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

Wenwen JIANG[1], **Keshet RONEN**[1], **Lusi OSBORN**[2], **Alison L. DRAKE**[1], **Jennifer A. UNGER**[1], **Daniel MATEMO**[2], **Daniel A. ENQUOBAHRIE**[1], **John KINUTHIA**[2], **Grace JOHN-STEWART**[1]

[1]University of Washington, Seattle, Washington, United States

[2]Kenyatta National Hospital, Nairobi, Kenya

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.

Author for correspondence: Wenwen Jiang, wenwenj@uw.edu.

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.

Declaration of interests: We declare no competing interests

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[2]. 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[3]. 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[3]. Global scale-up of ART has resulted in more WLWH in Africa accessing ART and continued decline in new pediatric HIV infections[4].

There is evidence that ART use in pregnancy may affect pregnancy outcomes[5–9], 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)[10]. 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[11], and the DART trial in Uganda/Zimbabwe showed no difference in neonatal mortality between TDF (+NVP) and non-TDF ART[12].

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[14]. This may be due to immune activation or immune compromise with resultant vulnerability to other infections[15]. Dysregulation of inflammatory cytokine production at the maternal-fetal interface may also contribute to APOs, and this may differ by ART regimen and timing[16–20]. Other HIV-related factors, including clinical stage of disease and CD4 cell count, have been associated with APOs[10,13,21–23]. 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[24]. 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[24]. 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[25]), stigma (using 4-item instrument adapted from the stigma scale for chronic illnesses [SSCI][26]), depression (using Patient Health Questionnaire 9 [PHQ9][27]), intimate partner violence (IPV) (using Abuse Assessment Screen [AAS][28]), food security (using Household Food Insecurity Access Scale [HFIAS][29]), disclosure of HIV status, history of any STI, and ART knowledge (using 15 items from the LifeWindows ART adherence questionnaire[30]). 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[24].

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 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 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 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 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). 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). 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). 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). 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). 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).

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). 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).

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 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 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 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 3). Adjusting for both site and HIV VL at enrollment, the association between NND and PTB remained similar (Table 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%[31]) a 2.4-fold higher PTB risk (28.3% vs.12.0%[32]), and a similar NND risk (2.2% vs. 2.7%[33]). 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[34,35], inflammation, or placental dysfunction[36]. Almost one quarter of women experienced at least moderate depressive symptoms, similar to rates of antenatal

depression among African WLWH in a systematic review[37]. 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[38] 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[23,39,40]. 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[15–19]. There is evidence of PTB being associated with syphilis[41–43], chlamydia[44–47], gonorrhea[43,47,48], trichomoniasis[49], and cervicitis[50] during pregnancy in general population, however, there is mixed evidence regarding the association in WLWH[51–55], 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[56,57] but lower effect of psychosocial stressors on PTB[58]. Studies which demonstrated significant effects of stress on PTB risk were often based on extreme depression[59–61]. 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[62]. 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[63,64]. 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[63,65], probably due to limited statistical power for this analysis.

NND in this cohort was predominantly associated with PTB, consistent with global data[66]. 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[67]. 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[68]. 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[69], and potential risk-based re-screen later in pregnancy[70,71]. 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[11,12,72] and EFV-based regimens[73–75]. Few women in our study received PIs, which have been linked with elevated PTB risk[76–78]. Our findings on ART use provide re-assurance for >90% of pregnant WLWH following WHO recommendations to use TDF/FTC/EFV[3]. 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[79], it can be problematic due to uncertainty of the true LMP[80], recall bias leading to overestimates of GA[81], 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[82,83]. 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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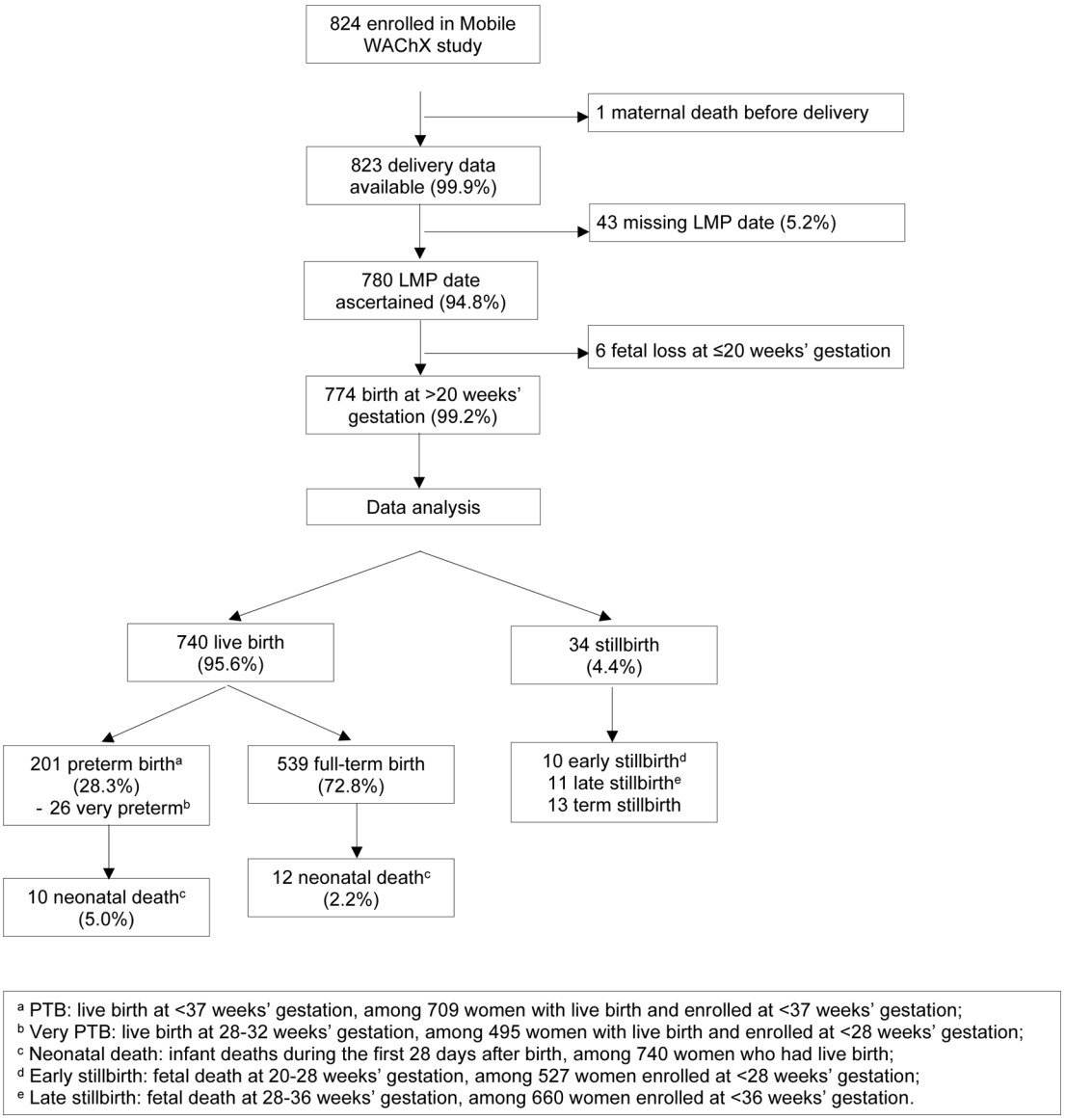
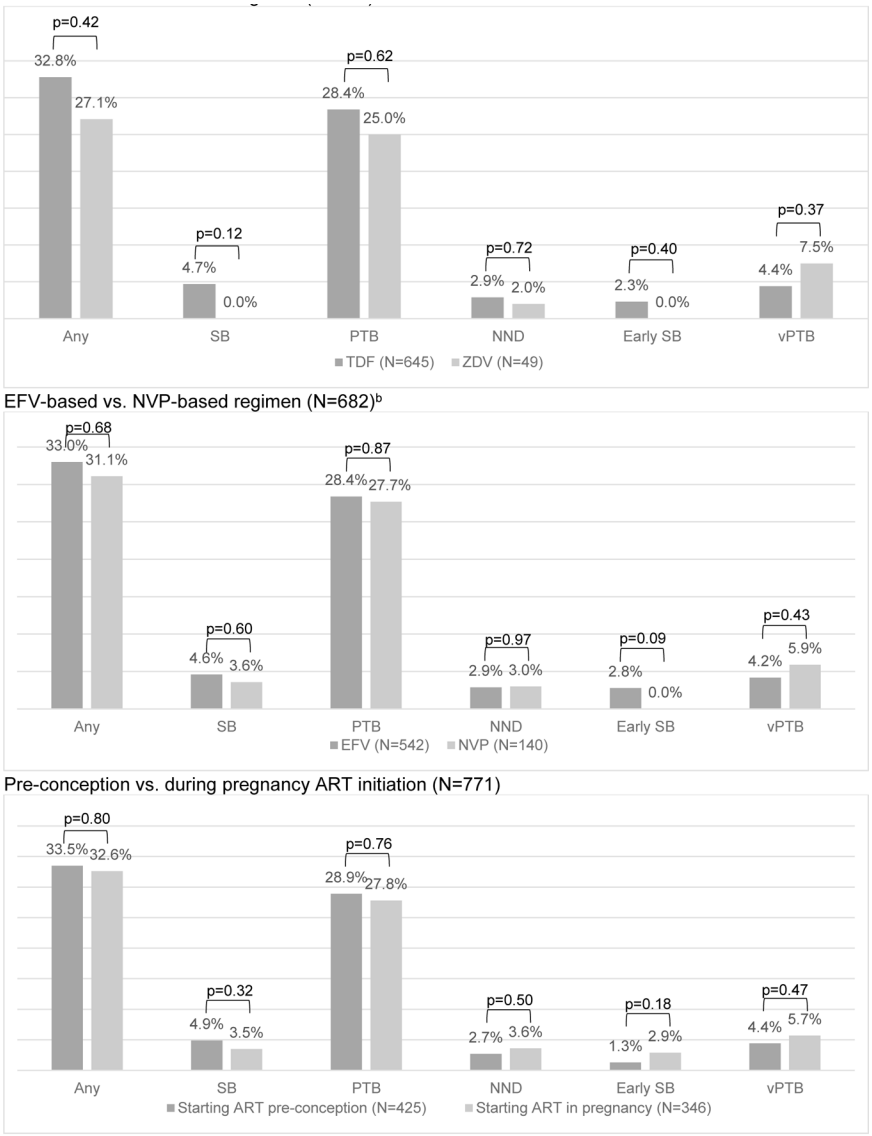


Figure 1.
Study flowchart



[a]Prevalences compared by chi-square tests

Figure 2. Prevalence of adverse pregnancy outcome by ART use[a]
TDF-based vs. ZDV-based regimen (N=694)

Table 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	

	N	n (Percent) or median (IQR)
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.

Table 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								

	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)	
>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 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)