Adverse pregnancy outcomes, non-retention, eligibility of differentiated care and virologic failure among women living with HIV in prevention of vertical transmission programs

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Abstract

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Provision of antiretroviral treatment (ART) to women living with HIV (WLWH) before and during pregnancy is key to prevention of vertical HIV transmission (or prevention of mother-to-child transmission [PMTCT]), including suppressed maternal HIV viral loads (VL) and improved maternal health. Studies have reported that ART use during pregnancy may affect the risks of adverse pregnancy outcomes (APOs), but underlying mechanisms are undefined. Current WHO guidelines recommend all pregnant and breastfeeding WLWH initiate lifelong ART, and prevention of vertical transmission requires women maintain long-term retention in care. However, there is no standard definition to evaluate retention in PMTCT programs and studies have used a wide range of methodologies, making it difficult to compare results comprehensively across different study designs, measurement approaches and follow-up durations. For people living with HIV and stable on ART, differentiated service delivery (DSD) approaches have shown promising health outcomes and implementation benefits, but it is unclear how to build DSD models for breastfeeding women with suppressed VL in PMTCT programs.

In the following dissertation aims, we address these questions. In Chapter 2, we evaluated the risks of APOs including stillbirth (SB), preterm birth (PTB) and neonatal death (NND) among pregnant WLWH in Kenya enrolled in PMTCT programs and identified potential predictors of APOs with a focus on HIV-related factors including ART use, sexual and reproductive history and sexual partnership. In Chapter 3, we assessed three aspects of women's non-retention in care, including loss to follow-up (LTFU), incomplete visit coverage, and late visits, to identify different insights on engagement in care during the peripartum period of WLWH from pregnancy to 24-month postpartum. We also explored factors that influenced non-retention. In Chapter 4, we performed trajectory analysis to describe longitudinal HIV VL patterns among WLWH in 24 months follow-up periods. We also evaluated the proportion of women who would have been classified as DSD-eligible according to the WHO general guidelines, and determined risk factors of subsequent viral failure among DSD-eligible women to inform future DSD implementation in PMTCT programs.

We demonstrated that APO was not associated with particular ART regimen or timing of ART initiation, but was associated with maternal viremia, psychosocial stressors, education level, and sexual and reproductive factors. We reported cofactors of non-retention in care may differ depending on which retention measures were assessed, and late visit attendance may be a sentinel indicator of subsequent LTFU. We found most women maintained viral suppression from early postpartum to 24 months and may be suitable for DSD referral, and women with depression, drug resistance and detectable VL may need enhanced services to prevent further VF.

This dissertation provides important insights regarding the safety of ART use in pregnancy outcomes, comprehensive monitoring of women's retention and HIV VL in long-term follow-up, as well as implication of integrating differentiated healthcare services into PMTCT programs.

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DEDICATION

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Chapter 1. Introduction

Pregnant women living with HIV face high risks of adverse pregnancy outcomes

An estimated 90% of the 1.4 million pregnancies in women living with HIV (WLWH) annually occur in sub-Saharan Africa (SSA)[1]. Elevated maternal viral load (VL) in the plasma or genitourinary tract increase the risk of mother-to-child HIV vertical transmission[1–3]. Without intervention, high HIV VL have been associated with a 20-25% high risk of transmission[4]. Antiretroviral therapy (ART) has shown efficacy in reducing it to a ≤2% risk among women with plasma VL >1000 c/mL[5,6]. With universal eligibility for ART for all WLWH of reproductive age based on the WHO Option B+ guidelines[7], ART coverage for WLWH has increased from 47% in 2010 to 93%[8].

WLWH had substantially worse pregnancy outcomes than HIV-uninfected women[2–4], and maternal HIV infection has been reported as a main risk factor, with the strongest and most consistent evidence identified in WLWH in SSA[5]. The current World Health Organization (WHO) guidelines recommend ART administration to all pregnant WLWH, irrespective of CD4 or disease stage for prevention of mother-to-child HIV transmission (PMTCT) and maternal health benefits[6]. The global scale-up of ART has resulted in more WLWH in Africa having access to ART and continued decline in new pediatric HIV infection rates[7]. However, ART use has not eliminated the disparity in risk of adverse pregnancy outcomes (APOs), as multivariate analyses reported independent associations between maternal HIV infection and adverse obstetric and neonatal outcomes, even in the presence of continued ART[8–10]. The past decade has also offered an increased number of reports that ART use may affect pregnancy outcomes other than vertical transmission, and that may disrupt PMTCT programs in both developed and developing countries (Table 1.1).

APOs are also associated with other HIV-related factors, including progression clinical stages of disease, antiretroviral use (e.g., specific regimen and initiation time), CD4 cell count, plasma HIV VL and immune suppression status as reported in studies in resource limited

areas[8,11–14]. In addition, evaluation should also consider particular sociodemographic characteristics among WLWH including maternal food security, lifestyle behaviors (e.g., smoking, alcohol), family planning use and comorbidity (e.g., gestational diabetes, hypertension, thyroid disorders)[13]. Therefore, determining predictors is particularly challenging given that the outcomes may result from a direct effect of the infection, from HIV-related or non-HIV-related factors, or from an integrated consequence of these together. These realizations have led to an appreciation of the importance to understand the effectiveness of HIV treatment among WLWH in the context of PMTCT, as well as safety regarding maternal and child health outcomes, in order to optimize the health of women and children through their life course.

In Chapter 2, we evaluated three APOs among WLWH in Kenya including stillbirth, preterm birth and neonatal death, and determined potential predictors, with a focus on HIV-related factors as well as mental health, sexual and reproductive history, and partnership characteristics.

Women with HIV have sub-optimal retention in PMTCT programs and measures vary

Effective PMTCT programs require women and their infants to access healthcare services throughout the risk period of vertical transmission (e.g., to the end of breastfeeding). The PMTCT cascade[15–17], which describes the programmatic steps for pregnant and breastfeeding women that influence HIV transmission risk, has served as a framework to analyze the efficiency and performance of HIV care services. Adherence to sequential steps is crucial, with one modeling study indicating that virtual elimination of vertical transmission could be attained by 95% adherence to each step[18]. In resource-limited settings, despite the uptake of Option B+ increased integration of ART and antenatal care services, obstacles still exist due to high potential for disengagement and lost after ART initiation[19–21], which poses a threatening challenge to achieve elimination of vertical transmission and to improve health outcomes for mothers and infants[22–24].

It is necessary to identify barriers to retention in long-term care to develop evidence-based intervention strategies to support women.

However, little is known about long-term patterns of engagement and retention in HIV care among women on lifelong ART during their reproductive years or what predicts re-engagement. Currently there is no standard definition or methodologies to evaluate retention. Studies have used a wide range of approaches under published guidelines[25–30], and have yielded to large variations in estimates[31,32] (Table 1.2). A recent analysis pooling six INSPIRE PMTCT intervention studies in Malawi, Nigeria and Zimbabwe observed a large variability in comparing nine definitions of retentions based on number of clinic and/or missed visits (ranging from 30% to 76%) when different definitions were applied within the same dataset[31]. This could be a significant problem when considering retention in PMTCT. In a high HIV-burden country such as Kenya, women's engagement should be more precisely assessed in order to identify opportunities for possible improvement throughout the PMTCT care continuum. In the absence of an agreed standard definition for PMTCT retention and methodologies for estimating rates, these variations highlight the importance of understanding data availability, the questions being addressed, the principal rationale of study, and methods of ascertaining outcomes to best understand their implications.

In Chapter 3, we evaluated three non-retention measures of potential utility to the peripartum period in a cohort of WLWH from pregnancy to 2-year postpartum. We also determined how these measures influenced identification of cofactors of non-retention.

Postpartum women stable on ART may benefit from differentiated care models

A range of intervention strategies have been suggested to help improve women's retention to HIV care during postpartum periods. These include cash incentive interventions[33], mobile phone communications[34–36] and integration of postpartum health services for women and their children[37,38]. Data to support these interventions are heterogenous in terms of both the strength

of the evidence and quality of evaluation, and there is a need for rigorous evaluations of different interventions that may improve engagement in care among postpartum WLWH.

Differentiated service delivery (DSD) approaches adapt the frequency of clinical visits for individuals who are clinically stable on ART[39]. This approach aims to simplify HIV services to better address patient needs and enable healthcare to focus on those in need of more intensive clinical care[40,41]. DSD models usually include delivery of services by lay health workers, less frequent visit schedules, and delivery of care outside of health care facilities[42].

The WHO has recommended that the DSD definition of being stable apply to all populations[43], however, DSD models for postpartum women on ART are not well-studied. It is also unclear how to implement DSD models for mothers with HIV, given their need for routine antenatal and postnatal care visits and HIV-exposed infant follow-up visits. In Kenyan guidelines in 2017, individuals on ART for at least 6 months with suppressed VL <1,000 copies/mL[44] were qualified for DSD with 6-monthly clinic visits and annual VL testing[44], while pregnant and breastfeeding women were defined as unstable and not DSD-qualified[44]. there are also concerns of non-sustained viral suppression during a long-follow-up throughout postpartum, with risks of viremia episodes, detectable VL and significant rebound after being suppressed[4546]. Overall these data provide important implications for research to consider repeat HIV testing longitudinally for pregnant and postpartum women. Women stable with HIV in the later postpartum period may benefit from DSD approaches, but there is limited evidence to inform tailored DSD models for this population.

In Chapter 4, we described longitudinal HIV VL patterns and identified cofactors among postpartum women living with HIV (PWLH) in PMTCT programs in Kenya. We also assessed the frequency of DSD-eligibility and potential subsequent risk of virologic failure among DSD-eligible women.

Summary

In this dissertation, we aimed to provide a comprehensive understanding of key health concerns in PMTCT programs among Kenyan women living with HIV throughout pregnancy and postpartum periods. (1) We identified the risks of adverse pregnancy outcomes and correlative factors including ART use. (2) We evaluated different retention measures regarding diverse aspects of engagement in care and how difference in measures may affect the identification of predictors. (3) We also modelled longitudinal HIV VL patterns in 2-year program follow-up time, and the possibility of women receiving DSD using the general DSD criteria with subsequent risks of virologic failure. The implications of this work include the need to closely monitor birth outcomes as different PMTCT ART regimens are implemented, assess retention and viral suppression in long-term care, and focus on potential DSD model implementation in MCH settings for postpartum women stable on ART.

Table 1.1. Literature review of potential mechanisms of ART on adverse pregnancy outcomes

First author, year	Study type	Study population	Findings about safety in pregnancy
NRTI: TDF, FTC, 3TC, ZDV			
Copper, 2010[47]	Meta-analysis of 17 studies (9 RCTs)	10,892 patients with HIV	Greater risks of kidney dysfunction and acute renal failure
Monteiro, 2014[48]	Retrospective analysis of clinical data in Portuguese	176 patients with HIV starting TDF between Jan-Dec 2008.	No significant change in renal safety profile during a four-year follow-up
McComsey, 2011[49]	Multicenter RCT in US	269 treatment-naïve patients with HIV	Significant decrease in spine and hip bone mineral density among TDF-FTC-treated patients compared to ABC-3TC treated patients
Stellbrink, 2010[50]	Multicenter RCT in Europe	385 antiretroviral-naive patients with HIV	Greater increases in bone turnover and decreases in bone mineral density among TDF-FTC than ABC-3TC
Wang, 2013[51]	Systematic review of 19 studies (3 animal studies and 16 pertained to humans)	Not provided	Three animal studies at 2-fold higher doses than those for human therapeutic use showed decreased fetal growth and reduction in fetal bone porosity within 2 months of maternal ART initiation. Human studies reported no link to LBW.
Benabound, 2012[52]	Pharmacokinetics study	186 WLWH (25% pregnant) in Europe	Pregnant women had a 39% higher clearance of tenofovir compared to nonpregnant women.
Colbers, 2013[53]	Phase IV pharmacokinetics study	34 pregnant WLWH receiving TDF or FTC in Europe	Pharmacokinetic parameters of TDF and FTC during pregnancy is 25% lower in the third trimester than postpartum.

Gibb, 2012[54]	RCT in Uganda/Zimbabwe	302 ART-naïve WLWH with CD4<200 enrolled in DART study	In utero TDF exposure had no significant effects on congenital, renal, or growth abnormalities.
Florida, 2013[55]	Retrospective analysis of national survey in Italy	1257 WLWH receiving ARV in pregnancy	First-trimester ART (NRTIs, NNRTIs, or PIs) does not increase risks of congenital abnormalities in newborns.
Ransom, 2013[56]	Multicenter prospective cohort in US	2099 HIV-negative live births born to WLWH receiving ART in pregnancy	No difference between TDF exposed (vs. unexposed) in birthweight or gestational age- and sex-adjusted birth weight z-score
Chenadec, 2003[57]	Longitudinal study	>4000 HIV uninfected infants born to WLWH in the French Perinatal Study	The hemoglobin level was reduced in newborns exposed to perinatal ZDV
Ziske, 2013[58]	Prospective cohort study	144 pregnant WLWH in Tanzania (57% exposed to ZDV)	Antenatal ZDV was associated with lower hemoglobin level, red blood cells, white blood cells, granulocytes among women and higher frequency of anemia among infants at birth.
INSTI: DTG			
Hill, 2018[59]	Systematic review of six large databases	1200 pregnant WLWH	No evidence for increased risk of adverse outcomes for women treated with DTG compared with EFV.
Zash, 2019[60]	Prospective surveillance at hospitals in Botswana	119033 live-born and stillborn infants	Slightly increased risk of NTDs in infants born to women initiating DTG pre-pregnancy or received it at the time of conception compared to non-TDF regimen.
NNRTI: EFV			

Ford, 2010[61]	Meta-analysis with 16 studies	8295 live births born to WLWH exposed to ART during first trimester pregnancy	No increased risk of overall birth defects among women exposed to EFV vs. non-EFV ART regimen.
Ford, 2014[62]	Updated meta-analysis with 23 studies	an additional 589 live births compared with the last review	No difference in congenital anomalies between women exposed to EFV and non-EFV ART. The incidence of NTDs was as low as 0.05%, similar to that in the general population.
PI: LPV/r			
Cohan, 2015[63]	Secondary analysis of the PROMOTE trial	389 pregnant WLWH initiating ART in rural Uganda	Women on LPV/r had higher risk of gastrointestinal side events compared to women on EFV. RTV should only be used as low-dose booster for other PIs.

NRTI: Nucleoside Reverse Transcriptase Inhibitor; TDF: Tenofovir Disoproxil Fumarate; FTC: Emtricitabine; ABC: Abacavir; 3TC: Lamivudine; ZDV: Zidovudine; INSTI: Integrase Strand Transfer Inhibitor; DTG: Dolutegravir; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; EFV: Efavirenz; PI: Protease Inhibitor; LPV/r: Lopinavir/Ritonavir

Table 1.2. Summary of retention measures among WLWH in PMTCT programs with Option B+ in Africa

First author, year	Study design, setting and sample size	Retention measure
Lettow, 2014[64]	Cohort in Malawi (N=141 health facilities)	Retention: percent of women retained on ART by 6 or 12 months
Tenthani, 2014[65]	Retrospective analysis in Malawi (N=21939)	LTFU: did not return to care for ≥ 60 days after starting ART for 3-6 months
Mitiku, 2016[66]	Retrospective cohort in Ethiopia (N=346)	LTFU: no show in 90 days since last visit and not known died or transferred out
Reece, 2016[67]	Retrospective review in Ghana (N=141)	Optimal retention: completing ≥1 visit every 6 months after delivery
Woelk, 2016[68]	Retrospective cohort in Rwanda (N=348)	Retained: NOT ever missing 3 consecutive visits
Yotebieng, 2016[33]	RCT in Congo (N=433)	Retention: attendance of all scheduled clinic visits and acceptance of proposed services up to 6 weeks' postpartum
Atanga, 2017[69]	Prospective cohort in Cameroon (N=268)	Treatment discontinuation: intentionally stopped ART or unreachable > 90 days of tracing
Hoffman, 2017[70]	Case-control in Malawi (N=203)	Retention: NOT defaulted from Option B+ (out of ART for >60 days)
Miller, 2017[71]	Retrospective cohort in Uganda (N=1062)	Retained: ≥1 visit in 1 year after pregnancy detection
Wesevich, 2017[72]	Secondary analysis of an RCT in Malawi (N=200)	Retention: attending HIV clinic follow-up within one day of running out of pills
Etoori, 2018[73]	Prospective cohort in Swaziland (N=496)	LTFU: ≥4.5 months without visit or known death

Gill, 2018[74]	Clustered RCT in Kinshasa (N=36 facilities)	Missed the second antenatal visit
Kiwanuka, 2018[75]	Retrospective cohort in Uganda	LTFU: out of care at the time of conducting the interviews at 25-month follow-up
Cichowitz, 2019[76]	Retrospective cohort in Tanzania (N=650)	Time-to-LTFU during postpartum period
Ahoua, 2020[32,77]	Retrospective cohort in Mozambique (N=44377)	LTFU: never returned to care in 12 months after ART initiation
		Non-retention: dropped out from care after the second visit
Alamdo, 2021[77]	Retrospective cohort in Ethiopia (N=356)	Retained: mother–infant pairs retain in HIV care until the 18–24 months follow-up period

Chapter 2. Predictors of adverse pregnancy outcomes among Kenyan women living with HIV on antiretroviral treatment in pregnancy

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Predictors of adverse pregnancy outcomes among Kenyan women living with HIV on antiretroviral treatment in pregnancy

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Abstract

Objective: To understand predictors of adverse pregnancy outcomes (APOs) among women on antiretroviral treatment (ART).

Design: Longitudinal cohort

Methods: Participants from the Mobile WAChX trial were evaluated for APOs, including stillbirth (SB, fetal death at ≥20 weeks' gestation), preterm birth (PTB, livebirth at <37 weeks' gestation) and neonatal death (NND, ≤28 days after live birth). Predictors were determined by univariable and multivariable Cox proportional hazards and log-binomial models.

Results: Among 774 women included, median age was 27 years and 29.0% had unsuppressed HIV viral load (VL >1,000 copies/mL) at enrollment. Half (55.1%) started ART pre-pregnancy, 89.1% on tenofovir-based regimens. Women with depression had higher risk of SB (adjusted hazard ratio [aHR] 2.93, 95%CI 1.04-8.23), and women with lower social support score had higher risk of late SB (aHR 11.74, 2.47-55.86). Among 740 livebirths, 201 (27.2%) were preterm and 22 (3.0%) experienced NND. PTB was associated with unsuppressed maternal VL (adjusted prevalence ratio [aPR] 1.28, 95%CI 1.02-1.61), intimate partner violence (IPV) in pregnancy (aPR 1.94, 1.28-2.94), and history of any sexually transmitted infection (STI) (aPR 1.63, 1.06-2.51). NND was associated with PTB (PR 2.53, 1.10-5.78) and STI history (PR 4.25, 1.39-13.06). Most associations retained significance in the subgroup of women with viral suppression.

Conclusions: Maternal viremia during pregnancy predicted PTB as did IPV, lower education and STI history, while psychosocial stressors predicted SB. Implementing mental health services, ART adherence, partner support, and routine STI screening and treatment could reduce APOs among women with HIV in sub-Saharan Africa settings.

Keywords: pregnant women; HIV infection; reverse transcriptase inhibitors; stillbirth; preterm birth; neonatal death; viral load

Introduction

An estimated 90% of the 1.4 million pregnancies in women living with HIV (WLWH) annually occur in sub-Saharan Africa (SSA)[1]. There is consistent evidence that WLWH have worse pregnancy outcomes, including preterm birth (PTB), low birth weight (LBW), small for gestational age (SGA), stillbirth (SB), and neonatal death (NND) than women without HIV infection[5]. World Health Organization (WHO) guidelines recommend antiretroviral therapy (ART) for all pregnant WLWH for prevention of mother-to-child HIV transmission (PMTCT) and maternal health benefits[6]. First-line ART regimens for pregnant WLWH include a dual-nucleotide reverse transcriptase inhibitor (NRTI) [tenofovir disoproxil fumarate (TDF) with lamivudine (3TC) or emtricitabine (FTC)], plus a protease inhibitor (PI)-based regimen or a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen; more recently dolutegravir (DTG)-based regimens are recommended[6]. Global scale-up of ART has resulted in more WLWH in Africa accessing ART and continued decline in new pediatric HIV infections[7].

There is evidence that ART use in pregnancy may affect pregnancy outcomes[78–82], however, ART associations with adverse pregnancy outcomes (APOs) may differ depending on the specific APO evaluated as well as the regimen and duration of treatment. For example, the PROMISE trial reported significantly higher risk of APOs and infant mortality among women receiving TDF-based ART (TDF/FTC/LPV/r) than women receiving zidovudine (ZDV) plus single-dose nevirapine (NVP)[14]. In contrast, the TSEPAMO study in Botswana showed women receiving TDF/FTC/efavirenz (EFV) had the lowest rate of any APO among all women on ART[83], and the DART trial in Uganda/Zimbabwe showed no difference in neonatal mortality between TDF (+NVP) and non-TDF ART[54].

There is also mixed evidence regarding how sociodemographic factors such as food security, stress, sexually transmitted infections (STIs), and mental health status influence pregnancy

outcomes among WLWH[13]. Elevated maternal HIV viral load (VL) during pregnancy, even in the context of ART, has been associated with poor perinatal outcomes compared to HIV-negative women[84]. This may be due to immune activation or immune compromise with resultant vulnerability to other infections[85]. Dysregulation of inflammatory cytokine production at the maternal-fetal interface may also contribute to APOs, and this may differ by ART regimen and timing[86–90]. Other HIV-related factors, including clinical stage of disease and CD4 cell count, have been associated with APOs[8,11–14]. In this prospective cohort study, we evaluated APOs among WLWH in Kenya and determined potential predictors, with a focus on HIV-related factors as well as mental health, sexual and reproductive history, and partnership.

Methods

Study design and population

This study leveraged data collected from a completed 3-armed randomized clinical trial (RCT) (Mobile WAChX study, ClinicalTrial.gov number NCT02400671, 2015/11/22-2017/05/04). The parent RCT assessed short messaging service (SMS) to improve ART adherence and retention among WLWH in Kenya attending the PMTCT program. Parent study procedures and results have been previously reported[34]. Briefly, the trial enrolled pregnant WLWH from six public maternal-child health (MCH) clinics in Nairobi and Western Kenya if they were aged ≥14 years and had daily access to a mobile phone at the time of enrollment. Women were randomized to receive one-way SMS, two-way SMS or no SMS, and followed-up throughout 2 years postpartum[34]. One woman died before delivery. Gestational age (GA) at delivery was determined based on last menstrual period (LMP) date and delivery date. This study used all available data from the RCT; no additional sample size calculations were conducted prior to secondary analyses. The parent study was approved by the University of Washington (UW) Institutional Review Board (IRB) and the Kenyatta National Hospital/University of Nairobi Ethical Review Committee; no additional IRB approval was required for this analysis.

Data collection

At enrollment in the parent trial, a standardized survey on a tablet using Open Data Kit (ODK) was administered. Data was collected on demographics, family planning, social support (using Medical Outcomes Study [MOS] survey[91]), stigma (using 4-item instrument adapted from the stigma scale for chronic illnesses [SSCI][92]), depression (using Patient Health Questionnaire 9 [PHQ9][93]), intimate partner violence (IPV) (using Abuse Assessment Screen [AAS][94]), food security (using Household Food Insecurity Access Scale [HFIAS][95]), disclosure of HIV status, history of any STI, and ART knowledge (using 15 items from the LifeWindows ART adherence questionnaire[96]). Data on ART use was abstracted from the Mother Child Health (MCH) booklet. HIV VL testing was conducted with maternal plasma samples collected at enrollment[34].

Study outcome

This study assessed three APOs. Stillbirth (SB) was defined as fetal death at ≥20 weeks' gestation. Analysis of SB was restricted to women enrolled prior to 20 weeks' gestation, and a second analysis of late SB (defined as SB at 28-36 weeks' gestation) was conducted among women enrolled prior to 28 weeks' gestation. Preterm birth (PTB) was defined as live birth at <37 weeks' gestation. Analysis of PTB was restricted to women enrolled prior to 37 weeks' gestation, and a secondary analysis of very PTB (defined as live birth at 28-32 weeks' gestation) was conducted among women enrolled prior to 28 weeks' gestation. Neonatal death (NND) was defined as an infant death within 28 days. Analysis of NND was conducted among women with live birth.

Statistical analysis

Chi-square tests were used to compare categorical variables and Welch two sample t-tests for continuous variables between women having APOs and women without APOs. Kaplan-Meier survival curves were used to assess time-to-SB and incidence rate (IR) of SB. Cox proportional

hazards regression counting time-at-risk from enrollment to delivery was used to identify predictors of SB. Log-binomial regression was used to identify predictors of PTB and NND. Proportions of each APO and an overall proportion of having any APO were compared by TDF- or ZDV-based NRTI ART regimen, EFV- or NVP-based NNRTI ART regimen, and ART initiation time before or during pregnancy using chi-square tests. Study site, dichotomized as Nairobi (Mathare, Riruta) and Western Kenya (Ahero, Bondo, Siaya, Rachuonyo), was identified as an a priori confounder in all regression models to account for potential geographical differences in maternal characteristics and underlying APOs. Covariates with p-value <0.05 in univariate models were included in multivariate analyses. Sub-group stratified analyses were conducted among women who were virally suppressed at enrollment. All models used robust standard errors. All analyses were conducted using RStudio Version 1.2.5042 (RStudio, Inc).

Results

Among 824 women enrolled in the RCT, 1 died prior to delivery, 53 had no LMP data available, 6 had a miscarriage and 774 (93%) women were included in the APO analysis (Figure 2.1). Among the 774 included women, median age was 27 (interquartile range [IQR] 23-31) years, and median GA of pregnancy at enrollment was 24 (IQR 18-30) weeks (Table 2.1). Most women completed primary school (77.3%) and were married or cohabiting with a partner (84.2%). About half (46.9%) reported moderate or severe food insecurity (by HFIAS scoring) and 24.4% women had at least moderate depression symptoms (PHQ9 score >5). Seven percent (53/762) of women reported travel time >60 minutes from home to clinic. Among 26 (3.4%) women who reported ever having STI, 57.7% had syphilis. Overall, 21 (2.7%) women reported ever experienced IPV since pregnancy. At enrollment, 28.8% of women had unsuppressed VL. Most women (92.5%) were already on ART at enrollment, 59.6% (461/773) reported diagnosis with HIV before pregnancy, 55.1% (425/771) reported starting ART before pregnancy, and among 723 women who reported ART regimen, most (74.1%) were on TDF+3TC/FTC+EFV as recommended by WHO guidelines.

Any adverse pregnancy outcome

Overall, 34 (4.4%) women experienced a SB, including 10 early SB, 11 late SB and 13 term SB (Figure 2.1). Among 740 women with live birth, 201 (28.3%) had a PTB (including 26 very PTB) and 22 (3.0%) had a NND (Figure 2.1). The prevalence of SB, PTB or NND did not significantly differ between TDF-based vs. ZDV-based NRTI regimen, or EFV-based vs. NVP-based NNRTI regimen (Figure 2.2). Similarly, a combined prevalence of women experiencing any APO did not significantly differ by regimen. There was no difference in prevalence of APOs between women who started ART pre-conception versus those who started ART in pregnancy (Figure 2.2). In addition, we did not find a difference in APOs between women on NNRTI-based regimens versus TDF/ZDV-based regimens.

Incidence and cofactors for stillbirth

Among 235 women who were enrolled at <20 weeks' gestation, 17 (7.2%) had a SB. The overall IR of SB was 17.2 per 100 person-years (Table 2.2). Adjusting for site, the risk of SB was significantly higher in women having at least moderate depressive symptoms (HR 2.92, 95%CI 1.09-7.81), and in women reporting a partner had been tested for HIV (HR 0.36, 95%CI 0.13-1.01; p=0.05) (Table 2.2). To determine if partner HIV testing reflected better social support, we compared social support in women who reported partner HIV testing versus those who did not and found significantly higher prevalence of high social support in women reporting partner HIV testing versus those who did not (53.4% vs. 42.3%, p=0.02). Among 517 women enrolled at <28 weeks' gestation, 11 (2.1%) had late SB, with the overall IR of late SB of 6.2 per 100 person-years. Adjusting for site, the risk of late SB was significantly higher in women who had social support score below a median of 63 (HR 11.62, 95%CI 1.58-85.5) (Table 2.2). Adjusting for site and HIV VL at enrollment, the association between SB and depression remained similar (adjusted

HR [aHR] 2.93, 95%CI 1.04-8.23), as did the association between late SB and lower social support score (aHR 11.74, 95%CI 2.47-55.86) (Table 2.2).

Sub-group stratified analysis among women enrolled with viral suppression

In a subset of 170 women enrolled at <20 weeks' gestation, the association of SB with depression remained but was not statistically significant (HR 2.41, 95%CI 0.81-7.14) while the association with partner HIV testing became more protective (HR 0.18, 95%CI 0.06-0.55, p=0.003). Women with lower social support had higher risk of SB (HR 3.15, 95%CI 1.12-8.90), while women diagnosed before pregnancy had lower risk (HR 0.31, 95%CI 0.11-0.90) (Table 2.2). The association between late SB and lower social support score also remained in the subgroup (HR 10.05, 95%CI 1.33-76.0) (Table 2.2).

Prevalence and cofactors for preterm birth

Among 709 women enrolled at <37 weeks' gestation and delivered a live birth, 201 (28.3%) had PTB (Table 2.3). In multivariable analyses, prevalence of PTB was significantly higher among women who were virally unsuppressed (adjusted prevalence ratio [aPR] 1.28, 95%CI 1.02-1.61), exposed to IPV since pregnancy (aPR 1.94, 95%CI 1.28-2.94), and with STI history (aPR 1.63, 95%CI 1.06-2.51). Women who reported traveling from home to clinic >1 hour had higher risk of PTB, though this was not statistically significant (PR 1.46, 95%CI 0.98-2.15; p=0.06). Among 619 (87.3%) infants with data available on sex, male infants were more likely to be preterm than female infants (31.2% vs. 23.1%, p=0.02), and the association remained significant when adjusting for site (PR 1.35, 95%CI 1.04-1.76) (Table 2.3). Among 495 women enrolled at <28 weeks' gestation, 26 (5.3%) delivered very preterm. No characteristics were significantly related to very PTB (Table 3). Results of PTB, very PTB from sensitivity analyses among women enrolled at <20 weeks' gestation remained the same (data not shown).

Sub-group stratified analysis among women enrolled with viral suppression

Among 372 women enrolled at <37 weeks' gestation in this subgroup, 130 (25.9%) had PTB. Site-adjusted associations between PTB and IPV since pregnancy remained (PR 1.97, 95%CI 1.07-3.62), as did maternal STI history (PR 1.87, 95%CI 1.16-3.02). Among 350 women enrolled at <28 weeks' gestation, 15 (4.3%) delivered very preterm. Primigravida women had a trend for increased risk of very PTB (PR 3.21, 95%CI 0.94-11.0; p=0.06) (Supplementary Table).

Prevalence and cofactors for neonatal death

Among 740 liveborn neonates, 22 (3.0%) died within 28 days after delivery (Table 2.3). Livebirths resulting in a NND had significantly lower GA at birth than those who survived (median 37 [IQR 30-40] vs. median 39 [IQR 37-40] weeks; p=0.004). After adjusting for site, PTB was significantly associated with NND (PR 2.46, 95%CI 1.10-5.51). Women with any maternal STI history had significantly higher risk of NND (PR 4.25, 95%CI 1.39-13.06), with the association driven by syphilis (PR 4.57, 95%CI 1.17-17.79) in analyses adjusting for each STI separately. Women who were diagnosed with HIV before pregnancy had a trend for a lower risk of NND (PR 0.50, 95%CI 0.23-1.07; p=0.07). Categories of ART regimen, ART initiation time or other maternal sociodemographic did not show significant associations with NND (Table 2.3). Adjusting for both site and HIV VL at enrollment, the association between NND and PTB remained similar (Table 2.3). Results of NND from sensitivity analyses among women enrolled at <20 weeks' gestation remained the same (data not shown).

Sub-group stratified analysis among women enrolled with viral suppression

Risk of NND among neonates in this subgroup of women was 2.66% (14/526). Site-adjusted association between NND and PTB remained (PR 3.35, 95%CI 1.13-9.91), as did maternal STI history (PR 6.90, 95%CI 2.17-21.99) (Supplementary Table).

Discussion

This study evaluated risks and predictors of APOs among pregnant WLWH on ART in Kenya. Compared to published estimates in the general population in sub-Saharan Africa, women in this study experienced a 1.5-fold higher SB risk (4.4% vs. 2.9%[97]) a 2.4-fold higher PTB risk (28.3% vs.12.0%[98]), and a similar NND risk (2.2% vs. 2.7%[99]). We found that SB risk was associated with having at least moderate depressive symptoms, and not having partner been tested for HIV. Late SB was associated with low social support score. PTB risk was associated with IPV during pregnancy, incomplete secondary education, unsuppressed VL at enrollment, and any maternal STI history. Very PTB was significantly higher among women from Western Kenya sites. We found that women previously diagnosed with STIs, particularly syphilis, had increased risk of NND and 45.5% of NND occurred among preterm infants.

Our finding of significant association between depression and SB suggests the importance of emotional stressors as a determinant of SB. Our finding of association between low social support and late SB echoed these results. Depression may reflect persistent stress, and we found women whose partner tested for HIV had a high social support score than women whose partner did not. Our findings are consistent with studies that have reported maternal stress, anxiety, or depression can influence the developing fetus potentially through maternal hormone changes[100,101], inflammation, or placental dysfunction[102]. Almost one quarter of women experienced at least moderate depressive symptoms, similar to rates of antenatal depression among African WLWH in a systematic review[103]. Given the high prevalence of depression and the association with SB, standard depression screening during early pregnancy along with interventions may be important to improve maternal outcomes and ensure fetal survival. We found protective effects of partner HIV testing on SB. It is unclear why women with untested partners had higher risk for SB. Differences in sociodemographic, access to care, quality of partnership, or social stressors could play a role. Among women enrolled with viral suppression, social factors persisted or newly emerged as significant contributors to risk of SB; these data are relevant to increasing numbers

of women who are suppressed in early pregnancy. Incorporating more intensive support to women with depression, low social support or those unaware of their partner's HIV status may be useful within PMTCT programs. Although other studies[104] have noted associations between food insecurity and SB, we did not find a difference, perhaps due to generally high levels of food insecurity in this cohort.

Our finding of associations of unsuppressed HIV VL with PTB demonstrates independent impacts of maternal VL on adverse perinatal outcomes, despite ART use, which is consistent with published evidence[8–10]. In addition, we found a significant effect of STI history on PTB risk. Both maternal STIs and viremia are potentially associated with immune activation that could influence likelihood of PTB[85–89]. There is evidence of PTB being associated with syphilis[105–107], chlamydia[108–111], gonorrhea[107,111,112], trichomoniasis[113], and cervicitis[114] during pregnancy in general population, however, there is mixed evidence regarding the association in WLWH[115–119], and not all studies have specified ART use among their study populations, which is a unique contribution of this study. Incorporating STI testing within PMTCT and promoting ART adherence to achieve viral suppression could contribute to lower PTB rates in WLWH.

PTB was associated with IPV during pregnancy and not associated with depression in our study. This is consistent with systematic reviews reporting detrimental impacts of physical violence[120,121] but lower effect of psychosocial stressors on PTB[122]. Studies which demonstrated significant effects of stress on PTB risk were often based on extreme depression[123–125]. Due to the low prevalence of severe depressive symptoms (PHQ9 score >10: 7.6%) in our study population, our analyses may have been underpowered to detect small effects of moderate depression on PTB. Our findings also suggest routine IPV screening among pregnant women is important. Developing evidence-based interventions to involve partners in maternal HIV care may reduce IPV. Our finding of women not completing secondary education contributing to higher risk of PTB is

consistent with other studies[126]. Low education may be a proxy for unbalanced partnership, sociodemographic status, or non-adherence to care, all which also contribute to risk for PTB. Infant sex was a risk factor for PTB, with a higher risk for male fetus than female, consistent with prior studies[127,128]. We did not observe a difference in very PTB by fetal sex, in contrast to some studies reporting increased risk for males for very PTB[127,129], probably due to limited statistical power for this analysis.

NND in this cohort was predominantly associated with PTB, consistent with global data[130]. We also found a 6-7-fold increased risk of NND among women with STI history among women with full-term infants, mainly driven by syphilis. This finding is consistent with a systematic review and meta-analysis showing more frequent NNDs among pregnant women with late diagnosed or untreated syphilis[131]. One study in Botswana reported no significant difference in NND between mothers with HIV/syphilis coinfection and mothers with HIV alone, but the authors noted that data on NND was limited to infants who had not been discharged from the hospital after birth[132]. To our knowledge, our study is the first to evaluate the effects of STI history on PTB and NND among WLWH on ART enrolled in a PMTCT program in SSA. WHO guidelines recommend STI screening for women at the first ANC visit[133], and potential risk-based re-screen later in pregnancy[134,135]. While we did not have data on whether women were still having STI or long-term sequelae in pregnancy, our study suggests that WLWH diagnosed with STI may need enhanced follow-up to ensure adequate care. Scaling up routine STI screening and treatment during ANC visits through point-of-care assays will be helpful to decrease the risk of PTB and NND.

We did not find differences in associations of specific ART regimen with risk of any APO, consistent with studies reporting no difference in APOs of TDF-based[54,83,136] and EFV-based regimens[62,137,138]. Few women in our study received PIs, which have been linked with elevated PTB risk[139–141]. Our findings on ART use provide re-assurance for >90% of pregnant WLWH

following WHO recommendations to use TDF/FTC/EFV[6]. It is also important to note that as new ART regimens are expanded, their effectiveness and safety among WLWH and their infants will be important to evaluate.

This study has unique strengths. We assessed several important APOs, and we restricted analyses to women who were truly "at-risk" with assessment of separate outcomes. Baseline data on social factors, HIV VL, and ART use were collected at enrollment; and outcome data including delivery date and adverse events were verified by comparing several data sources. Our study has limitations. Our estimation of GA at delivery was based primarily on self-reported LMP, given the limited availability of ultrasound at clinics. While LMP dating is commonly used in resource-limited settings[142], it can be problematic due to uncertainty of the true LMP[143], recall bias leading to overestimates of GA[144], and therefore underestimates of PTB. Unreliable GA estimation may also lead to misclassification in determining SB. Exclusion of women with missing LMP data may contribute selection bias. However, we observed no differences in prevalence of any APOs between women with and without LMP date. We did not assess history of prior PTB, which is a risk factor of recurrent PTB[145,146]. The predominant use of TDF+3TC/FTC+EFV limited statistical power to evaluate some regimens. STI data was self-reported with unclear timing, limiting precision and validity of this variable. We had limited birthweight data in MCH records which prevented us from assessing SGA as another APO.

Conclusions

This study provides a comprehensive analysis of APOs among WLWH on ART, including social determinants of health. SB was associated with psychosocial stressors, including depression, poor social support and partners not engaged with HIV services. We found PTB associated with IPV during pregnancy, STI history, and NND. Neither ART regimen nor ART initiation timing was associated with APOs, however, maternal viremia during pregnancy predicted PTB. Most

associations were retained and some enhanced in the subset of women with viral suppression at enrollment, suggesting broad relevance of these factors as wider ART coverage increases the proportion of women suppressed before conception. Implementation of mental health screening and counselling, IPV screening and prevention, social support (perhaps through peer support), partner support, and routine STI screening and treatment could reduce APOs in PMTCT programs.

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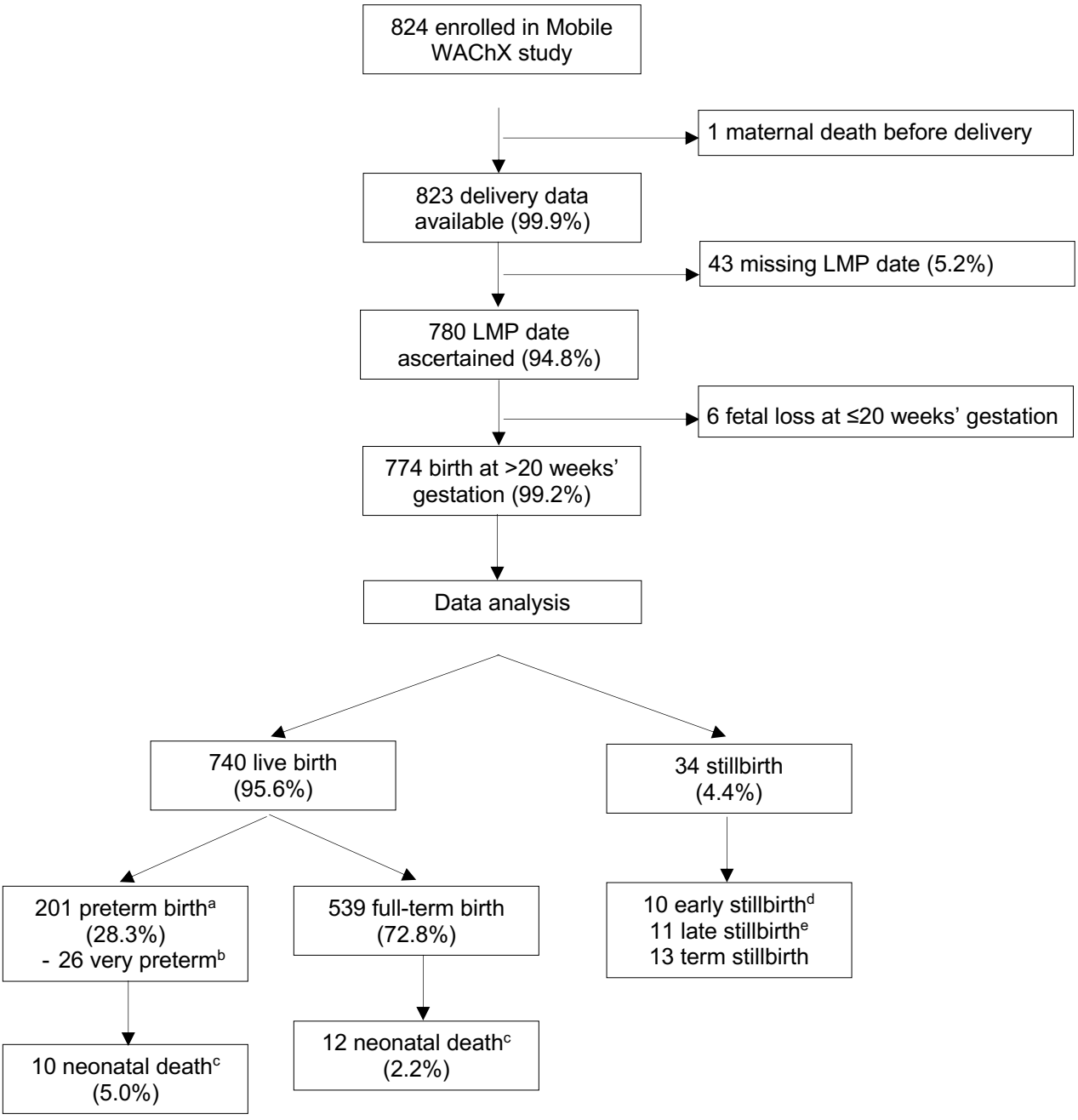
Author Contributions

Wenwen Jiang performed the data analysis and wrote the paper. Keshet Ronen checked the analysis and reviewed the paper. Grace John-Stewart obtained funding, led the overall project, checked the analysis, edited and reviewed the paper. Daniel A. Enquobahrie reviewed the paper. Lusi Osborn, Alison L. Drake, Jennifer A. Unger, Daniel Matemo, and John Kinuthia collected the data of the Mobile WAChX study and reviewed the paper.

Tables and Figures

Figure 2.1. Study flowchart



[a] PTB: live birth at <37 weeks' gestation, among 709 women with live birth and enrolled at <37 weeks' gestation;
[b] Very PTB: live birth at 28-32 weeks' gestation, among 495 women with live birth and enrolled at <28 weeks' gestation;
[c] Neonatal death: infant deaths during the first 28 days after birth, among 740 women who had live birth;
[d] Early stillbirth: fetal death at 20-28 weeks' gestation, among 527 women enrolled at <28 weeks' gestation;
[e] Late stillbirth: fetal death at 28-36 weeks' gestation, among 660 women enrolled at <36 weeks' gestation.

Table 2.1. Participant baseline characteristics (N=774)

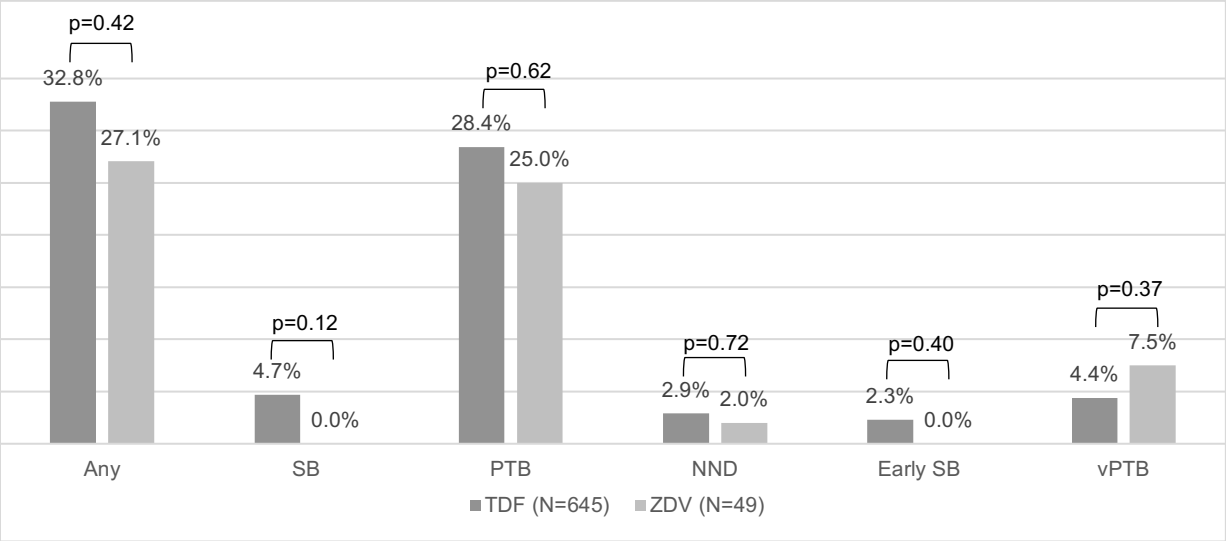
	N	n (Percent) or median (IQR)
Study site	774	
Western Kenya		487 (62.9%)
Nairobi		287 (37.1%)
Sociodemographic		
Age (year)	774	27 (23-31)
Education level	774	
Primary school completed		598 (77.3%)
Secondary school completed		198 (25.6%)
Married/cohabiting	774	652 (84.2%)
Food insecurity[a]	774	
Level 1 (secure)		326 (42.1%)
Level 2 (mild)		85 (11.0%)
Level 3 (moderate)		151 (19.5%)
Level 4 (severe)		212 (27.4%)
Employed*	772	391 (50.6%)
Depression[b]	774	189 (24.4%)
Social support score[c] (percent)	774	64 (50-72)
IPV since pregnancy	774	21 (2.7%)
Travel time to clinic >60 min*	762	53 (7.0%)
Obstetric		
Gestational age at enrollment (week)[d]	774	24 (18-30)
Primigravida	774	109 (14.1%)
History of sexually transmitted infection	774	26 (3.4%)
Genital infection		4 (15.4%)
Gonorrhea		4 (15.4%)
Syphilis		15 (57.7%)
Chlamydia		1 (3.8%)
Acute HIV infection		1 (3.8%)
Cervicitis		1 (3.8%)
Pregnancy intended*	771	433 (56.2%)
HIV/ART		
Diagnosis before pregnancy*	773	461 (59.6%)
Disclosure to anyone*	759	623 (82.1%)
Unsuppressed viral load (>1,000 copies/mL)	774	226 (29.0%)

ART status	774	
Yes, on ART at enrollment		716 (92.5%)
No, newly prescribed ART		43 (5.6%)
No, not on ART		15 (1.9%)
ART regimen*	723	
TDF + 3TC/FTC + EFV		536 (74.1%)
TDF + 3TC + LPV/r		10 (1.4%)
TDF + 3TC/FTC + NVP		99 (13.7%)
ZDV + 3TC + NVP		41 (5.7%)
ZDV + 3TC + EFV		4 (0.6%)
Other		33 (4.6%)
Started ART before pregnancy*	771	425 (55.1%)
IMB score[e]	716	75 (67-80)
Partner tested for HIV[f]	616	479 (77.8%)

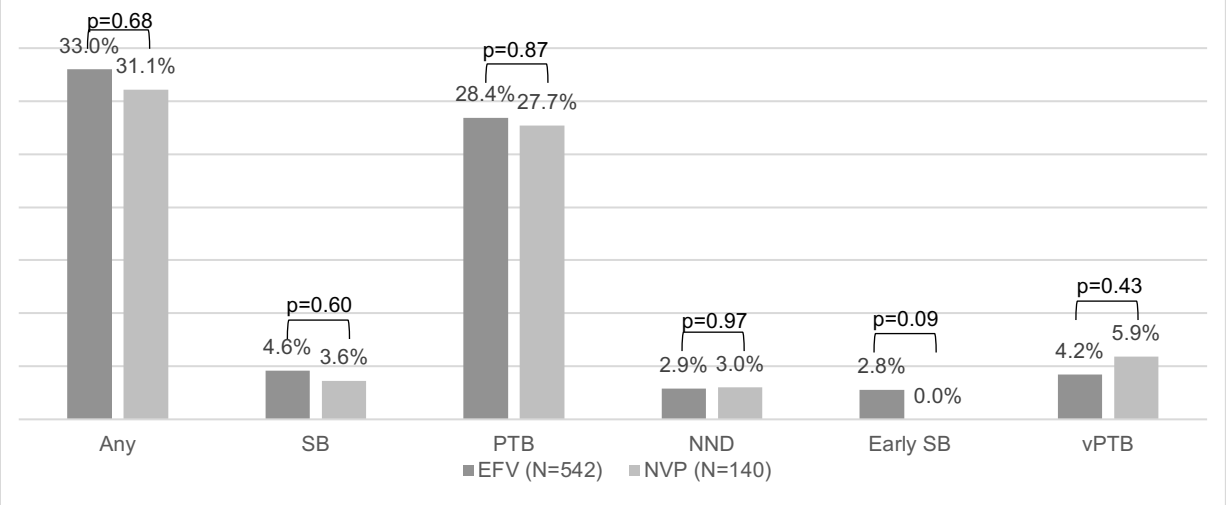
[a] evaluated by Household Food Insecurity Access Scale (HFIAS); [b] evaluated by Patient Health Questionnaire 9 (PHQ9), a score >5 indicating at least moderate depressive symptoms; [c] evaluated by Medical Outcomes Study (MOS) survey; [d] estimated by self-reported date of last menstruation period (LMP); [e] Information-Motivation-Behavioral (IMB) score evaluated by 15 items from LifeWindows ART adherence questionnaire; [f] among women who reported having a partner.
* denominator <774 due to missing data.

Figure 2.2. Prevalence of adverse pregnancy outcome by ART use[a]

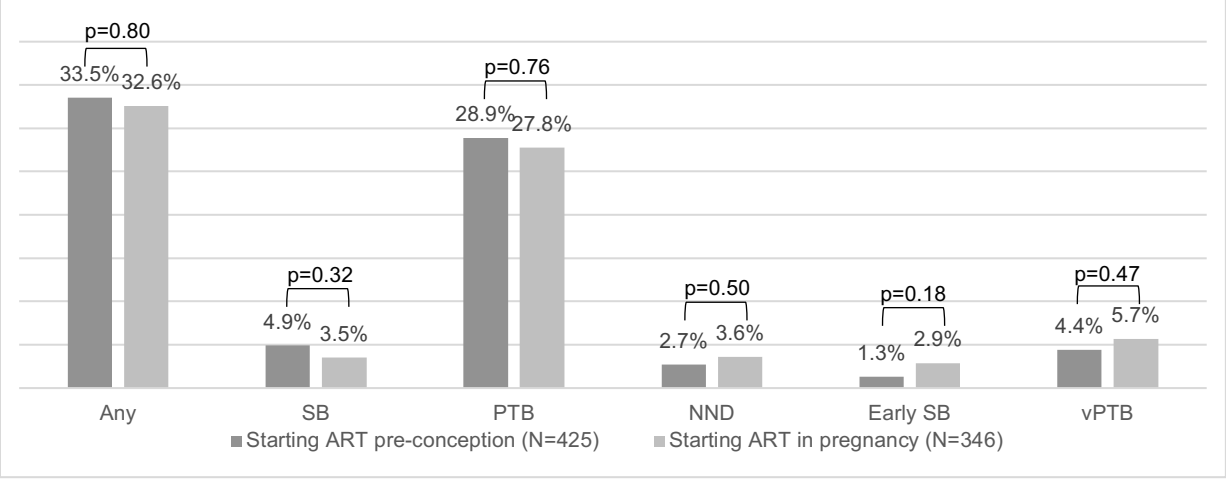
TDF-based vs. ZDV-based regimen (N=694)



EFV-based vs. NVP-based regimen (N=682)[b]



Pre-conception vs. during pregnancy ART initiation (N=771)



[a]Prevalences compared by chi-square tests

Table 2.2. Incidence and covariates of stillbirth

	Any SB among women enrolled at <20 weeks' gestation				Late SB among women enrolled at <28 weeks' gestation			
	All (N=235)*		VL suppressed (N=170)		All (N=517)*		VL suppressed (N=367)	
Group	Event/py (IR/100py)	HR[a] (95%CI); p	Event/py (IR/100py)	HR[a] (95%CI); p	Event/py (IR/100py)	HR[a] (95%CI); p	Event/py (IR/100py)	HR[a] (95%CI); p
Overall	17/99 (17.16)		13/72.7 (17.89)		11/176.1 (6.25)		9/127.2 (7.07)	
Site								
Western Kenya	8/66.0 (12.11)	0.43 (0.18-1.07); 0.069	7/50.4 (13.9)	0.50 (0.18-1.39); 0.182	7/114.9 (6.09)	0.94 (0.28-3.19); 0.918	5/85.9 (5.82)	0.60 (0.16-2.22); 0.441
Nairobi	9/32.9 (27.33)	Ref	6/22.3 (26.88)	Ref	4/61.1 (6.55)	-	4/41.3 (9.67)	Ref
Age								
AYA (15-24 years)	5/35.5 (14.08)	0.87 (0.3-2.52); 0.794	5/24.0 (20.86)	1.67 (0.52-5.34); 0.384	4/57.3 (6.99)	1.24 (0.36-4.25); 0.731	3/36.3 (8.25)	1.34 (0.34-5.27); 0.677
Older adult (≥25 years)	12/63.5 (18.91)	Ref	8/48.7 (16.42)	Ref	7/118.7 (5.9)	Ref	6/90.9 (6.6)	Ref
Depression[b]								
Moderate/severe symptoms	7/27.0 (25.9)	**2.92 (1.09-7.81); 0.033**	5/18.0 (27.84)	2.41 (0.81-7.14); 0.112	3/43.8 (6.85)	1.21 (0.33-4.39); 0.771	2/26.1 (7.66)	1.26 (0.26-6.04); 0.769
None/mild	10/71.9 (13.9)	Ref	8/54.7 (14.62)	Ref	8/132.2 (6.05)	Ref	7/101.1 (6.92)	Ref
Food insecurity[c]								
Level 4	8/29.7 (26.93)	1.68 (0.63-4.51); 0.3	7/20.3 (34.55)	2.33 (0.73-7.49); 0.155	2/48.2 (4.15)	0.61 (0.14-2.75); 0.521	1/33.7 (2.97)	0.37 (0.05-2.88); 0.342
Level 1/2/3	9/69.3 (12.99)	Ref	6/52.4 (11.45)	Ref	9/127.8 (7.04)	Ref	8/93.5 (8.55)	Ref
Social support[d]								
<median	9/46.2 (19.46)	1.65 (0.68-4.02); 0.266	9/32.9 (27.36)	**3.15 (1.12-8.9); 0.03**	10/81.7 (12.24)	**11.62 (1.58-85.54); 0.016**	8/58.0 (13.79)	**10.05 (1.33-76); 0.025**
≥median	8/52.7 (15.17)	Ref	4/39.8 (10.05)	Ref	1/94.3 (1.06)	Ref	1/69.2 (1.44)	Ref
Travel time to clinic								

>60 min	2/9.0 (22.21)	1.63 (0.41-6.53); 0.489	2/6.0 (33.1)	2.05 (0.54-7.74); 0.288	1/13.5 (7.39)	1.28 (0.16-10.06); 0.812	0/9.2 (0)	-
≤60 min	15/88.2 (17.01)	Ref	11/65.8 (16.71)	Ref	10/159.7 (6.26)	Ref	9/116.7 (7.71)	Ref
History of STI[e]								
Yes	1/4.1 (24.46)	2.41 (0.33-17.63); 0.385	1/3.1 (32.5)	2.54 (0.34-18.74); 0.36	1/6.9 (14.47)	2.62 (0.31-22.41); 0.378	1/5.0 (19.86)	3.49 (0.41-29.59); 0.251
No	16/94.4 (16.94)	Ref	12/69.1 (17.36)	Ref	10/168.6 (5.93)	Ref	8/121.7 (6.57)	Ref
Diagnosis								
Before pregnancy	8/67.9 (11.78)	0.49 (0.2-1.22); 0.126	7/59.3 (11.81)	**0.31 (0.11-0.9); 0.032**	6/114.8 (5.23)	0.88 (0.27-2.88); 0.838	5/100.2 (4.99)	0.55 (0.15-1.95); 0.353
During pregnancy	9/31.1 (28.95)	Ref	6/13.4 (44.78)	Ref	4/61.2 (6.53)	Ref	3/27.0 (11.09)	Ref
VL at enroll								
Unsuppressed	4/26.3 (15.21)	0.74 (0.25-2.15); 0.575	-	-	2/48.7 (4.1)	0.57 (0.12-2.78); 0.487	-	-
Suppressed	13/72.7 (17.89)	Ref	-	-	9/127.2 (7.07)	Ref	-	-
Partner tested for HIV								
Yes	10/69.8 (14.34)	0.36 (0.13-1.01); 0.052	7/56.2 (12.46)	**0.18 (0.06-0.55); 0.003**	6/118.7 (5.06)	0.34 (0.09-1.27); 0.11	6/95.6 (6.28)	0.28 (0.07-1.15); 0.076
No	6/12.9 (46.44)	Ref	6/7.6 (78.58)	Ref	4/24.7 (16.17)	Ref	3/12.3 (24.3)	Ref

[a] Hazard ratio estimated by Cox proportional hazards regression calculating time-at-risk from enrollment to delivery, and adjusting for site as a covariate; [b] evaluated by Patient Health Questionnaire 9 (PHQ9), a score >5 indicating at least moderate depressive symptoms; [c] level 1,2,3,4 indicating secure, mild, moderate, severe; [d] evaluated by Medical Outcomes Study (MOS) survey, median of 64 among 235 women enrolled at <20 weeks and median of 63 among 517 women enrolled at <28 weeks; [e] including genital infection, gonorrhea, syphilis, chlamydia, candidiasis, cervicitis.
***** In models adjusting for site and VL at enrollment, the association between SB and depression remained similar (adjusted HR [aHR] 2.93, 95%CI 1.04-8.23), as did the association between late SB and lower social support score (aHR 11.74, 95%CI 2.47-55.86).

Table 2.3. Prevalence and covariates of PTB, very PTB and NND

	PTB among women who enrolled <37 weeks and had live birth (N=709)				Very PTB among women who enrolled <28 weeks and had live birth (N=495)*			NND among women with live birth (N=740)*		
	n (Pr)		PR (95%CI); p[a]	aPR (95%CI); p[b]	n (Pr)		PR (95%CI); p[a]	n (Pr)		PR (95%CI); p[a]
	Full-term (n=508)	PTB (n=201)			Birth at ≥32 weeks (n=469)	Very PTB (n=26)		No NND (n=718)	NND (n=22)	
Western Kenya (ref: Nairobi)	317 (62.4%)	126 (62.7%)	1.01 (0.80-1.28); 0.943	1.01 (0.80-1.29); 0.917	303 (64.6%)	23 (88.5%)	**3.97 (1.24-12.76); 0.020**	451 (62.9%)	15 (65.2%)	1.10 (0.48-2.53); 0.818
AYA (age 15-24 years)	171 (33.7%)	72 (35.8%)	1.07 (0.84-1.36); 0.579		152 (32.4%)	12 (46.2%)	1.82 (0.86-3.84); 0.115	27 (23, 31)	28 (23, 32)	0.99 (0.91-1.08); 0.841
Incomplete secondary school	366 (72.0%)	161 (80.1%)	**1.39 (1.03-1.89); 0.033**	**1.33 (0.99-1.79); 0.055**	345 (73.6%)	24 (92.3%)	3.38 (0.78-14.62); 0.103	530 (73.9%)	20 (87.0%)	2.3 (0.67-7.86); 0.185
Depression[c]	126 (24.8%)	40 (19.9%)	0.81 (0.61-1.08); 0.157		109 (23.2%)	6 (23.1%)	0.90 (0.38-2.15); 0.811	172 (24.0%)	5 (22.7%)	0.87 (0.33-2.32); 0.784
Severe food insecurity[d]	134 (26.4%)	57 (28.4%)	1.07 (0.83-1.39); 0.595		124 (26.4%)	9 (34.6%)	1.26 (0.57-2.78); 0.570	196 (27.3%)	4 (18.2%)	0.56 (0.19-1.63); 0.284
Low social support score[e]	241 (47.4%)	108 (53.7%)	1.20 (0.95-1.50); 0.120		234 (49.9%)	12 (46.2%)	0.73 (0.35-1.51); 0.394	349 (48.7%)	14 (60.9%)	1.61 (0.68-3.84); 0.280
IPV since pregnancy	9 (1.8%)	11 (5.5%)	**2.00 (1.31-3.04); 0.001**	**1.94 (1.28-2.94); 0.002**	16 (3.4%)	0 (0.0%)	-	19 (2.6%)	2 (8.7%)	3.41 (0.83-13.99); 0.089
Travel time to clinic >60 min	27 (5.4%)	18 (9.1%)	1.46 (0.98-2.15); 0.060		33 (7.2%)	1 (3.8%)	0.47 (0.07-3.43); 0.46	46 (6.5%)	2 (9.1%)	1.34 (0.33-5.49); 0.683
History of STI[f]	13 (2.6%)	11 (5.5%)	**1.65 (1.07-2.53); 0.023**	**1.63 (1.06-2.51); 0.025**	18 (3.8%)	1 (3.8%)	0.84 (0.11-6.64); 0.870	22 (3.1%)	3 (13.0%)	**4.25 (1.39-13.06); 0.011**

Syphilis	11 (2.2%)	4 (2.0%)	0.94 (0.42-2.11); 0.877		12 (2.6%)	0 (0.0%)	-	13 (1.8%)	2 (8.7%)	**4.57 (1.17-17.79); 0.029**
Diagnosis before pregnancy	312 (61.4%)	116 (57.7%)	0.89 (0.70-1.13); 0.347		298 (63.5%)	17 (65.4%)	0.90 (0.42-1.91); 0.783	433 (60.3%)	10 (45.5%)	0.50 (0.23-1.07); 0.073
Unsuppressed VL at enrollment	136 (26.8%)	71 (35.3%)	**1.33 (1.05-1.67); 0.016**	**1.28 (1.02-1.61); 0.036**	134 (28.6%)	11 (42.3%)	1.92 (0.91-4.06); 0.087	206 (28.7%)	8 (36.4%)	1.59 (0.7-3.62); 0.265
Infant sex male (vs. female)	223 (49.6%)	101 (59.8%)	**1.35 (1.04-1.76); 0.024**		214 (51.6%)	15 (68.2%)	1.94 (0.82-4.57); 0.130	336 (52.7%)	5 (50.0%)	0.89 (0.26-3.05); 0.856
Preterm birth	-	-	-	-	-	-	-	191 (26.6%)	10 (45.5%)	**2.53 (1.10-5.78); 0.028**

[a] Prevalence ratio estimated by Log-binomial regression adjusting for site as a covariate; [b] adjusted prevalence ratio estimated by multivariate Log-binomial regression adjusting for covariates with crude-p-value <0.05; [c] evaluated by Patient Health Questionnaire 9 (PHQ9), a score >5 indicating at least moderate depressive symptoms; [d] compared to secure, mild, or moderate level; [e] evaluated by Medical Outcomes Study survey, a score <median of 64 indicating low level; [f] including genital infection, gonorrhea, syphilis, chlamydia, candidiasis, cervicitis.

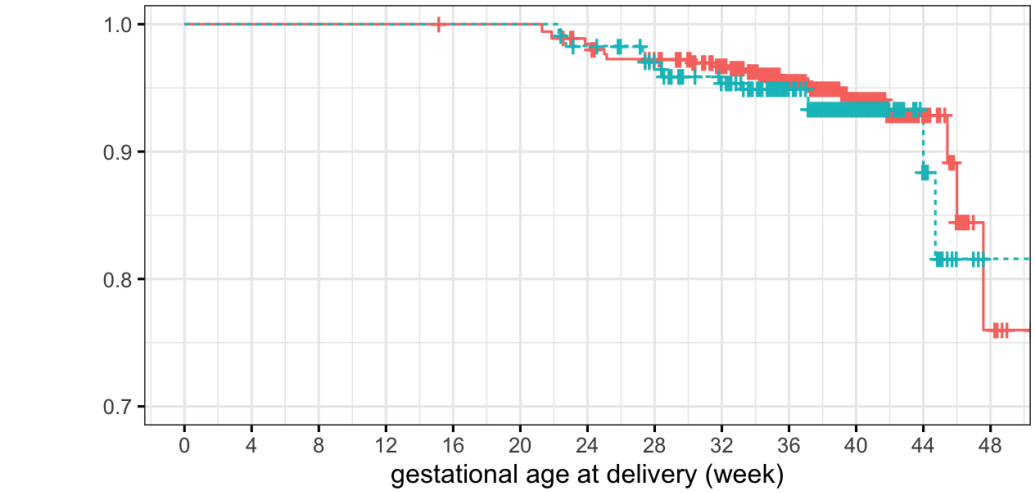
* Adjusting for site and HIV VL at enrollment, results of no characteristics significantly associated with very PTB remained the same, and the association between NND and PTB remained (aPR 2.42, 95%CI 1.03-5.66)

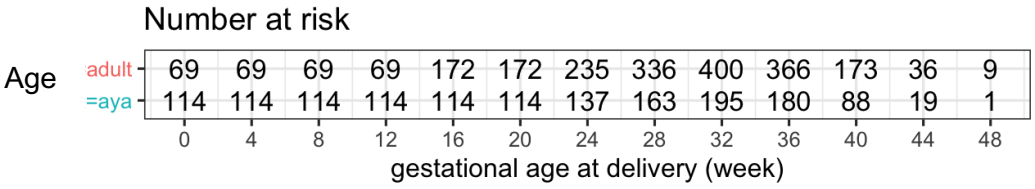
Supplementary Table 2.1. Prevalence of adverse pregnancy outcomes

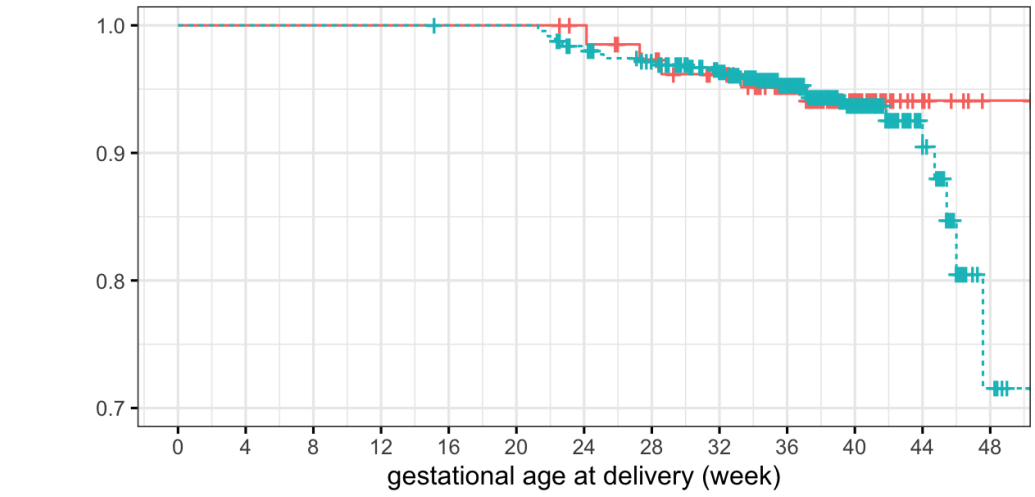
	n / N	Pr
Among all women enrolled (N=774)		
Early stillbirth[a]	10 / 527	1.90%
Late stillbirth[b]	11 / 660	1.67%
Term stillbirth	13 / 774	1.68%
Any stillbirth	**34 / 774**	**4.39%**
Alive birth	**740 / 774**	**95.61%**
Among women with alive birth (N=740)		
Very preterm birth[c]	31 / 628	4.94%
Preterm birth[d]	201 / 709	28.35%
Neonatal death[e]	22 / 740	2.97%

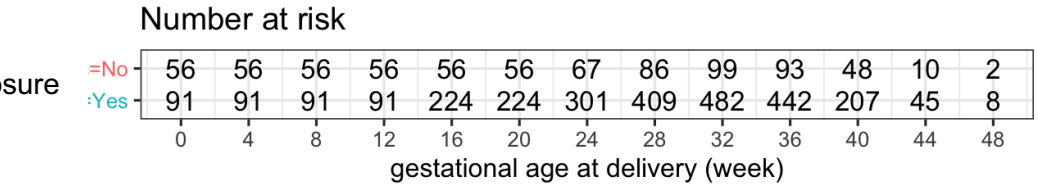
a. Early stillbirth = fetal death at 20-28 weeks' gestation, among women enrolled at <28 weeks' gestation;
b. Late stillbirth = fetal death at 28-36 weeks' gestation, among women enrolled at <36 weeks' gestation;
c. Very PTB= alive birth at 28-32 weeks' gestation, among women who had alive birth and enrolled at <32 weeks' gestation;
d. PTB = alive birth at <37 weeks' gestation, among women who had alive birth and enrolled at <37 weeks' gestation;
e. Neonatal death = infant deaths during the first 28 days after birth, among women who had alive birth.

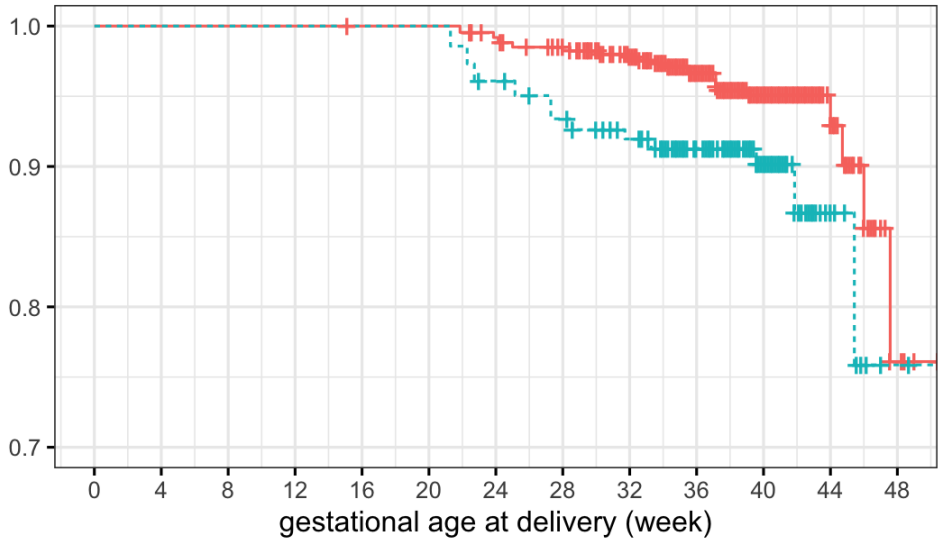
Supplementary Figure 2.1. Survival probability of stillbirth by age, disclosure, depression, number of ANC visits, VL at enrollment and travel time to clinic









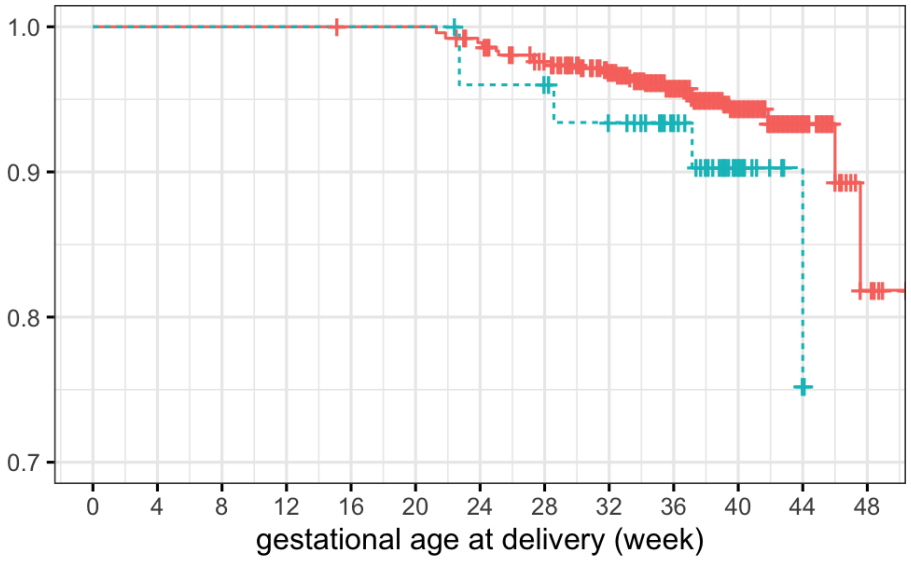


Number at risk

Depression

	0	4	8	12	16	20	24	28	32	36	40	44	48
=No	73	73	73	73	222	222	279	381	457	416	188	44	7
=Yes	70	70	70	70	70	70	92	119	139	130	73	11	3

gestational age at delivery (week)

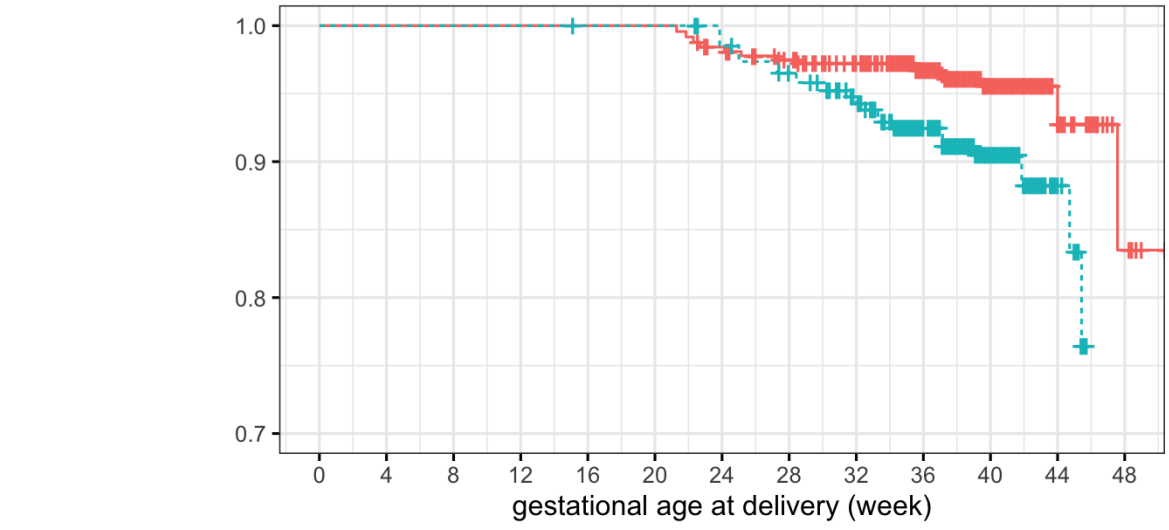


Number at risk

Time to clinic >60 min

	0	4	8	12	16	20	24	28	32	36	40	44	48
FALSE	89	89	89	89	242	242	334	454	543	501	238	48	10
=TRUE	26	26	26	26	26	26	37	37	42	35	17	6	0

gestational age at delivery (week)

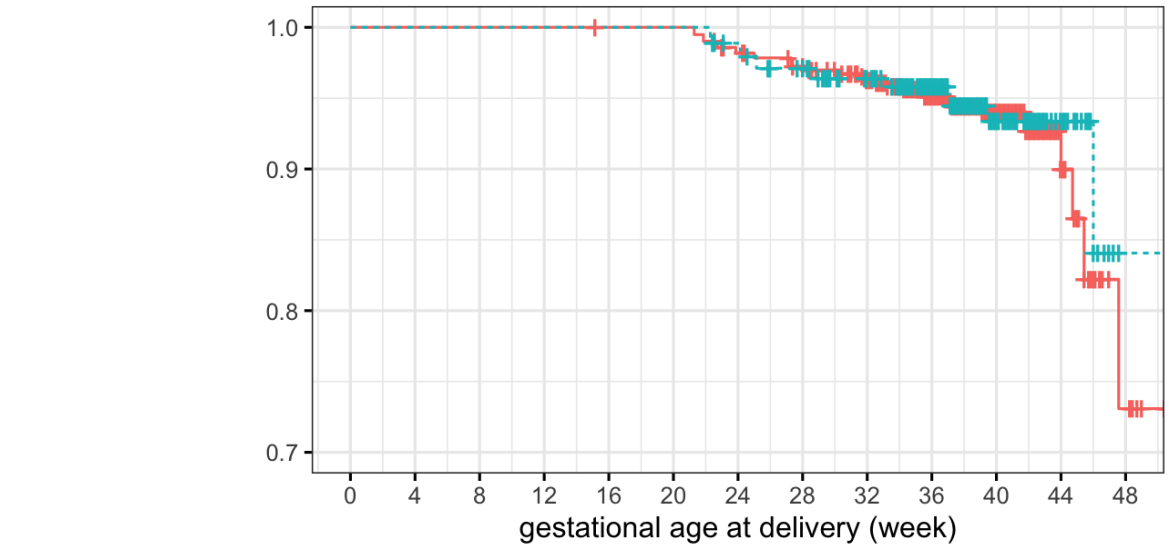


Number at risk

≥1 ANC visits before enroll

	0	4	8	12	16	20	24	28	32	36	40	44	48
=No	232	232	232	232	232	232	298	372	392	342	149	34	9
=Yes	8	8	8	8	50	50	80	131	203	204	112	21	1

gestational age at delivery (week)



Number at risk

Unsuppressed VL at enroll

	0	4	8	12	16	20	24	28	32	36	40	44	48
FALSE	78	78	78	78	194	194	263	357	430	397	189	35	8
=TRUE	89	89	89	89	89	89	109	142	165	149	72	20	2

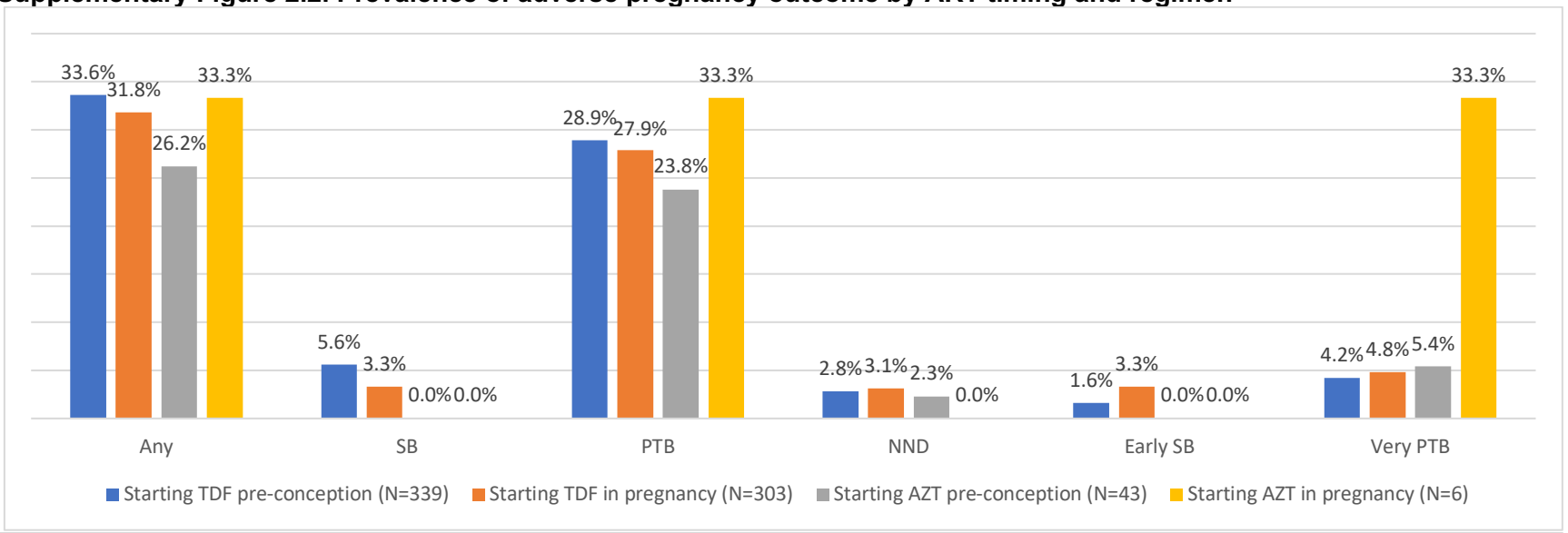
gestational age at delivery (week)

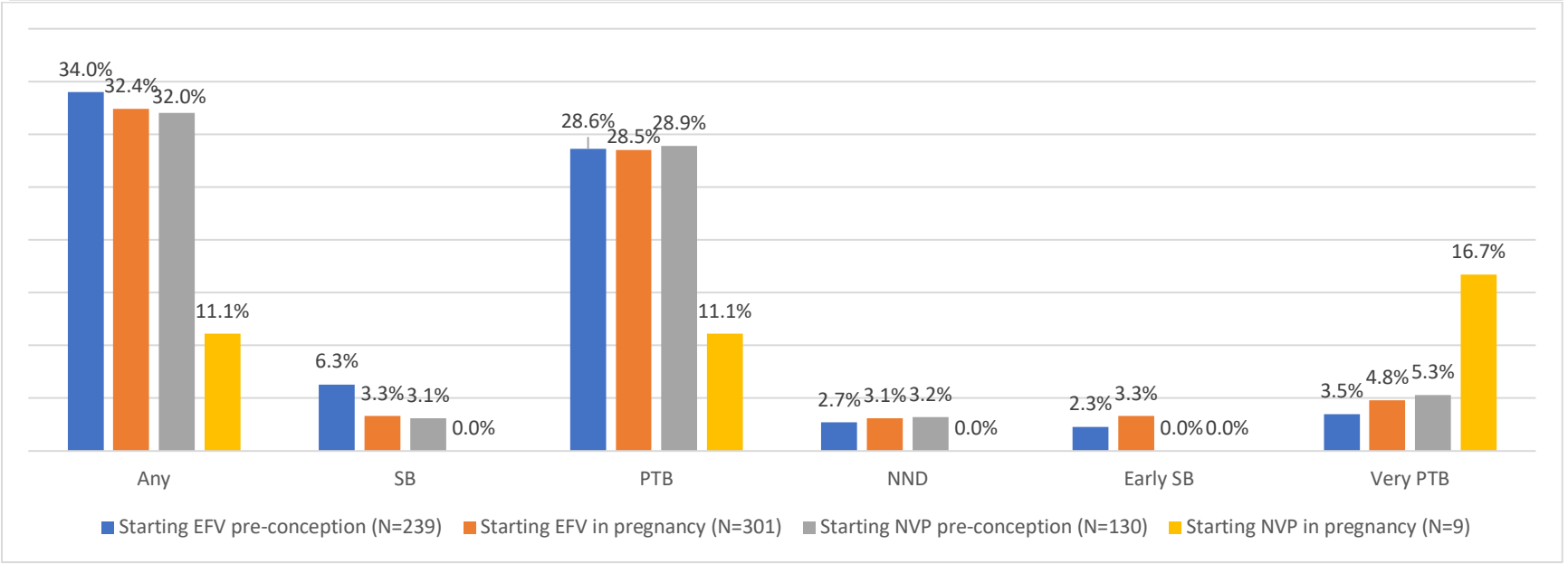
Supplementary Table 2.2. Prevalence and covariates of PTB, very PTB and NND in women with suppressed VL at enrollment

	PTB among women who enrolled <37 weeks and had live birth (N=502)			Very PTB among women who enrolled <28 weeks and had live birth (N=350)			NND among women with live birth (N=526)		
	n (Pr)		PR (95%CI); p[a]	n (Pr)		PR (95%CI); p[a]	n (Pr)		PR (95%CI); p[a]
	Full-term (n=372)	PTB (n=130)		Birth at ≥32 weeks (n=335)	Very PTB (n=15)		No NND (n=512)	NND (n=14)	
Western Kenya (ref: Nairobi)	239 (64.2%)	86 (66.2%)	1.06 (0.79-1.44); 0.688	225 (67.2%)	13 (86.7%)	3.06 (0.71-13.14); 0.133	332 (64.8%)	9 (64.3%)	0.98 (0.34-2.80); 0.965
Incomplete secondary school	265 (71.2%)	102 (78.5%)	1.34 (0.92-1.93); 0.125	242 (72.2%)	14 (93.3%)	4.38 (0.55-34.89); 0.163	372 (72.7%)	12 (85.7%)	2.26 (0.51-10.08); 0.286
IPV since pregnancy	6 (1.6%)	6 (4.6%)	**1.97 (1.07-3.62); 0.029**	10 (3.0%)	0 (0.0%)	-	11 (2.1%)	1 (7.1%)	3.31 (0.49-22.42); 0.221
Primigravida	46 (12.4%)	12 (9.2%)	0.79 (0.46-1.34); 0.377	35 (10.4%)	3 (20.0%)	3.21 (0.94-11.0); 0.063	62 (12.1%)	2 (14.3%)	1.20 (0.24-6.04); 0.823
History of STI[b]	10 (2.7%)	9 (6.9%)	**1.87 (1.16-3.02); 0.01**	13 (3.9%)	1 (6.7%)	1.48 (0.18-12.24); 0.714	17 (3.3%)	3 (21.4%)	**6.90 (2.17-21.99); 0.001**
Infant sex male (vs. female)	160 (47.6%)	64 (56.1%)	1.29 (0.94-1.76); 0.109	152 (50.0%)	7 (50.0%)	1.02 (0.37-2.81); 0.964	235 (50.3%)	3 (50.0%)	0.95 (0.20-4.57); 0.948
Preterm birth	-	-	-	-	-	-	123 (25.2%)	7 (53.8%)	**3.35 (1.13-9.91); 0.029**

[a] Prevalence ratio estimated by Log-binomial regression adjusting for site as a covariate; [b] including genital infection, gonorrhea, syphilis, chlamydia, candidiasis, cervicitis

Supplementary Figure 2.2. Prevalence of adverse pregnancy outcome by ART timing and regimen





Chapter 3. Programmatic retention in prevention of mother-to-child transmission (PMTCT) programs: estimated rates and cofactors using different non-retention measures

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Programmatic retention in prevention of mother-to-child transmission (PMTCT) programs: estimated rates and cofactors using different non-retention measures

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We report no real or perceived vested interests related to this article that could be construed as a conflict of interest.

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Abstract

Background: PMTCT programs serve women continuing and initiating ART in pregnancy, and follow-up schedules align to delivery rather than ART initiation, making conventional HIV retention measures (assessed from ART initiation) challenging to apply. We evaluated three measures of peripartum non-retention in Kenyan women living with HIV from pregnancy to 2-years postpartum.

Methods: This longitudinal analysis used programmatic data from the Mobile WAChX trial (NCT02400671). Outcomes included loss to follow-up (LTFU) (no visit for ≥6 months), incomplete visit coverage (<80% of 3-month intervals with a visit), and late visits >2 weeks after scheduled date). Predictors of non-retention were determined using Cox proportional hazards, log-binomial, and generalized estimating equation models.

Results: Among 813 women enrolled at a median of 24 weeks gestation, incidence of LTFU was 13.6/100 person-years; cumulative incidence of LTFU by 6, 12 and 24 months postpartum was 16.7%, 20.9% and 22.5%, respectively. Overall, 35.5% of women had incomplete visit coverage. Among 794 women with 12,437 scheduled visits, a median of 11.1% of visits per woman were late (IQR 4.3%-23.5%). Younger age, unsuppressed viral load, unemployment, ART initiation in pregnancy, and non-disclosure were associated with non-retention by all measures. Partner involvement was associated with better visit coverage and timely attendance. Women who became LTFU had higher frequency of previous late visits (16.7% vs. 7.7%, p<0.0001).

Conclusion: Late visit attendance may be a sentinel indicator of LTFU. Identified cofactors of PMTCT programmatic retention may differ depending on retention measure assessed, highlighting need for standardized measures.

Keywords: Women, HIV care continuum, retention, Africa, loss-to follow-up, cohort studies

Background

Effective prevention of mother-to-child transmission (PMTCT) programs support women living with HIV (WLWH) to access care and antiretroviral therapy (ART) throughout pregnancy and postpartum[15–17]. Adherence to sequential steps of the PMTCT cascade[147] is crucial, with one modeling study indicating that virtual elimination of vertical HIV transmission could be attained by 95% adherence to each step[18]. However, loss-to follow-up (LTFU) rates are often high in PMTCT programs with 16-22% of women LTFU during peripartum period[66,67,148,149].

Despite recognition of the crucial need for high retention in PMTCT programs, there is no standard definition or methodology to evaluate retention in this context, and studies have used a wide range of definitions[25–30]. For surveillance purposes, the WHO consolidated guidelines define retention in general HIV care as attendance at a health facility at 12-months post-ART initiation[25]. In 2015, the Inter-Agency Task Team (IATT) on Children and HIV/ AIDS assessed maternal retention as continuous longitudinal engagement, defined as the proportion of women on ART per 3-month intervals until 12 months after ART initiation[26]. However, for pregnant and breastfeeding WLWH, the 12-months post-ART initiation timepoint is often challenging to align with routine PMTCT visits which are scheduled based on gestational age and time since delivery: most women initiate ART prior to pregnancy and for those who initiate ART in pregnancy, gestational age at ART initiation varies. Differences in outcome definitions have yielded variations in estimates of LTFU or retention within PMTCT programs[65–68,70–74,150–152]. A meta-analysis pooling six PMTCT intervention studies in Malawi, Nigeria and Zimbabwe observed marked variability in retention estimates ranging from 30% to 76% when different definitions were applied within the same dataset[31]. This variability makes charting progress and identifying effective interventions challenging across programs.

In the absence of a standard definition for non-retention in PMTCT programs, we evaluated three retention measures of potential utility to the peripartum period in a cohort of WLWH from pregnancy to 2-year postpartum. We also determined how these measures influenced identification of cofactors of non-retention.

Methods

Study design and population

This study leveraged data collected from a completed 3-armed randomized clinical trial (RCT) (Mobile WAChX study, ClinicalTrial.gov number NCT02400671[34,153]). The RCT assessed the effect of short messaging service (SMS) on ART adherence and retention among WLWH attending PMTCT programs. The RCT intervention did not have an impact on any non-retention measures; results have been previously reported[34]. Briefly, the trial enrolled pregnant WLWH from six public maternal-child health (MCH) clinics in Nairobi and Western Kenya if they were aged ≥14 years and had daily access to a mobile phone at the time of enrollment. Women were randomized to receive one-way SMS, two-way SMS or no SMS, and followed-up through 2 years postpartum[34]. This study aimed to determine effect of the intervention on programmatic retention and used medical record data from routine clinic visits for the retention outcomes; no additional sample size calculations were conducted. The RCT was approved by the UW Institutional Review Board and the Kenyatta National Hospital/University of Nairobi Ethical Review Committee.

Data Collection

At enrollment, a standardized survey was administered on a tablet using Open Data Kit (ODK). Data was collected on demographics, social support (using Medical Outcomes Study [MOS] survey[91]), stigma (using 4-item instrument adapted from the stigma scale for chronic illnesses [SSCI][92]), depression (using Patient Health Questionnaire 9 [PHQ9][93]), intimate partner violence (IPV) (using Abuse Assessment Screen [AAS][94]), food security (using Household Food Insecurity

Access Scale [HFIAS][95]), disclosure of HIV status, and ART knowledge based on the Information–Motivation and Behavioural Skills (IMB) model, which was adapted from 15 items from the LifeWindows ART adherence questionnaire[96]. Data on ART use history was abstracted from the mother's Mother Child Health (MCH) booklet. HIV VL testing results were obtained from the routine VL monitoring system of the Kenya National AIDS & STI Control Program (NASCOP). If programmatic VL results were not available, VL testing was done by the study on maternal plasma samples. Programmatic data of clinic visits was obtained from clinic paper records and electronic medical records (EMRs)[154]. Briefly, at in-person study visits at enrolment in pregnancy, 6 weeks postpartum and 6, 12, 18, and 24 months postpartum, study staff checked medical records and EMR for appointments, deliveries, clinic visits, and medication refills. For women with a recorded transfer-out status (based on self-report or official transfer report at the facility), data was extracted at other sites where participants received care after obtaining the approval from the sites.

Study outcomes

This study assessed three aspects of non-retention: programmatic LTFU, incomplete visit coverage, and late visits. Programmatic LTFU was defined as no clinic visit for at least 6 months, with no report of death or transfer. This was based on a study integrating data from 19 countries which proposed ≥6 months since the last clinic visit as a standard LTFU definition in general HIV care [30]. Visit coverage was defined for each participant as a proportion of 3-month intervals with at least one clinic visit over the entire follow-up period from pregnancy to 2 years postpartum. This approach aligns with the recommended schedule of maternal ART refills, follow-up visits for antenatal/postnatal care, and immunization windows for HIV exposed infants, according to the WHO guidelines of integrating PMTCT services into standard MCH services[155] and the overall visit continuum[156]. The numerator is equal to the number of intervals since enrollment in which at least one clinic visit was attended, and the denominator is equal to the total number of intervals

during follow-up (depending on gestational age at enrollment in this cohort)[68,155]. A late visit was defined for each participant as a scheduled visit that was not attended within 2 weeks of the expected date of clinic visit and was assessed for each scheduled visit.

In all analyses, participants who died, exited from the trial, or completed 2-year postpartum follow-up were censored at the time of corresponding events. In the analysis of LTFU and visit coverage, visit data abstracted both from the original study sites and from transfer sites was used. In the analysis of late visits, only data abstracted at the study sites was used. For women who transferred out, data after transfer was censored and subsequent scheduled visits were not included. In addition, women who stopped follow-up with dates known to be before their scheduled visit date + 14 days (defined attendance window for late visits) were also censored before the final scheduled visit, i.e. attendance of the final scheduled visit was marked as missing and not included in the analyses.

Statistical analysis

Kaplan-Meier survival curves were used to assess time to LTFU. Person-time at risk was calculated from enrollment to the last visit when participants were assessed for LTFU by definition. Cox proportional hazards regression was used to identify predictors of LTFU. Log-binomial regression was used to identify predictors of cumulative LTFU by 24-months postpartum and predictors of visit coverage <80%. Generalized estimating equation (GEE) models clustered by participant, with log-binomial link and exchangeable correlation structure were used to identify predictors of late visits. Two-sample t-tests were used to compare the proportion of late visits between women who were LTFU and not, excluding the last scheduled visit of women who were LTFU, because by definition LTFU involved no attendance of the last scheduled visit (and would be considered ‘late’). Study site, dichotomized as Nairobi (Mathare, Riruta) or Western Kenya (Ahero, Bondo, Siaya, Rachuonyo), was identified as an a priori confounder in all regression

models to account for potential geographical differences in maternal characteristics and underlying retention in care. All models used robust standard errors. All analyses were conducted using RStudio Version 1.2.5042 (RStudio, Inc).

Results

Overall, 813 women from the Mobile WAChX trial had programmatic visit data available for inclusion in this analysis. At enrollment, median age was 27 years (interquartile range [IQR] 23-31) and median gestational age was 24.3 weeks (IQR 18.3-29.6). Over 1,349 person-years (py) of follow-up, the incidence rate of LTFU was 13.6/100 person-years (Table 3.1a, Figure 3.1a). The cumulative incidence of LTFU by delivery, 6, 12 and 24 months postpartum was 12.6%, 16.7%, 20.9% and 22.5%, respectively (Table 3.1c, Figure 3.1b). Depending on their gestational age at enrollment, women were expected to have a median of 10 (IQR 9-10) 3-month intervals during study follow-up (Table 3.1b), and a total of 7,771 expected intervals were included in the analysis. The proportion of intervals with ≥1 visit among all women was 74.9%, and each participant had a median of 88.9% (IQR 66.7%-90.9%) of quarterly intervals covered with at least 1 visit attended (Table 3.1b). Visit coverage per interval declined from 83.5% in the first 3 months after delivery, to 65.8% at 24 months postpartum (Figure 3.1c). Among 147 (18.1%) women documented as transferred out during study follow-up, 94 (63.9%) had data retrieved and abstracted from clinics they transferred to. In a secondary analysis not including visit data after transfer-out, the rate of LTFU by 24 months postpartum would be over-estimated as 28.8% (234/812), 6.3% higher than the 22.5% observed, and the overall proportion of quarterly intervals with at least 1 visit attended by 24 months postpartum would be 70.5%, 4.4% lower than the 74.9% observed.

A total of 794 women had ≥1 clinic appointment scheduled, with a median of 16 scheduled visits (IQR 10-22) per woman (Table 3.1c), for a total of 12,437 scheduled visits, of which 11.5% were

late. Among late attended visits, the median duration from the scheduled date was 32 days later (IQR 27-59). The median proportion of late visits per woman was 11.1% (IQR 4.3%-23.5%) by 24-month postpartum (Table 3.1c). The proportion of late visits declined from 17.7% at 1-month postpartum, to 9.8% at 6 months postpartum, and remained around 11% until 18 months postpartum (Table 3.1c, Figure 3.1d). The proportion slightly increased to 20.0% at 20 months postpartum, potentially due to the total number of scheduled visits decreased after 20 months.

Most (85.0%, 675/794) women were late for at least 1 scheduled visit, and 61.2% (483/789) women had a late visit within 6 months after delivery. Women who were ever late for visits during the first 6 months postpartum, had a higher risk of subsequent LTFU (22.2% vs. 16.4%, p=0.05) (Figure 3.2a). Over follow-up through 2 years postpartum, women who became LTFU had a significantly higher proportion of previous late visits than those who did not (16.7% vs. 7.7%, p<0.0001) (Figure 3.2b). In a sensitivity analysis among 625 women who had at least 10 previous scheduled visits, women who became LTFU had higher frequency of prior late visits (13.4% vs. 7.7%, p<0.0001) (data not shown).

In site-adjusted regression models, younger age was associated with higher risks of non-retention by all three measures (Figure 3.3). Women aged 15-24 years were more likely to be LTFU (adjusted hazard ratio [aHR] 2.13, 95%CI 1.59-2.86; p<0.0001), have a low visit coverage (<80%) (adjusted prevalence ratio [aPR] 1.60, 95%CI 1.35-1.90; p<0.0001), and be late for a scheduled visit (aPR 1.21, 95%CI 1.08-1.36; p=0.001) (Table 2). Unsuppressed VL at enrollment, being employed, HIV diagnosed before pregnancy, disclosure to others, and starting ART before pregnancy were significantly associated with better retention in all measures (Figure 3.3, Table 3.2).

The relationship between some covariates and non-retention depended on which non-retention measure was used. Women who were married or cohabiting were less likely to be LTFU (aHR 0.61, 95%CI 0.42-0.89; p=0.01), and to have low visit coverage (aPR 0.72, 0.58-0.89; p=0.003), but not late visits (Table 3.2). Similarly, women with at least moderate food insecurity also had lower risk of LTFU (aHR 0.69, 95%CI 0.51-0.93; p=0.016) and low visit coverage (aPR 0.81, 95%CI 0.66-0.98; p=0.031) but not late visits. Having a male partner tested for HIV was associated with lower risk of low visit coverage (aPR 0.76, 95%CI 0.61-0.96; p=0.018) and late visits (aPR 0.85, 95%CI 0.73-0.98; p=0.027). Women with standardized IMB score <75% had a significantly higher risk of late visits (aPR 1.18, 95%CI 1.05-1.32; p=0.005) (Table 3.2). Women's education level, depressive symptoms, or travel time from home to clinic were not associated with any non-retention measures (Table 3.2).

The parent trial found no significant impact of the SMS system on outcomes; thus, we pooled the results. Results from stratified analysis by each intervention arm yielded similar findings to the pooled data from the three arms in this study (data not shown).

Discussion

We evaluated three measures of non-retention in care among a cohort of women receiving PMTCT services in Kenya from pregnancy to 2 years postpartum. We found that among 813 participants, 22.5% were LTFU and the incidence rate was 13.6/100 person-year; 55.0% had low visit coverage per quarterly interval (<80%); and 85.0% were late for at least 1 scheduled visit. The incidence rate and cumulative incidence of LTFU in our study were similar to PMTCT studies in Malawi and Ethiopia. In Ethiopia, a LTFU incidence rate of 13.2 per 100 person-year was observed over the 2-year postpartum[152]. Cumulative incidence of LTFU at 24 months postpartum in Malawi and Ethiopia were 24.5% and 23.0%, respectively[21,66]. Studies with shorter follow-up periods have reported higher LTFU than our study[22,65,150,157,158]. When a one-time indicator of

LTFU is used, estimates of retention have varied widely in similar population and settings [22,28,157,158]. Some patients thought to be LTFU may receive care at other facilities or return after a period of disengagement [29,75,159,160]. If transfer-out data was not obtained from other sites we would have over-estimated LTFU by 24-month postpartum as 28.8%, 6.3% higher than the 22.5% we observed.

Timely attendance of clinic visits in our study varied over pregnancy and postpartum, and we found a higher risk of late visits prior to delivery, consistent with a study in Nigeria[161]. We found that late visit attendance was associated with subsequent LTFU. Given the particular concern for LTFU during the postpartum period[23,162], late visits may be a useful sentinel indicator to alert clinicians to initiate additional strategies to optimize retention.

We found that the proportion of women attending ≥1 clinic visits within each 3-month interval declined over time. In a large Nigerian study of WLWH conducted over a 10-year period, 66% of women had at least one visit during each of the antenatal, delivery, and 18 months postpartum periods[149]; however, aside from that study, studies analyzing visit coverage throughout the PMTCT care cascade including breastfeeding period is scarce. In our study, 22.5% of women were LTFU by 24 months' postpartum, however, an additional 12.9% women had less than 80% visit coverage. Irregular PMTCT visits may lead to late drug refill and inadequate infant care, elevating risk of development of drug resistance in both mothers and infants[163]. Adding the frequency and regularity of visits into the concept of retention may enhance PMTCT program efficacy and evaluations, and HIV drug resistance surveillance should be planned alongside implementation, enabling a distinction to be made between women who attend all, or some care and treatment, and those who are late for scheduled visits and are less engaged in care.

Our study demonstrates variability of retention estimates and cofactors. As clinics seek to monitor retention, standardized definitions of late visits, LTFU and visit coverage will be important. Data sources may need to be combined or triangulated, with counseling registers, general MCH visits and pharmacy records. As women transfer to other clinics over the course of pregnancy and postpartum, obtaining data from multiple sites may necessary. Ideally, national unique identifiers and linked data systems could optimize assessment of transfer. Currently, capturing timeliness and regularity of women's longitudinal visit data remains a complex task. Furthermore, as retention estimates are often used for the modeling of vertical transmission rates of HIV, a consensus on definitions is urgently needed. Lack of precision could lead to unclear interpretation of program achievements.

We also found that different non-retention measures yielded distinct cofactors of non-retention. Young maternal age and HIV non-disclosure were associated with all non-retention measures. There has been consistent evidence showing younger WLWH are at higher risk of non-retention[66,70,71,76,77,151,164,165], late ART initiation, low service uptake and poor adherence[18,19,157,166,167]. Non-disclosure has also emerged as a consistent barrier to retention in PMTCT programs in sub-Sahara Africa[151,168,169]. We found that HIV diagnosis during pregnancy, late ART initiation and unsuppressed viral loads were associated with all three measures of non-retention, consistent with results from other studies[34,66,67,170,171]. Addressing disclosure, tailoring services for younger clients, those who are unsuppressed or starting ART late could improve all retention measures. Other cofactors (partner not HIV tested, low IMB score) were associated specifically with late visits, perhaps reflecting episodic lack of support or self-efficacy to navigate on-time clinic attendance. Marital support and need for food support were associated with lower likelihood of LTFU. Episodic lack of finances or support may delay ability to attend visits on-time, while other factors lead to disengagement and ultimately LTFU. Late visits reflect a less

consequential outcome than LTFU; understanding what drives both late visits and LTFU is useful for programmatic improvements.

This study had several limitations. The RCT was conducted among six MCH clinics in two regions in Kenya, and among women who had daily access to a mobile phone, which may limit generalizability. We obtained clinic attendance data from routine medical records which can have data quality issues, and 11 (1.3%) women had no available medical records. EMR data were only available at two Nairobi sites, and although we adjusted for site in all models, there may be residual confounding. However, the combination of paper records at multiple sites and EMR data enabled us to monitor clinical visits for each participant, which added precision to our LTFU estimate. A significant strength of this study was direct comparisons of different retention measures using data from the same cohort. In addition, we identified late visits as a potential indicator of future LTFU in PMTCT programs. We also identified distinct risk factors associated with different retention measures.

Conclusion

This study provides a comprehensive analysis of non-retention rates in PMTCT programs using three different measures, including late visits, 3-month visit coverage and LTFU. We found late visits are an important sentinel indicator of subsequent LTFU. Adding visit timeliness into assessments may enhance PMTCT program evaluations. We also found that distinct risk factors may be associated with different aspects of retention. In summary, standardizing longitudinal definitions of visit timeliness, coverage and LTFU in PTMCT programs will be useful in comparing studies and programmatic interventions to optimize retention in long-term PMTCT programs.

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Authors' contributions

GJS, JAU, ALD and JK developed and obtained funding for the RCT. JK, DM, and KR led the implementation of RCT. WJ conducted data analysis for this study with input from BAR, KR and GJS. GJS and WJ conceptualized the idea for the manuscript. WJ developed the manuscript with input from GJS. All authors have reviewed and approved the final manuscript.

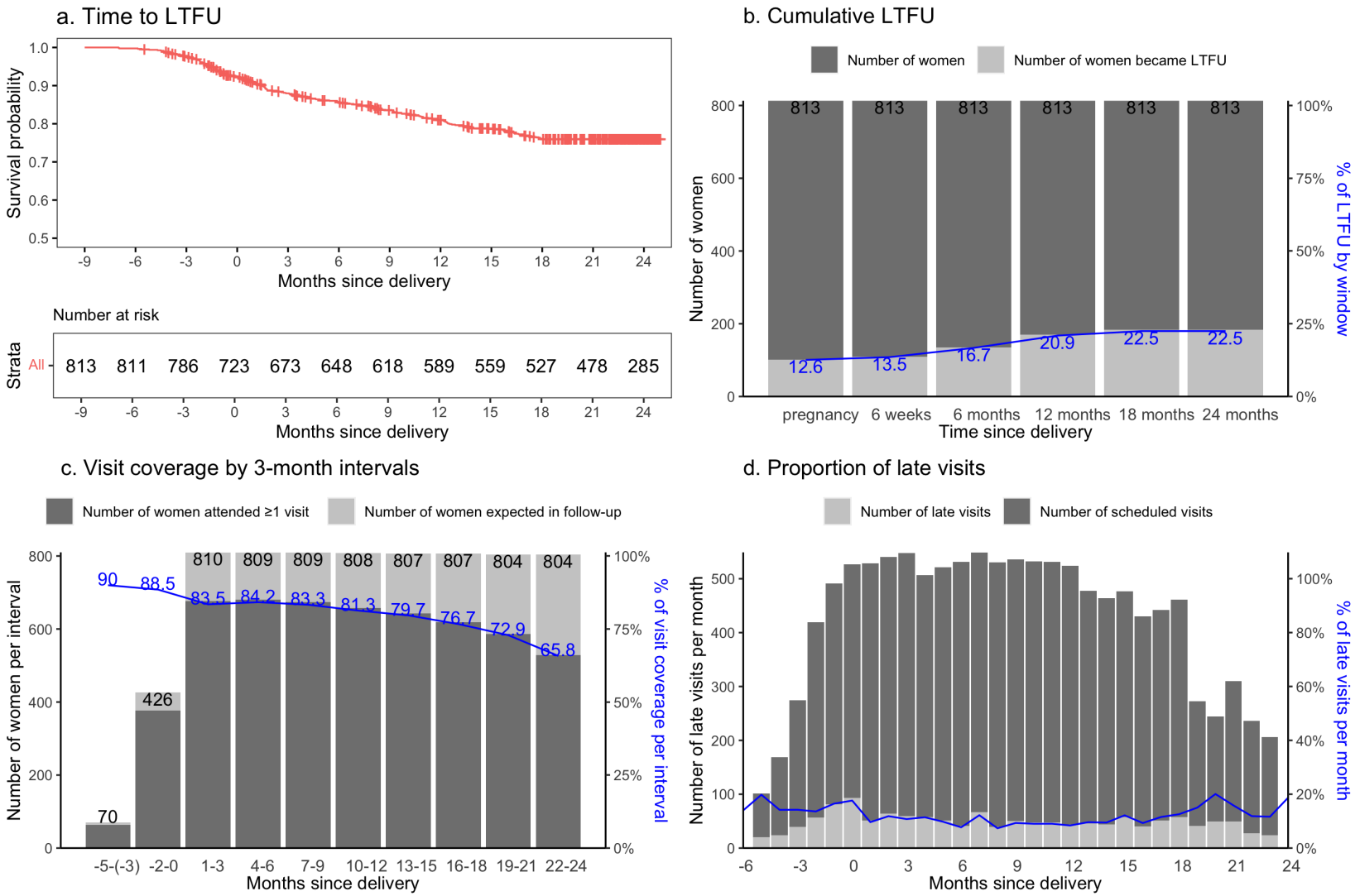
Tables and Figures

Table 3.1. Measures of non-retention

a. LTFU[a]					
Postpartum period	Number of women	Event / person-year		Incidence rate / 100 py	Cumulative incidence (n/N)[a]
By delivery	813	101 / 374.6		27.0	12.6% (101/813)
By 6 weeks	813	109 / 452.5		24.1	13.5% (109/813)
By 6 months	813	135 / 699.7		19.3	16.7% (135/813)
By 12 months	813	170 / 996.7		17.0	20.9% (170/813)
By 18 months	813	183 / 1,231.7		14.9	22.5% (183/813)
By 24 months	813	183 / 1,349.0		13.6	22.5% (183/813)
b. Visit coverage[b]					
Postpartum period	Number of women[b]	Among all women (n/N)	Per woman [median (IQR)]		
		Proportion of intervals with ≥1 visit	Number of expected intervals	Number of intervals with ≥1 visit	Proportion of intervals with ≥1 visit
By 24 months	812	74.9% (5,822/7,771)	10 (9-10)	8 (6-9)	88.9% (66.7-90.9%)
c. Late visits[c]					
Postpartum period	Number of women[†]	Among all women (n/N)	Per woman [median (IQR)]		
		Proportion of late visits	Number of scheduled visits	Number of late visits	Proportion of late visits
By delivery	569	14.4% (190/1,320)	2 (1-3)	0 (0-1)	0% (0-33.3%)
By 6 weeks	711	15.9% (324/2,041)	3 (1-4)	0 (0-1)	0% (0-40.0%)
By 6 months	783	13.0% (589/4,518)	6 (3-8)	1 (0-1)	12.5% (0-33.3%)
By 12 months	791	11.5% (891/7,776)	11 (6-13)	1 (0-2)	10.0% (0-25.0%)
By 18 months	793	11.0% (1158/10,535)	14 (9-18)	1 (1-2)	10.5% (4.5%-23.1%)
By 24 months	794	11.5% (1431/12,437)	16 (10-22)	2 (1-3)	11.1% (4.3%-23.5%)

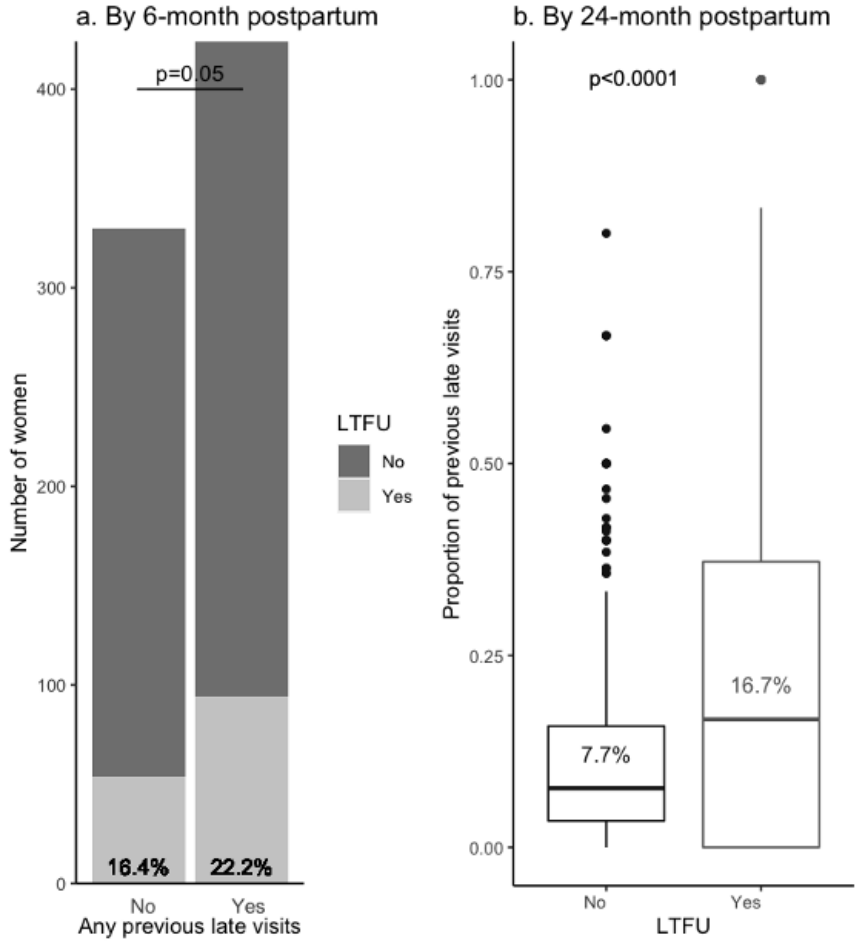
a. LTFU was defined as no clinic visit for at least 6 months since the last clinic visit and not known to have died or transferred; b. visit coverage was defined for each participant as a proportion of 3-month intervals with at least one clinic visit over the entire follow-up period from pregnancy to 2 years postpartum; excluding one woman who had a visit beyond 24-month postpartum; c. late visit was defined for each participant as a scheduled visit that was not attended within 2 weeks of the expected date of clinic visit.

Figure 3.1. Retention over the follow-up period using the 3 measures (late visits, visit coverage, LTFU)



a. time-to-LTFU (no visit for ≥6 months since last visit) described by Kaplan-Meier survival curves; b. cumulative incidence of LTFU calculated as the proportion of women ever LTFU among women in follow-up; c. visit coverage calculated as the proportion of 3-month intervals with a visit; d. Late visit defined as no visit within 2 weeks of scheduled date.

Figure 3.2. Comparison of any previous late visits and LTFU at 24-month postpartum*



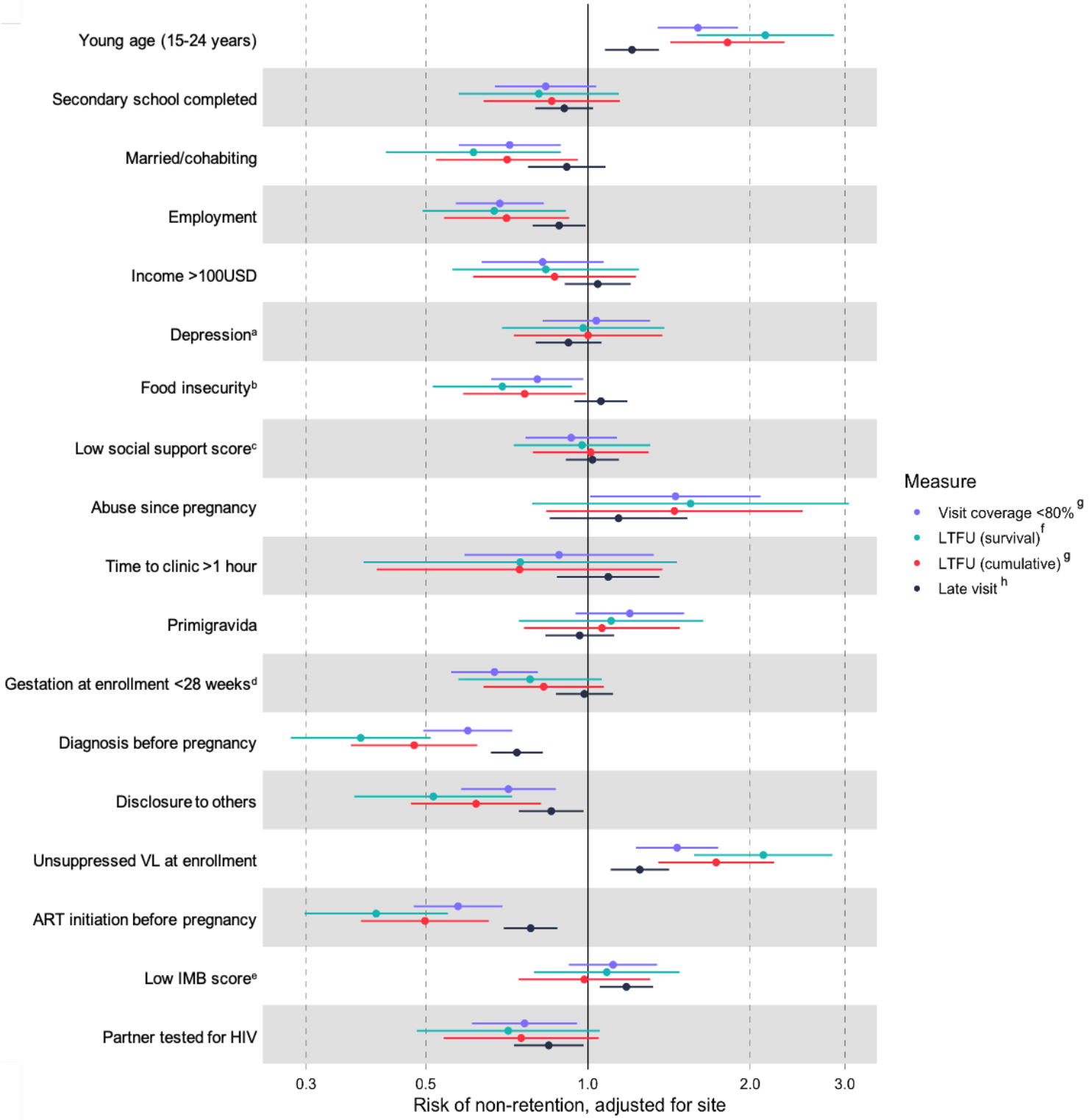
*Among 759 women with at least two visits during follow-up; a. risk of LTFU compared by chi-square test; b. proportion of last visits compared by two-sample t-test

Table 3.2. Hazard ratio (HR) and prevalence ratio (PR) of loss-to follow-up (LTFU), and PRs of visit coverage <80% and late visits

	LTFU	Cumulative LTFU	Visit coverage<80%	Late visit
	aHR[f] (95%CI); p-value	aPR[g] (95%CI); p-value	aPR[g] (95%CI); p-value	aPR[h] (95%CI); p-value
Young age (15-24 years)	**2.13 (1.59-2.86); <0.001**	**1.82 (1.42-2.32); <0.001**	**1.60 (1.35-1.90); <0.001**	**1.21 (1.08-1.36); 0.001**
Secondary school completed	0.81 (0.58-1.14); 0.228	0.86 (0.64-1.15); 0.298	0.83 (0.67-1.04); 0.102	0.90 (0.8-1.02); 0.109
Married/cohabiting	**0.61 (0.42-0.89); 0.01**	**0.71 (0.52-0.96); 0.026**	**0.72 (0.58-0.89); 0.003**	0.91 (0.77-1.08); 0.283
Employment	**0.67 (0.49-0.91); 0.01**	**0.71 (0.54-0.92); 0.011**	**0.69 (0.57-0.83); <0.001**	**0.88 (0.79-0.99); 0.032**
Income>100USD	0.84 (0.56-1.24); 0.376	0.87 (0.61-1.23); 0.422	0.82 (0.63-1.07); 0.146	1.04 (0.91-1.20); 0.56
Depression[a]	0.98 (0.69-1.39); 0.908	1.00 (0.73-1.37); 0.998	1.04 (0.82-1.30); 0.763	0.92 (0.8-1.06); 0.245
Moderate/severe food insecurity[b]	**0.69 (0.51-0.93); 0.016**	**0.76 (0.59-0.99); 0.043**	**0.81 (0.66-0.98); 0.031**	1.06 (0.94-1.18); 0.339
Low social support score (<median)[c]	0.97 (0.73-1.31); 0.863	1.01 (0.79-1.30); 0.926	0.93 (0.77-1.13); 0.471	1.02 (0.91-1.14); 0.74
Abuse since pregnancy	1.55 (0.79-3.05); 0.204	1.45 (0.84-2.50); 0.186	**1.45 (1.01-2.09); 0.044**	1.14 (0.85-1.53); 0.384
Time to clinic >1 hour	0.75 (0.38-1.46); 0.397	0.75 (0.41-1.37); 0.348	0.88 (0.59-1.32); 0.549	1.09 (0.88-1.36); 0.438
Primigravida	1.10 (0.74-1.64); 0.622	1.06 (0.76-1.48); 0.725	1.20 (0.95-1.51); 0.131	0.97 (0.83-1.12); 0.637
Gestation at enrollment <28 weeks[d]	0.78 (0.57-1.06); 0.113	0.83 (0.64-1.07); 0.149	**0.67 (0.56-0.81); <0.001**	0.98 (0.87-1.11); 0.801
Diagnosis before pregnancy	**0.38 (0.28-0.51); <0.001**	**0.48 (0.36-0.62); <0.001**	**0.60 (0.49-0.72); <0.001**	**0.74 (0.66-0.83); <0.001**
Disclosure to others	**0.52 (0.37-0.72); <0.001**	**0.62 (0.47-0.82); 0.001**	**0.71 (0.58-0.87); 0.001**	**0.85 (0.74-0.98); 0.025**
Unsuppressed VL at enrollment	**2.12 (1.57-2.85); <0.001**	**1.73 (1.35-2.21); <0.001**	**1.46 (1.23-1.75); <0.001**	**1.25 (1.10-1.41); <0.001**
ART initiation before pregnancy	**0.40 (0.30-0.55); <0.001**	**0.50 (0.38-0.65); <0.001**	**0.57 (0.47-0.69); <0.001**	**0.78 (0.70-0.88); <0.001**
Low IMB score[e]	1.08 (0.79-1.48); 0.611	0.98 (0.74-1.30); 0.913	1.11 (0.92-1.35); 0.266	**1.18 (1.05-1.32); 0.005**
Partner tested for HIV	0.71 (0.48-1.05); 0.087	0.75 (0.54-1.05); 0.091	**0.76 (0.61-0.96); 0.018**	**0.85 (0.73-0.98); 0.027**

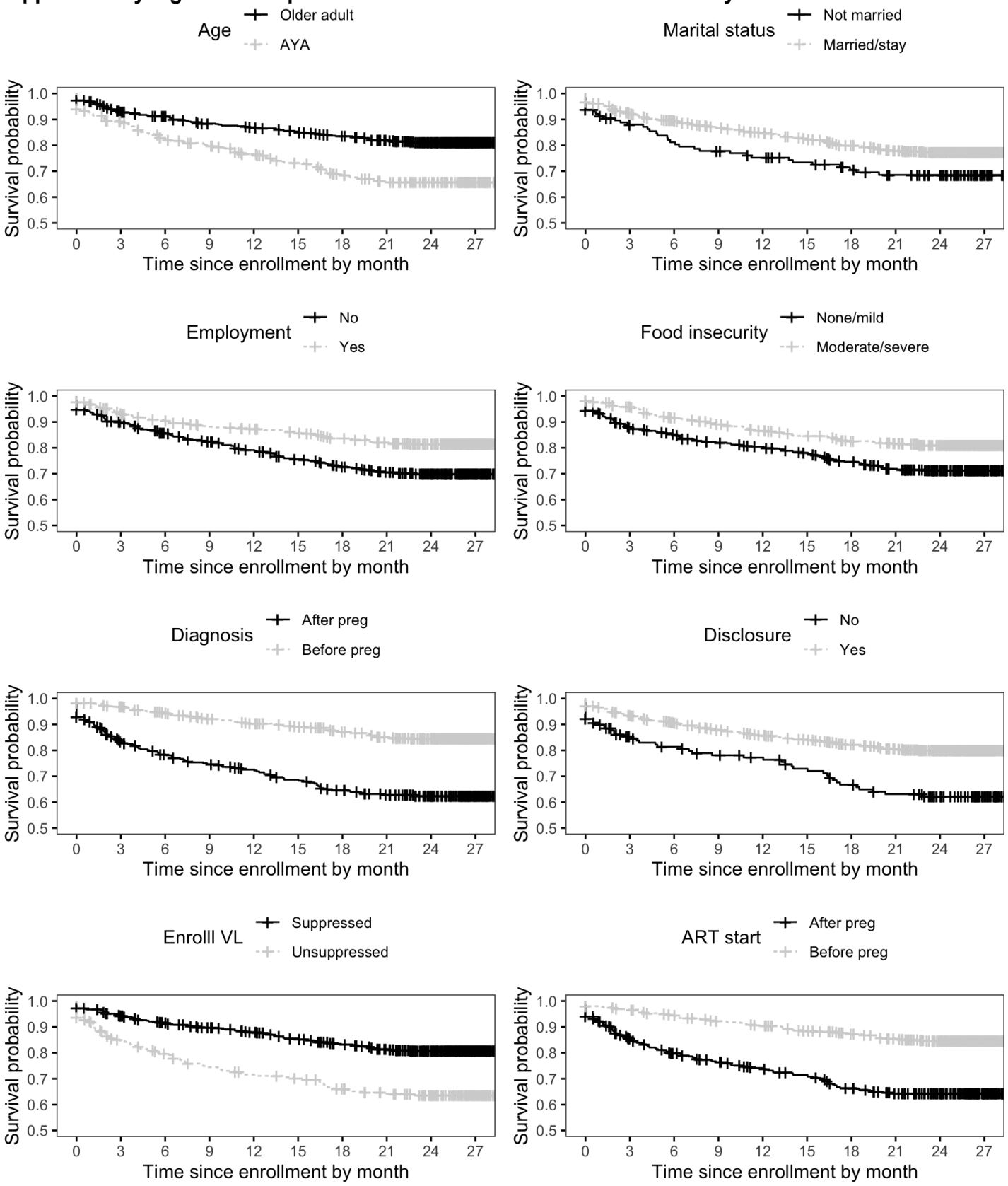
[a] evaluated by Patient Health Questionnaire 9 (PHQ9), a score >5 indicating at least moderate depressive symptoms; [b] evaluated by Household Food Insecurity Access Scale (HFIAS); [c] evaluated by Medical Outcomes Study (MOS) survey; [d] estimated by self-reported date of last menstruation period; [e] Information-Motivation-Behavioral (IMB) score evaluated by 15 items from LifeWindows ART adherence questionnaire; [f] HR estimated by cox proportional hazards regression calculating time-at-risk since enrollment and adjusting for site; [g] PR estimated by Log-binomial regression adjusting for site; [h] PR estimated by GEE regression adjusting for site

Figure 3.3. Forest plot of cofactors for non-retention, by non-retention measure

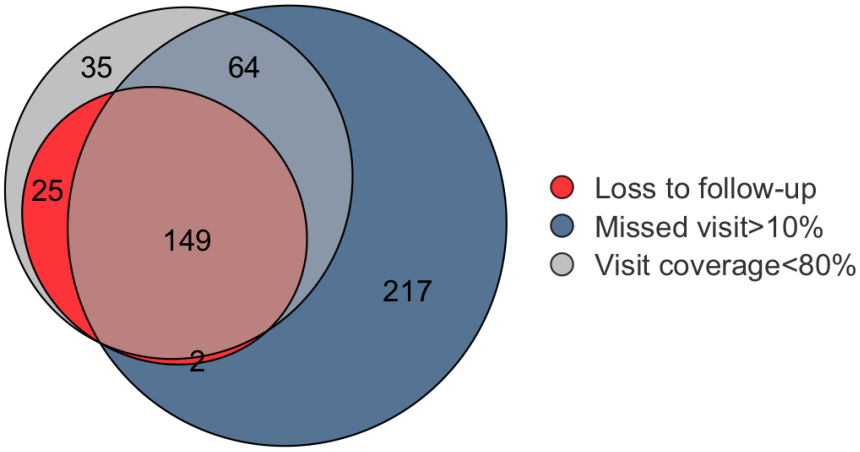


[a] evaluated by Patient Health Questionnaire 9 (PHQ9), a score >5 indicating at least moderate depressive symptoms; [b] evaluated by Household Food Insecurity Access Scale (HFIAS); [c] evaluated by Medical Outcomes Study (MOS) survey; [d] estimated by self-reported date of last menstruation period; [e] Information-Motivation-Behavioral (IMB) score evaluated by 15 items from LifeWindows ART adherence questionnaire; [f] HR estimated by cox proportional hazards regression calculating time-at-risk since enrollment and adjusting for site; [g] PR estimated by Log-binomial regression adjusting for site; [h] PR estimated by GEE regression adjusting for site.

Supplementary Figure 3.1. Kaplan-Meier survival curves of time to LTFU by characteristics



Supplementary Figure 3.2. Venn diagram of retention measurements



*Among 793 women with data available for all three measurements

		No LTFU (N=630)	Ever LTFU (N=183)	
Proportion of missed visit	≤10%	336 (54.4%)	25 (14.2%)	< 0.001
	>10%	282 (45.6%)	151 (85.8%)	
Visit coverage	≤80%	521 (82.8%)	3 (1.6%)	< 0.001
	>80%	108 (17.2%)	180 (98.4%)	

Chapter 4. HIV viral load patterns and risk factors among women in prevention of mother-to-child transmission (PMTCT) programs to inform differentiated service delivery (DSD)

Submitted for peer-reviewed publication at the time of dissertation completion

HIV viral load patterns and risk factors among women in prevention of mother-to-child transmission (PMTCT) programs to inform differentiated service delivery (DSD)

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Competing interests
We report no real or perceived vested interests related to this article that could be construed as a conflict of interest.

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Abstract

Background: Differentiated service delivery (DSD) approaches decrease frequency of clinic visits for individuals who are stable on antiretroviral therapy (ART). It is unclear how to optimize DSD models for postpartum women living with HIV (PWLH). We evaluated longitudinal HIV viral load (VL) and cofactors, and modelled DSD eligibility with virologic failure (VF) among PWLH in PMTCT programs.

Methods: This analysis used programmatic data from participants in the Mobile WAChX trial (NCT02400671). Women were assessed for DSD-eligibility using the WHO criteria among general people living with HIV (receiving ART for ≥6 months and having at least one suppressed VL [<1,000 copies/mL] within the past 6 months). Longitudinal VL patterns were summarized using group-based trajectory modelling (GBTM). VF was defined as having a subsequent VL ≥1,000 copies/mL after being assessed as DSD-eligible. Predictors of VF were determined using log-binomial models among DSD-eligible PWLH.

Results: Among 761 women with 3,359 VL results (median 5 VL per woman), a three-trajectory model optimally summarized longitudinal VL, with most (80.8%) women having sustained low probability of unsuppressed VL. Among women who met DSD criteria at 6 months postpartum, most (83.8%) maintained viral suppression until 24 months. Residence in Western Kenya, depression, reported interpersonal abuse, unintended pregnancy, nevirapine-based ART, low-level viremia (VL 200-1,000 copies/mL), and drug resistance were associated with VF among DSD-eligible PWLH.

Conclusions: Most postpartum women maintained viral suppression from early postpartum to 24 months and may be suitable for DSD referral. Women with depression, drug resistance and detectable VL need enhanced services.

Keywords: Women, PMTCT, VL suppression, differentiated service delivery, Africa, longitudinal analysis

Background

Differentiated service delivery (DSD) approaches adapt the frequency of clinic-based visits for individuals who are clinically stable on antiretroviral therapy (ART) [39]. This patient-centered approach enables healthcare to focus on individuals in need of more intensive clinical care and benefits patients, healthcare providers and health systems[40,41]. In 2017, Kenya implemented DSD for individuals on ART for at least 6 months with suppressed HIV viral load (VL <1,000 copies/mL)[44]. DSD allows for 6-monthly clinic visits and annual VL testing. Current Kenyan DSD guidelines recommend that pregnant and breastfeeding women have specific visits aligned with prevention of mother-to-child HIV transmission (PMTCT) programs[15–17] and include VL testing 6-monthly until cessation of breastfeeding[172], therefore as unstable and do not qualify for DSD[15–17].

The World Health Organization (WHO) has recommended that the DSD definition of being stable apply to all populations[43]. However, it is unclear how to implement DSD models for mothers with HIV, given their need for routine antenatal and postnatal care visits and HIV-exposed infant follow-up visits. In addition, retention in care and adherence have been challenging for PMTCT programs[66,67,76,148,149]. Studies in sub-Saharan Africa have reported facility-level reasons for women not engaging with clinic-based care, including lack of time and difficulty with transport to clinic[70], inadequate care[67,165,170], high staff turnover and long waiting time[69,173]. Women stable with HIV in late postpartum may benefit from DSD approaches through multi-month ART dispensing, community-based ART delivery, and longer intervals between HIV clinical visits. A randomized clinical trial (RCT) in South Africa reported improved viral suppression up to 24 months among women with HIV referred to community-based adherence clubs at their first postnatal visits compared to women who received standard of care[174]. DSD approaches require an understanding of long-term viral suppression trajectories and individuals who may be at risk for poorer outcomes with DSD. To date, there is limited evidence to inform tailored DSD models for women in PMTCT programs. In this study, we aimed to describe longitudinal HIV VL patterns and cofactors among

PWLH in PMTCT programs in Kenya and assess the frequency potentially eligible to receive DSD and subsequent risk of virologic failure (VF).

Methods

Study design and population

This nested observational study used data from a completed 3-arm RCT (Mobile WAChX, ClinicalTrial.gov number NCT02400671[34,153]). The parent study assessed the short messaging service (SMS) among women attending PMTCT programs followed-up through 2 years postpartum (study period: November 22, 2015 to May 4, 2017)[34]. Briefly, the trial enrolled pregnant women with HIV from six maternal-child health (MCH) clinics in Nairobi and Western Kenya who were aged ≥14 years and had daily access to a mobile phone. The intervention did not have an impact on maternal VL or retention as reported previously[34]. The RCT was approved by the Kenyatta National Hospital/University of Nairobi Ethical Review Committee and UW Institutional Review Board.

Data Collection

At enrollment, a standardized survey was administered to collect data on demographics, depression (using Patient Health Questionnaire 9 [PHQ-9][93]), abuse history (using Abuse Assessment Screen [AAS][94]), disclosure of HIV status, and ART knowledge based on the Information–Motivation and Behavioral Skills (IMB) model adapted from 15 items from the LifeWindows ART adherence questionnaire[96]. Pre-pregnancy ART initiation was determined based on last menstrual period date and ART starting date. Data on ART use history was abstracted from the mother's MCH booklet. HIV VL testing results were obtained from the routine VL monitoring system of the Kenya National AIDS & STI Control Program (NASCOP). If programmatic VL results were not available, VL testing was conducted by the study on maternal plasma samples. ART resistance was assessed using an oligonucleotide ligation assay (OLA) on

maternal plasma samples and was defined as detection of any resistance mutations by OLA at an abundance of ≥10%[34]. Programmatic data of clinic visits was obtained from clinic paper records and electronic medical records[154]. Pharmacy refill data was abstracted from records of ART doses administered during HIV care visits[34].

Study outcomes

Being DSD-eligible was defined according to WHO criteria as receiving ART for at least 6 months, with at least one suppressed VL (<1,000 copies/mL) within the past 6 months. Low-level detection (LLD) was defined as having HIV VL <1,000 copies/mL but ≥200 copies/mL. VF was defined as having HIV VL ≥1,000 copies/mL after being assessed as DSD-eligible. VL data in this analysis were restricted to data from ≥4 months since ART initiation, in order to include only data after it was biologically plausible for VL to be suppressed by ART; VF results within 30 days of a previous VF were excluded. ART adherence was calculated as the proportion of days between visits that were covered by ART doses dispensed based on self-report and was classified as adherent (100%) vs. non-adherent (<100%)[34]. Any missed daily pill in the past refill period was defined as non-adherence. Any appointment not made within 14 days of the scheduled visit was defined as a missed visit[175].

Statistical analysis

Chi-square tests were used to measure the difference in the distribution of characteristics for outcomes. Logistic group-based trajectory modeling (GBTM) was performed to identify discrete trajectories of HIV VL patterns. GBTM is an application of finite mixture modeling that assumes the population is composed of distinct groups, each with a different underlying trajectory and every individual in the group approximately follows the same patterns of behavior of outcome over time[176]. GBTM has been used to evaluate virologic outcomes in high-income countries[177–183]. One study in Zambia reported six engagement trajectories in medication possession ratio and

retention in care among new ART starters[184], but overall evidence on viral trajectories in resource-limited settings is limited due to lack of sufficient longitudinal VL data.

In this study, the number of trajectory groups was hypothesized *a priori* to be between 1 and 5. The number of trajectory groups and the appropriate function of trajectory polynomials of time window were tested based on observed plots and the Bayesian information criterion (BIC); the model with the lowest BIC value representing the statistically optimal number of latent groups[185]. Since not all women had equivalent observation times and VL testing results, posterior probabilities were based on comparisons between trajectories and observed data in study follow-up. Women were then assigned to the trajectory group with which they had the highest probability of membership based on their estimated posterior probabilities.

The proportion of women eligible for DSD was evaluated at different postpartum timepoints, and outcomes were assessed among women who had at least one subsequent VL result. Log-binomial regression with robust standard errors was used to identify predictors of VF by 24 months postpartum among women who were DSD-eligible estimated at 6 months. All analyses were conducted using RStudio Version 1.2.5042 (RStudio, Inc).

Results

Overall, 761 women from the Mobile WAChX trial were included in this study. At enrollment, median age was 27 years (interquartile range [IQR] 23-31) and median gestational age was 24.2 weeks (IQR 18.1-29.1). Sixty percent (456/761) of women started ART before the current pregnancy, and 82.6% (629/761) reported no health problems at pregnancy. By 24 months postpartum, a total of 3,359 VL testing results were available for analysis (Figure 4.1), and women had a median of 5 VL testing results (IQR 3-6) during study follow-up, with the median duration between two tests of 5.3 months (IQR 3.6-6.9). Among 761 women, 502 (66.0%) had VL results

at delivery, and the cumulative proportion with VL available was 87.8% and 96.5% by 6 weeks and 6 months postpartum, respectively (Figure 4.1). By 6 months postpartum, women had a median of 3 VLs (IQR 2-4), and 78.1% of women had at least 2 VLs (Figure 4.1). The cumulative proportion of women ever having VL ≥1,000 copies/mL by 24 months postpartum was 26.4% (201/761). Among 698 women with at least two VLs available, 614 had viral suppression at their first VL after enrollment, of whom 519 (84.5%) maintained viral suppression (<1,000 copies/mL). Among 84 women whose first VL after enrollment was unsuppressed, 8 (9.5%) had persistent non-suppression and 33 (39.3%) became virally suppressed and maintained suppression.

A three-trajectory model was selected to present longitudinal patterns of VL: (1) “sustained low probability of viral non-suppression” (80.8% of participants); (2) “high probability of delayed viral suppression” (5.9% of participants); and (3) “sustained high probability of viral non-suppression” (13.3% of participants) (Figure 4.2). The “high probability of delayed viral suppression” and “sustained high probability of viral non-suppression” groups were best represented by cubic trajectories, while the “sustained low probability of viral non-suppression” group was best represented by a non-time varying constant function. Most women (86.4%) were likely to achieve viral suppression by early postpartum and remain virally suppressed afterwards.

During pregnancy, 507 women were already on ART for at least 6 months, and 84.6% (429/507) women met WHO eligibility criteria to receive DSD (on ART ≥6 months and at least 1 suppressed in the past 6 months) (Figure 4.3). At 6 weeks and 3 months postpartum, the proportion eligible for DSD increased, mainly because women had more recent VL testing data available. Among women who met the DSD criteria assessed at early postpartum periods, most women maintained viral suppression until the 2-year postpartum endpoint (Figure 4.3). Among women who did not maintain suppression, the median time from viral suppression to the date of VF was 9.1 months (IQR 4.6-15.2). At late postpartum periods (18 months and 24 months), fewer women had

subsequent VL testing results available for assessing the maintenance status, but among those who had subsequent data, the proportion of those who maintained viral suppression increased (Figure 4.3). Starting ART pre-conception or in pregnancy did not significantly influence the proportion who developed VF (data not shown). In a sensitivity analysis among 371 women with VL data available in pregnancy and at least 1 VL available after 18 months postpartum, the proportions who developed VF remained similar (data not shown).

Among 580 women eligible for DSD when evaluated at 6 months postpartum, residence in Western Kenya was associated with higher risks of VF (prevalence ratio [PR] 2.48, 95% confidence interval [95%CI] 1.42-4.35; p=0.002) (Table 4.1). In site-adjusted regression models, women with at least moderate depressive symptoms (PHQ-9 score ≥5) (adjusted prevalence ratio [aPR] 2.19, 95%CI 1.36-3.54; p=0.001) and those with reported abuse in the past year (aPR 1.96, 95%CI 1.08-3.56; p=0.027) had increased risk of VF (Table 4.1). Women reporting their last pregnancy was intended had a lower risk of VF (aPR 0.63, 95%CI 0.41-0.96; p=0.030). Women who received nevirapine (NVP) as first-line regimen had higher risk of VF than women who received efavirenz (EFV) (aPR 2.03, 95%CI 1.25-3.31; p=0.005) as did women enrolled with a drug resistance mutation (aPR 8.73, 95%CI 4.30-17.7; p<0.001), and women who had LLD within the past 6 months (aPR 2.16, 95%CI 1.36-3.44; p=0.001) (Table 4.1). Women's age, education level, marital status, IMB score, self-reported ART adherence and ART initiation time were not associated with later VF.

In a multivariate model adjusting for variables with univariate p-value <0.1, residence in Western Kenya, depression, reported abuse and drug resistance remained significantly associated with VF among women who met DSD criteria (Table 4.1). In secondary analyses among 432 women eligible for DSD at 6 weeks postpartum, all associations remained the same, while among 591

women eligible for DSD at 12 months postpartum, associations with pregnancy intention and NVP-based ART use were no longer significant (data not shown).

Overall, 733 (96.3%) women had pharmacy refill data available, with a median of 18 refill cycles (IQR 12-22) per woman. Most (98.5%) women ever missed at least one dose within a refill cycle over time. When evaluating the effect of ART adherence on subsequent VF among DSD-eligible women, women who had a history of non-adherence by 6 weeks postpartum (missed at least one dose in the past 6 months) had a higher risk of VF (18.7% vs. 11.9%, p=0.029). At 6 months and 12 months, the frequency of VF among women who did not adhere were higher than among women who adhered to ART, but the differences were not significant (Table 4.2). Overall, 743 (97.6%) women had clinic visit data available from MCH records, with a median of 17 scheduled visits (IQR 12-22) per woman. Most (83.4%) women had one missed visit (late for >14 days for at least 1 scheduled visit) at some timepoint. Among DSD-eligible women, missed visits were not associated with VF, regardless of time of summarizing missed visits (Table 4.2).

Discussion

In this study, we evaluated longitudinal VL patterns among women living with HIV receiving PMTCT services in Kenya from pregnancy to 24 months postpartum. We found that most women met standard DSD eligibility criteria by 6 months postpartum (being on ART ≥6 months and at least one viral suppression within the past 6 months), and among women who had follow-up VL data, we found 84.5% of women were persistently suppressed; of women whose first VL since enrolment was unsuppressed, 39.3% later suppressed and maintained suppression until the end of follow-up. The frequency of suppression we observed was similar to a cohort study in South Africa, which reported that 16.6% of pregnant women with HIV ever had VL ≥1,000 copies/mL by 24 months postpartum[186]. Studies in Ethiopia and Malawi with shorter follow-up periods have also

reported similar frequencies of viral non-suppression (10.3% in pregnancy and 12.1% at 6 months postpartum, respectively)[45,187].

Prior clinical trials among individuals in the general population stable on ART in sub-Saharan Africa have shown that those receiving community-based ART services had comparable VL or significantly lower risks of unsuppressed VL than those receiving clinic-based standard of care[188–191]. While many countries have endorsed DSD models in national guidelines[192], postpartum women regardless of VL level are often not considered as stable[193,194] and excluded from DSD models, even though the global community seeks to find ways to offer DSD to all people stable on ART[43]. Breastfeeding period can extend two to three years in resource-limited settings, and fertility rates are such that women can spend much of their adult life pregnant or breastfeeding. Thus, many mother-infant pairs will have prolonged time of restricted access to DSD models. There is a need to align the criteria determining individuals as “stable” with what has already been established by WHO for non-pregnant adults[43] while still recognizing the continued need for routine antenatal and postnatal care.

The three distinct group based VL trajectory patterns identified using GBTM yielded comparable patterns to those described in a study of women living with HIV in Canada[177]. Achieving and maintaining viral suppression is the key to minimize vertical HIV transmission and to optimize women's health outcomes[195]. Our study provided supportive evidence for inclusion of PWLH in DSD models. We focused on those who were clinically stable during early postpartum periods for DSD in later postpartum, reasoning that women and children may need more intensive services than DSD in the peripartum period.

We found depression and reported abuse in the last year significantly predicted subsequent VF among women eligible for DSD at 6 months postpartum. These results suggest the importance of

emotional stressors as a determinant of VF. In our study, 23% of women experienced at least mild depressive symptoms, similar to rates of antenatal depression among African women with HIV in a systematic review[103]. Depression has been reported as risk factors of poor adherence[196–198] and high HIV VL[197,199]. While our study did not find significant effects of self-reported ART adherence and retention on VF, it is likely that depression influenced ART adherence and self-reported adherence overestimates actual adherence[200]. Given the high prevalence of depression, and association with VF, standard depression screening during pregnancy and postpartum and referral for mental health services may be required to ensure sustained viral suppression.

We found that women with LLD (HIV VL ≥200 copies/mL) had significantly higher risks of subsequent VF even when they met DSD eligibility criteria with suppressed VL <1,000 copies/mL. There have been concerns regarding non-sustained viral suppression during a long follow-up throughout postpartum[195]. A study in Malawi reported increased risk of non-suppression at 24 months among women with prior detectable VL (40-1,000 copies/mL) at 1-6 months postpartum[201], and non-durable suppression has been linked to increased risks of vertical transmission in the same cohort[202]. A randomized clinical trial in Uganda and Kenya among ART-experienced patients with viremia reported that a DSD intervention with streamlined care was associated with higher rates of 3-year viral suppression (67% vs. 47%)[203]. Since risks of vertical transmission increase with maternal detectable VL[202,204], maintaining undetectable VL is essential for elimination of vertical transmission[205]. On a structural level, it is important to anticipate and avoid potentially detrimental impacts of less frequent DSD visits on the uptake of standard MCH services and timely HIV VL testing, as well as coverage of early infant diagnosis and vaccination. Models for ART-stable PWLH who have LLD VL need to include components to track closely until a final suppressed or undetected status can be established.

We found HIV drug resistance resulted in >8-fold increased risk for VF, and women taking an NVP-based regimen had a higher risk of VF than women taking an EFV-based regimen. In this cohort, women received fixed-dose ART in line with contemporaneous WHO guidelines. Currently, dolutegravir is the first-line regimen of choice[206] and has a high barrier to resistance[207]. Monitoring women for drug resistance in PMTCT programs may continue to be useful to identify those who need regimen switches and who may not be good candidates for DSD. We did not find a difference in the risks of VF between women who started ART pre-conception versus those who started ART in pregnancy, perhaps due to generally high levels of ART coverage in this cohort.

Our study had several limitations. First, the WHO criteria for DSD also includes evaluation of current illness[43]. In this study, women were asked about health conditions; however, we had limited systematic data on other illnesses. We relied on VL testing data, which may overestimate the proportion of those who were classified as stable in the cohort, but in a supplementary analysis excluding women who indicated any health problems at baseline, the effect of depression and drug resistance on VF persisted. Secondly, there have been variations in VL cutoff to define VF in PMTCT programs: a cluster trial with a 3-year follow-up in 32 communities in Kenya and Uganda used a threshold of 500 copies/mL[208], and 400 copies/mL has also been used in other studies[209–212]. We found a similar proportion of women who would be classified as DSD-eligible using lower cutoffs (88.4% with <500 copies/mL; 87.7% with <400 copies/mL; 86.2% with <200 copies/mL; 80.0% with <50 copies/mL), but fewer (55.8%) women with the lowest detection level at <20 copies/mL. Thirdly, our models did not accommodate time-varying socioeconomic factors, and the explanatory variables were measured at baseline only. Our definitions of pill count-based adherence and missed visit-based retention may not reflect the true temporal associations between poor engagement and VF. Finally, the primary study pre-dated DSD guidelines, so the study could not assess the impact of DSD on outcomes. Qualitative studies have reported that women in PMTCT programs may be reluctant to use fast-track queues, even when services are

in place[213,214], which suggests that women may prefer more clinical interactions, particularly if postpartum with maternal or infant health concerns. It is important to understand women's preference on DSD, as well as clinical facilitators and barriers affecting DSD model implementation.

Conclusion

This study has important implications for understanding DSD eligibility among women in PMTCT programs. Most women had sustained low probability of VF, and among women who met the general DSD-eligible criteria, most maintained viral suppression until the 24 months postpartum. Integration of patient-centered DSD strategies, choice in which DSD model is both clinically indicated but also preferred by women, for those stable on ART may be feasible and beneficial within the framework of perinatal care. Women with depression or reported abuse need enhanced mental health support to prevent VF. Drug resistance testing may be useful to exclude women from DSD. Lower VL threshold may exclude many women from DSD. Implementation science studies focused on DSD models in MCH settings are needed for postpartum women stable on ART.

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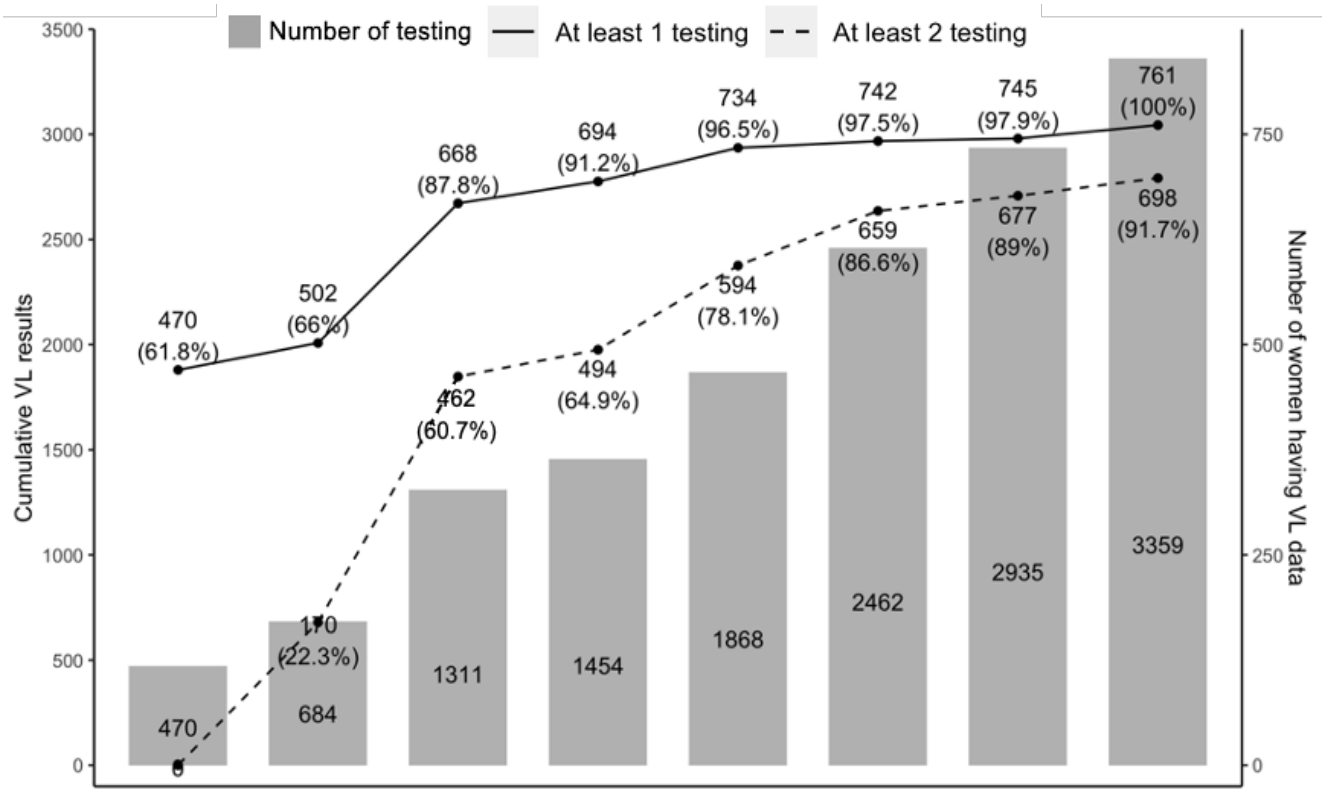
Authors' contributions

GJS, JAU, ALD and JK developed and obtained funding for the RCT. JK, DM, and KR led the implementation of RCT. WJ conducted data analysis for this study with input from BAR, KR and

GJS. GJS and WJ conceptualized the idea for the manuscript. WJ developed the manuscript with input from GJS. All authors have reviewed and approved the final manuscript.

Tables and Figures

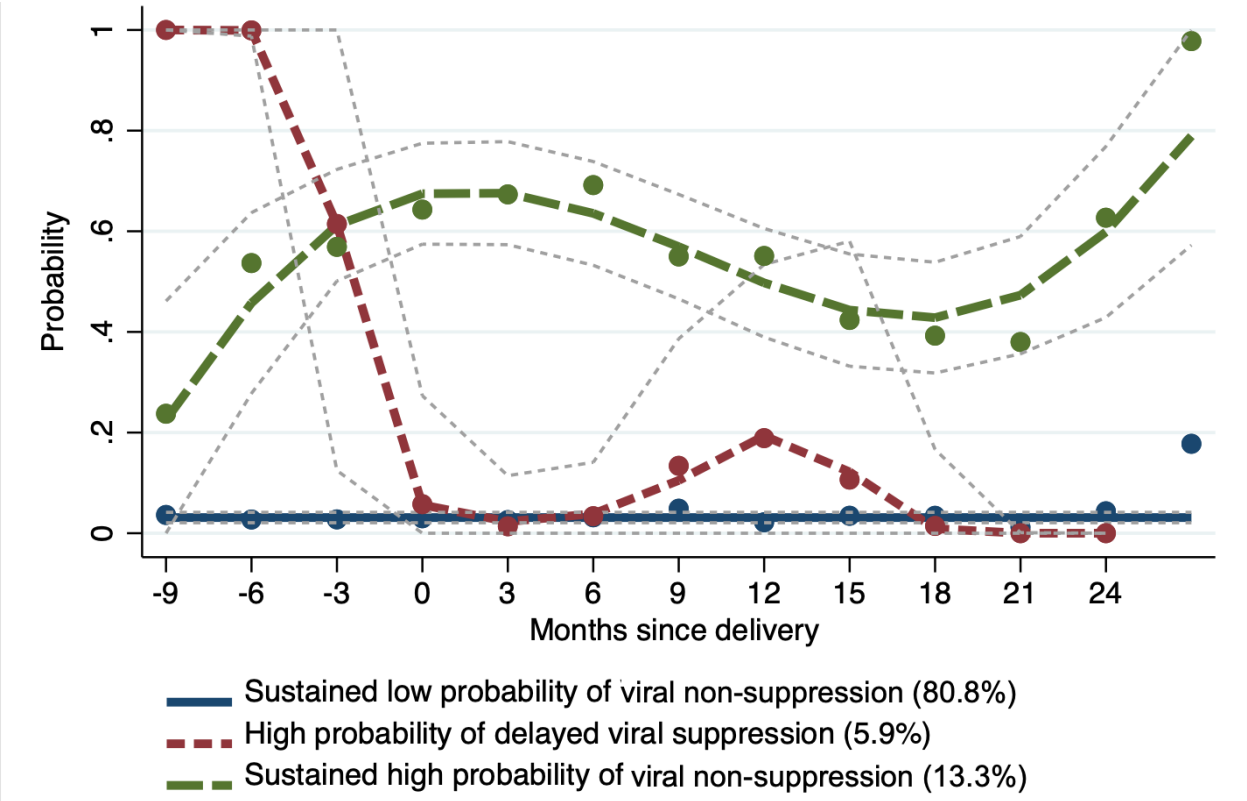
Figure 4.1. VL tests through 24 months postpartum (N=761 women)



	At enroll	By delivery[a]	By 6wk[b]	By 3mo[b]	By 6mo[b]	By 12mo[b]	By 18mo[b]	By 24mo[b]
VL tests per woman	1 (0-1)	1 (0-1)	2 (1-2)	3 (2-3)	3 (2-4)	3 (2-4)	4 (3-5)	5 (3-6)
Months between 2 tests[*]	3.9 (2.5-5.6)	4.0 (2.6-6.0)	4.6 (2.9-6.3)	4.7 (3.0-6.5)	4.9 (3.2-6.5)	5.2 (3.5-7.0)	5.3 (3.6-6.9)	5.3 (3.6-6.9)

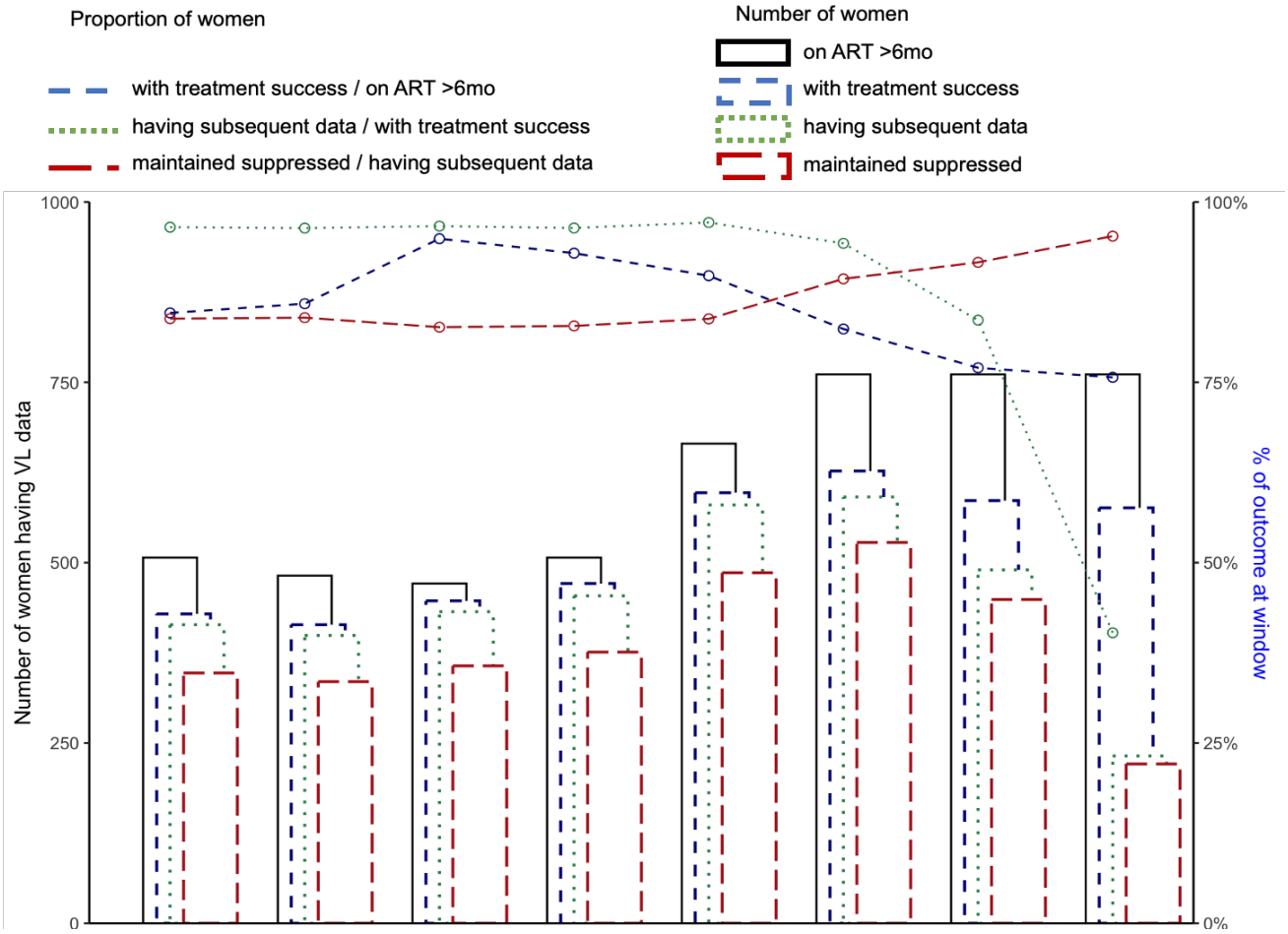
[a] Time window including 1 month after
[b] Time window including 3 months after
[*] Among women who had at least 2 VLs

Figure 4.2. VL trajectories for PBFW by probability of HIV VL ≥1,000 copies/mL



Longitudinal trajectories of unsuppressed (≥1,000 copies/mL) during 24-month study follow-up. Blue = 'Sustained low probability of viral non-suppression; red = 'High probability of delayed viral suppressed; green = 'Sustained high probability of viral non-suppression'. Dots represent the observed proportion of individuals with unsuppressed VL in a given interval among individuals assigned to distinct VL trajectory groups. The smoothed lines depict the predicted probability of unsuppressed VL for each trajectory group from the GBTM. The grey dashed lines represent 95% Confidence intervals for the predicted probability of unsuppressed VL at each time point. The y axis represents the probability of unsuppressed VL and the x axis represents the number of time points (every 3 months since delivery).

Figure 4.3. Proportion of women who would meet DSD criteria and likelihood of remaining suppressed, applying standard adult DSD guidelines and PMTCT monitoring window



Time	At pregnancy	At delivery [a]	At 6wk [b]	At 3mo [b]	At 6mo [b]	At 12mo [b]	At 18mo [b]	At 24mo [b]
N	507	482	471	507	665	761	761	761
N1 (N1/N)	429 (84.6%)	414 (85.9%)	447 (94.9%)	471 (92.9%)	597 (89.8%)	627 (82.4%)	586 (77.0%)	576 (75.7%)
N2 (N2/N1)	414 (96.5%)	399 (96.4%)	432 (96.6%)	454 (96.4%)	580 (97.2%)	591 (94.3%)	490 (83.6%)	232 (40.3%)
N3 (N3/N2)	347 (83.8%)	335 (84.0%)	357 (82.6%)	376 (82.8%)	486 (83.8%)	528 (89.3%)	449 (91.6%)	221 (95.3%)

N: women on ART >6mo; N1: women with treatment success; N2: women having subsequent data; N3: women maintained suppressed

[a] Time window including 1 month before and after

[b] Time window including 3 months before and after

Table 4.1. Risk factors of VF among women who would meet the DSD criteria at 6 months postpartum

Characteristic	Overall, N = 580	VF, N=94	Maintained VS, N=486	Site-adjusted PR[e] (95%CI); p-value	Multi-adjusted aPR[e] (95%CI); p-value
Western (ref. Nairobi)	**400 (69.0%)**	**78 (83.0%)**	**322 (66.3%)**	**2.48 (1.42-4.35); 0.002**	2.32 (1.20-4.47); 0.012
Young age (15-24 years)	187 (32.2%)	34 (36.2%)	153 (31.5%)	1.22 (0.78-1.91); 0.376	
Primary school completed	448 (77.2%)	73 (77.7%)	375 (77.2%)	1.16 (0.69-1.96); 0.568	
Married	504 (86.9%)	78 (83.0%)	426 (87.7%)	0.75 (0.41-1.34); 0.326	
Employed	313 (54.2%)	50 (53.2%)	263 (54.3%)	0.83 (0.54-1.29); 0.416	
At least mild depression symptoms [a]	**135 (23.3%)**	**35 (37.2%)**	**100 (20.6%)**	**2.19 (1.36-3.54); 0.001**	**1.95 (1.13-3.35); 0.016**
Abuse last year	**64 (11.0%)**	**16 (17.0%)**	**48 (9.9%)**	**1.96 (1.08-3.56); 0.027**	**2.17 (1.08-4.33); 0.029**
Time to clinic >1h	43 (7.5%)	5 (5.4%)	38 (7.9%)	0.61 (0.23-1.63); 0.326	
Primigravida	71 (12.2%)	12 (12.8%)	59 (12.1%)	1.27 (0.65-2.46); 0.483	
Pregnancy intended	**310 (53.7%)**	**40 (42.6%)**	**270 (55.9%)**	**0.63 (0.41-0.96); 0.030**	0.84 (0.50-1.39); 0.493
Start ART before pregnancy	408 (71.2%)	69 (73.4%)	339 (70.8%)	1.07 (0.65-1.77); 0.787	
Know status before pregnancy	423 (73.1%)	69 (73.4%)	354 (73.0%)	0.93 (0.57-1.54); 0.789	
Disclosed status to anyone	515 (89.6%)	85 (91.4%)	430 (89.2%)	1.21 (0.56-2.64); 0.631	
Ever missed a dose in the past 30 days [b]	61 (11.6%)	8 (9.4%)	53 (12.0%)	0.74 (0.34-1.63); 0.454	
Ever missed a dose in the past 90 days [b]	89 (17.3%)	16 (19.5%)	73 (16.9%)	1.23 (0.66-2.3); 0.517	
ZDV-based regimen (ref: TDF)	44 (8.4%)	10 (11.6%)	34 (7.8%)	1.51 (0.7-3.24); 0.294	
NVP-based ART regimen (ref: EFV)	**132 (26.0%)**	**33 (39.8%)**	**99 (23.3%)**	**2.03 (1.25-3.31); 0.005**	1.71 (0.96-3.02); 0.066
Mutations	**41 (7.1%)**	**22 (23.4%)**	**19 (3.9%)**	**8.73 (4.3-17.7); <0.001**	**8.00 (3.66-17.47); <0.001**
Low IMB score[c]	254 (46.4%)	45 (51.1%)	209 (45.4%)	1.13 (0.7-1.83); 0.616	
Ever LLD[d] within the last 6 months	**118 (20.3%)**	**32 (34.0%)**	**86 (17.7%)**	**2.16 (1.36-3.44); 0.001**	1.51 (0.85-2.68); 0.156

[a] evaluated by Patient Health Questionnaire 9 (PHQ9), a score >5 indicating at least moderate depressive symptoms; [b] Self-reported at baseline behavioral survey; [c] Information-Motivation-Behavioral (IMB) score evaluated by 15 items from LifeWindows ART adherence questionnaire; [d] LLD: having HIV VL ≥200 and <1000 copies/mL; [e] PR estimated by Log-binomial regression adjusting for site.

Table 4.2. ART adherence and retention in care among women who met the DSD criteria at different postpartum time of DSD assessment

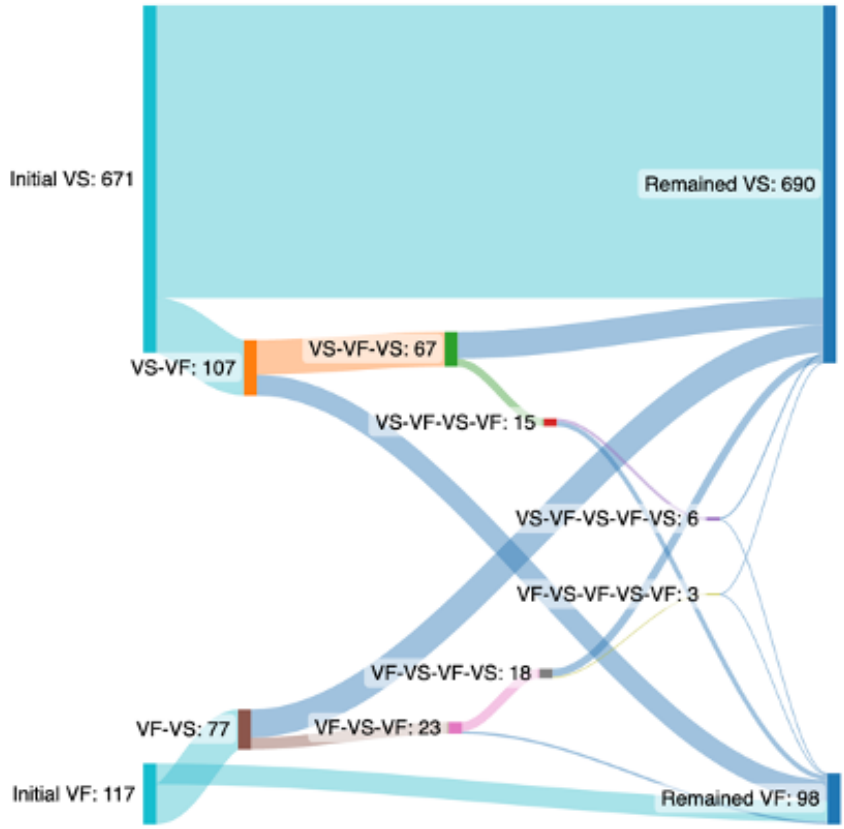
ART adherence*				Retention in care**			
	N	Proportion of VF	p-value		N	Proportion of VF	p-value
At 6 weeks postpartum [a]	407		0.2	At 6 weeks postpartum [a]	422		0.2
Not adherent		18.7% (65/348)		Not retained		13.7% (26/190)	
Adherent		11.9% (7/59)		Retained		20.3% (47/232)	
At 6 months postpartum [a]	563		0.4	At 6 months postpartum [a]	569		0.4
Not adherent		17.0% (91/536)		Not retained		15.4% (51/332)	
Adherent		7.4% (2/27)		Retained		18.1% (43/237)	
At 12 months postpartum [a]	579		0.8	At 12 months postpartum [a]	576		0.15
Not adherent		10.7% (58/544)		Not retained		9.1% (30/328)	
Adherent		11.4% (4/35)		Retained		12.9% (32/248)	

*ART adherence and DSD-eligibility were evaluated among women who had pharmacy refill visits within the past 6 months and had VL data after the evaluation window; not adhere: ever missed a daily dose within the past 6 months

**Retention and DSD-eligibility were evaluated among women who had clinic visits scheduled within the past 6 months and had VL data after the evaluation window; not retained: ever missed a visit within the past 6 months

[a] Time window including 3 months before and 3 months after

Supplementary Figure 4.1. Sankey diagram of VL suppression and non-suppression



*Adjacent VL results with same VF / VS status were collapsed

Chapter 5. Discussion

This dissertation delved into crucial issues concerning prevention of mother-to-child transmission (PMTCT) (programs in Kenya, encompassing the safety of antiretroviral therapy (ART) use for birth outcomes, retention of care during extended follow-up periods, and achieving maternal virologic suppression among women living with HIV (WLWH). We leveraged data from a completed randomized clinical trial of Kenyan women living with HIV from pregnancy prospectively to 24 months postpartum to elucidate these outcomes.

Main findings and interpretations

In Chapter 2, we presented compelling evidence indicating that WLWH faced a significantly higher risk of adverse pregnancy outcomes (APOs) compared to published estimates in the general population of sub-Saharan Africa. We observed that neither the specific ART regimen nor the timing of ART initiation showed any association with APOs. However, maternal viremia during pregnancy emerged as a strong predictor of preterm birth. Moreover, our research brought to light the role of psychosocial stressors in influencing the risks of stillbirth, and we underscored the importance of implementing mental health screening and counseling services, enhancing social support mechanisms (such as peer support), and promoting partner support as effective measures to mitigate APOs in PMTCT programs. Notably, many of the observed associations remained consistent and some exhibited heightened significance among a subset of women with viral suppression at enrollment. By investigating the risks and predictors of APOs, this Chapter contributed to the development of more effective strategies that enhance the safety of ART usage, improve birth outcomes, and bolster overall maternal health and well-being for WLWH in Kenya and similar settings.

Chapter 3 in this dissertation focused on assessing various measures of non-retention in care throughout the period from pregnancy to 2 years postpartum. We examined late visits, 3-month visit coverage, and loss to follow-up (LTFU) as three distinct definitions. Our investigation

revealed a significant association between late visit attendance and subsequent LTFU. By flagging these occurrences, clinicians can implement additional strategies to optimize retention by incorporating visit timeliness into assessments may lead to improved evaluations of PMTCT initiatives. Furthermore, we identified specific risk factors that may be linked to different aspects of retention, highlighting the complexity of the issue according to a lack of unified or standardized evaluation of retention in care in PMTCT programs. This diversity in evaluation methods depends heavily on research objectives, also factors influencing long-term engagement in care are highly interconnected and dynamic across healthcare settings. Given these variations, when comparing results and programmatic interventions from different studies, it becomes crucial to recognize the heterogeneity. Emphasizing comprehensive and tailored measures of longitudinal retention can better address the intricacies of each program's context and research interests, leading to more effective outcomes for women with HIV and their infants. This Chapter shed light on considering some risk factors associated with poor engagement in all retention measures, and acknowledged the heterogeneity of different dimensions of monitoring retention in care throughout long-term follow-up. This study provided valuable informed comparisons to design targeted interventions to strengthen PMTCT initiatives worldwide.

In Chapter 4, we conducted group-based trajectory analyses of longitudinal viral load (VL) patterns among postpartum women with HIV, aiming to provide valuable insights of implementing differentiated service delivery (DSD) models in PMTCT programs. Our findings revealed that by 6 months postpartum, the majority of women met the standard DSD eligibility criteria as described in the World Health Organization (WHO) guidelines. This criterion entails being on ART for at least 6 months and having at least one viral suppression within the past 6 months. Among women with follow-up VL data, we found most women maintained viral suppression consistently. Even among those whose first VL since enrollment was unsuppressed, an encouraging proportion of women achieved subsequent suppression and sustained it throughout 24 months. These findings

hold crucial implications that integrating patient-centered DSD strategies and offering women the choice of a preferred DSD model, where clinically indicated, could be both feasible and beneficial within the perinatal care framework. It is also important to note that women experiencing depression or reporting abuse may require enhanced mental health support to prevent virologic failure. Additionally, drug resistance testing would be a necessary tool to identify those who should not be included in DSD programs or with special concerns. This Chapter raised the need for implementation science studies focused on different DSD models to further enhance the care of postpartum women who are stable on ART. By tailoring DSD strategies to suit the needs of these women, we can ensure better long-term health outcomes and continued success in the management of HIV during the perinatal period and beyond.

Future directions for improving PMTCT services

Integration of maternal-child care and HIV services is well promoted by the WHO and Ministries of Health across much of sub-Saharan Africa settings. It has been noted that service integration cannot eliminate the existing human resource shortages or problems of inadequate healthcare infrastructure[215]. Qualitative studies among WLWH in Kenya have perceived barriers including provider and staff shortage, fragmented care, long waiting time at clinics and a lack of consensus on best practices of VL monitoring for women[216–219]. Although a great amount of effort has been made to identify patient-level factors associated with suboptimal retention with implementation programs targeting behavioral change, there still remains a long way to go in this era. The barriers in healthcare facilities and management systems within the PMTCT cascade prompt re-consideration of how services could be better provided and delivered.

Outside of maternal-child health services, innovative ART service delivery models at facility-based and community-based level have been rolled out, specifically for stable adult patients established on ART [220] endorsed by the WHO guidelines[39]. Interventions of decentralized medication

delivery[191], community-based ART initiation and refills by mobile van monitoring[221], multi-month dispensing of ART[222 223], and less frequent clinic visits[224] have shown promising improvements in engagement and viral outcomes among general individuals stable on ART. However, translating this success to PMTCT scale requires effective implementation of the model to achieve health impact aligning with more specialized or unique services of maternal ART refills, follow-up visits for antenatal/postnatal care, and immunization windows for HIV exposed infants according to the WHO guidelines of integrating PMTCT services into general MCH services[155] and the overall MCH visit continuum[156].

Qualitative research of differentiated postpartum care models has shown high rates of improved quality of care and increased confidence in health decision-making[225,226], and pilot studies reported comparable outcomes related to retention and viral suppression between postpartum women assigning to adherence clubs versus those using local primary health care clinic[174,227]. However, the authors observed frequent relocation and transfer between clinics. The shift from providing vertical services to the integration of postpartum HIV treatment services into maternal, and neonatal health care is a complex transformation that demands significant adjustments in major aspects of healthcare organization[226]. These factors, including but not limited to providers' workloads, infrastructural resource chain, together with stakeholder involvement, will need to be analytically studied in future implementation science programs. Research on maternal and child outcomes with varying degrees of DSD customization is also required to determine the optimal and effective approaches in different settings and to understand generalizability of these findings across diverse health systems.

Conclusion

Findings from this dissertation help to advance understanding and development of strategies to improve women's health in PMTCT programs including birth outcomes, retention in care and viral

suppression in the coming years. We demonstrated that particular ART regimen or timing of ART initiation was not associated with stillbirth, preterm birth or neonatal death among women on ART. Incorporating STI testing, implementation of mental health support, and promoting ART adherence to achieve viral suppression could contribute to lower rates of APOs in PMTCT programs. We reported cofactors of non-retention in care may differ depending on which retention measures were assessed therefore studies should recognize how their specific definitions of non-retention should be contextualized in the literature with studies that used similar measures. Addressing disclosure, tailoring services for younger clients and those who are unsuppressed or starting ART late could improve retention. Late visit attendance may be a sentinel indicator of subsequent LTFU, and understanding what drives both is useful for programmatic improvements. We found most women maintained viral suppression during the whole 24-month follow-up and may be suitable for DSD referral in early postpartum periods, and women with depression, drug resistance and detectable VL may need enhanced services to prevent further viral failure.

Overall, we believe this dissertation work contributes substantially to fields of global PMTCT programs. We anticipate seeing more in-depth research in the future to comprehensively monitor PMTCT accomplishments, and to identify efficient opportunities to improve well-being among pregnant individuals and mothers with HIV.

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