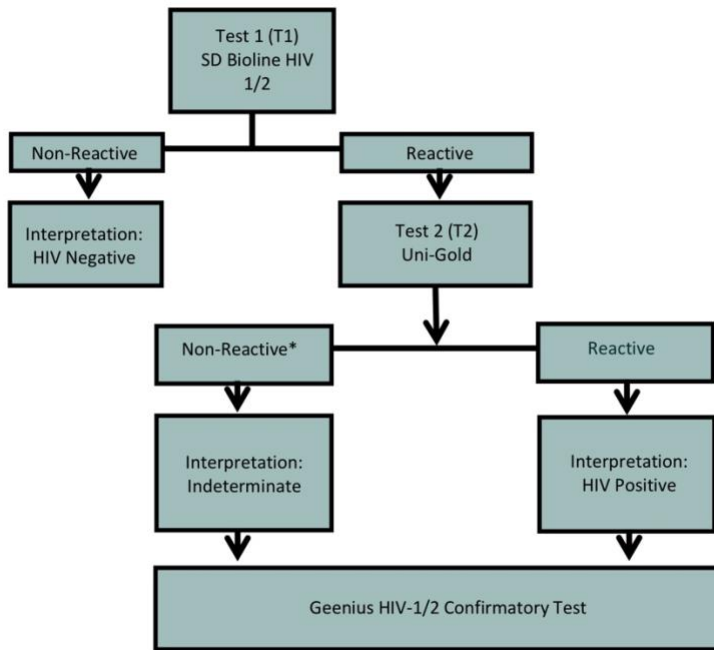
E. Eswatini PHIA Final Report: Household-based HIV testing algorithm, SHIMS2 2016-2017



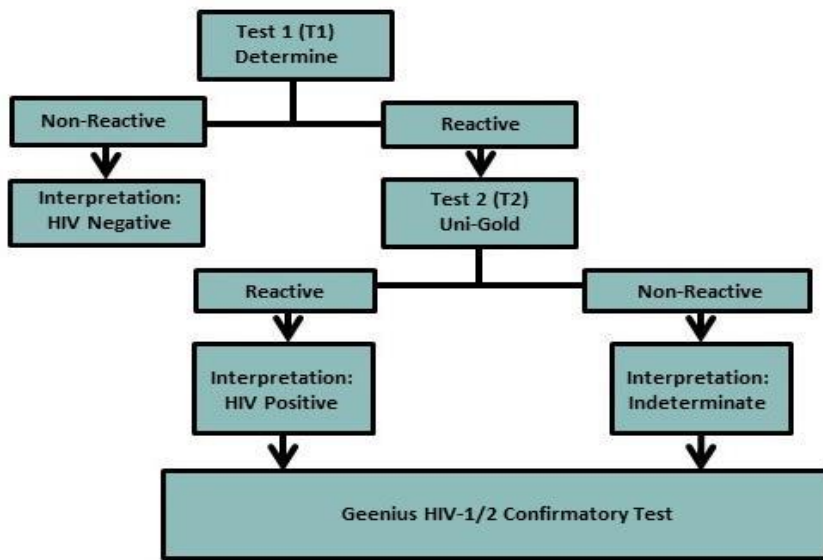
F. Malawi PHIA Final Report: Household-based HIV testing algorithm, MPHIA 2015-2016



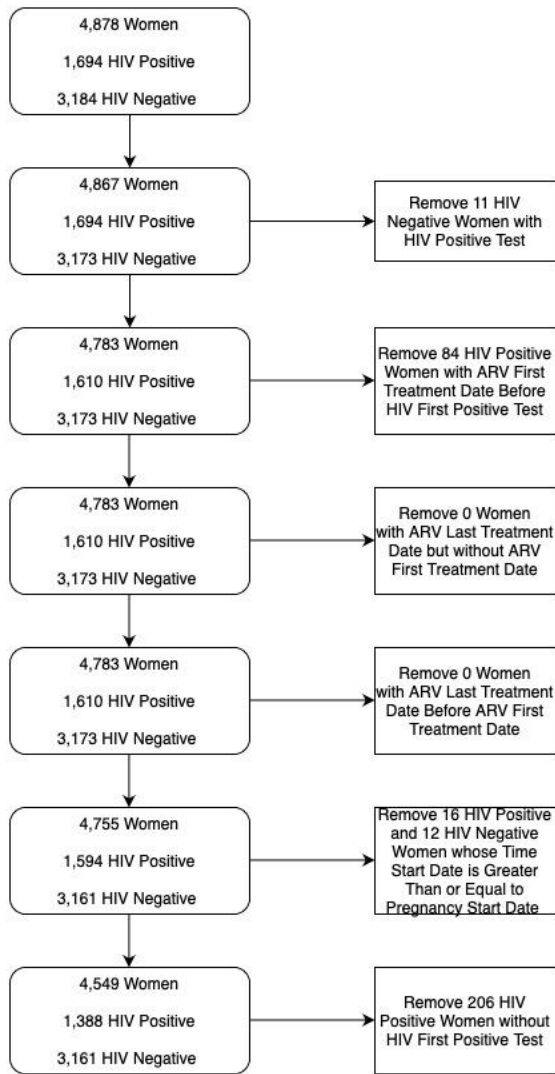
G. Tanzania PHIA Final Report: Household-based HIV testing algorithm, THIS 2016-2017



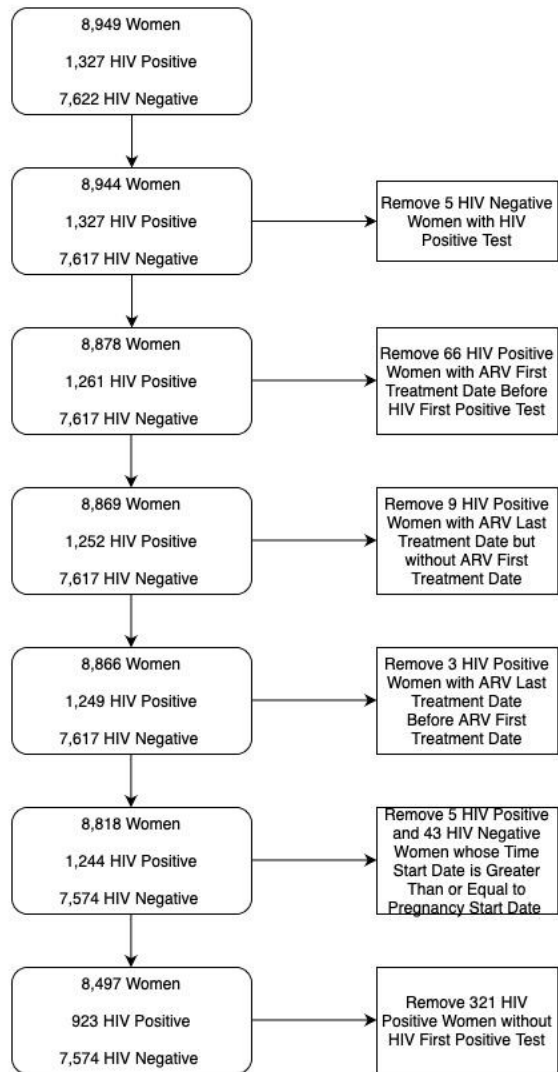
H. Zambia PHIA Final Report: Household-based HIV testing algorithm, ZAMPHIA 2016



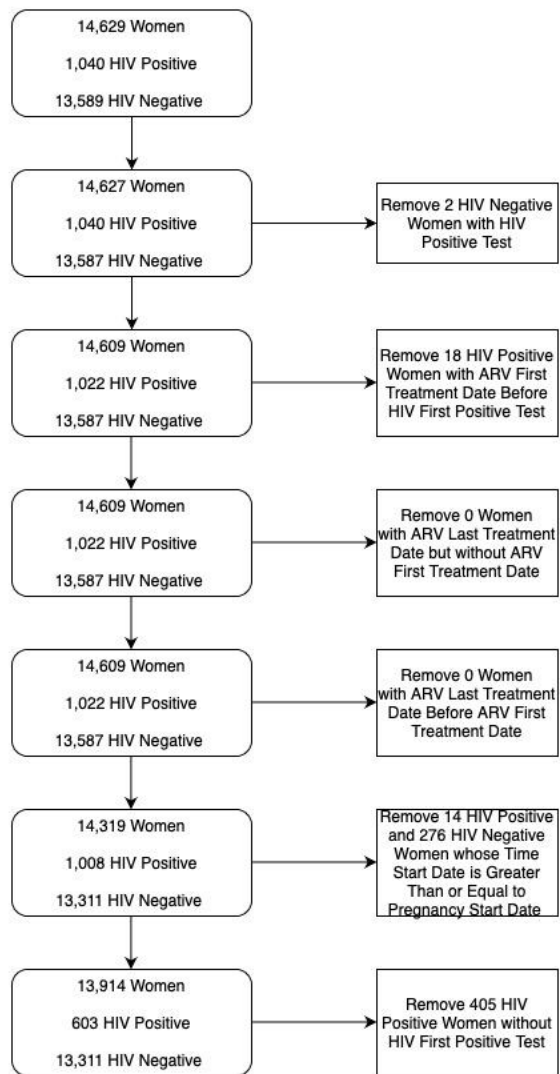
I. Eswatini Exclusion Flow Chart



J. Malawi Exclusion Flow Chart



K. Tanzania Exclusion Flow Chart



L. Zambia Exclusion Flow Chart

