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Viraemia before, during and after pregnancy in HIV-infected women on antiretroviral therapy in rural KwaZulu-Natal, South Africa, 2010–2015

Terusha Chetty^{1,2},

Marie-Louise Newell³,

Claire Thorne⁴,

Anna Coutsooudis⁵

¹Africa Health Research Institute, KwaZulu-Natal, South Africa

²Department of Public Health Medicine, School of Nursing and Public Health, University of KwaZulu-Natal, KwaZulu-Natal, South Africa

³Faculty of Medicine, Institute for Developmental Sciences, University of Southampton, Southampton, UK

⁴UCL Institute of Child Health, University College London, London, UK

⁵Department of Paediatrics and Child Health, University of KwaZulu-Natal, KwaZulu-Natal, South Africa

Abstract

Objectives—Pregnancy and post-partum viral load suppression is critical to prevent mother-to-child HIV transmission and ensure maternal health. We measured viraemia risk before, during and after pregnancy in HIV-infected women.

Methods—Between 2010 and 2015, 1425 HIV-infected pregnant women on lifelong antiretroviral therapy (ART) for at least six months pre-pregnancy were enrolled in a cohort study in rural KwaZulu-Natal, South Africa. Odds ratios were estimated in multilevel logistic regression, with pregnancy period time-varying.

Results—Over half of 1425 women received tenofovir-based regimens ($n = 791$). Median pre-pregnancy ART duration was 2.1 years. Of 988 women (69.3%) with pre-pregnancy viral loads, 82.0%, 6.8% and 11.2% had VL <50, 50–999 and 1000 copies/ml, respectively. During pregnancy and at six, 12 and 24 months, viral load was 1000 copies/ml in 15.2%, 15.7%, 17.8% and 16.6% respectively; viral load <50 was 76.9%, 77%, 75.5% and 75.8%, respectively. Adjusting for age, clinical and pregnancy factors, viraemia risk (viral load 50 copies/ml) was not significantly associated with pregnancy [adjusted OR (aOR) 1.31; 95% CI 0.90–1.92], six months (aOR 1.30; 95% CI 0.83–2.04), 12 months (aOR 0.96; 95% CI 0.58–1.58) and 24 months (aOR

Correspondence to: Terusha Chetty.

Corresponding Author Terusha Chetty, Africa Health Research Institute, P.O. Box 198, Mtubatuba 3935, South Africa. tchetty@africacentre.ac.za.

1.40; 95% CI 0.89-2.22) post-partum. Adjusting for ART duration–pregnancy period interaction, viraemia risk was 1.8 during pregnancy and twofold higher post-partum.

Conclusions—While undetectable viral load before pregnancy through post-partum was common, the UNAIDS goal to suppress viraemia in 90% of women was not met. Women on preconception ART remain vulnerable to viraemia; additional support is required to prevent mother-to-child HIV transmission and maintain maternal health.

Keywords

pregnancy; post-partum; viraemia; adolescents; HIV infection

Introduction

Mother-to-child transmission (MTCT) is the main acquisition route of infection for children; plasma viral load (VL) is the main driver of MTCT [1, 2]. Potent antiretroviral therapy (ART) reduces VL through HIV replication interruption, decreasing MTCT risk [3–5] and improving maternal survival [6, 7].

Although perinatal transmission risk increases at higher maternal VLs [2] and declines at lower maternal VLs [8, 9], MTCT may occur with low maternal viraemia [9, 10], and the association between VL and MTCT risk is not linear [2, 11, 12]. In the French Perinatal Cohort, VLs 50-400 copies/ml near delivery increased perinatal transmission risk fourfold vs VL <50 copies/ml [9].

With expanded ART access, HIV-infected women are increasingly likely to conceive on ART [13–16]. Maintaining viral suppression may be particularly challenging during pregnancy and post-partum with psychosocial, cultural and economic obstacles to adherence [17, 18]. Low adherence may lead to virological failure, increasing MTCT and maternal drug resistance risk [19–22]. Women on preconception ART may also be susceptible to viraemia risk; in the United Kingdom (UK), women on preconception ART and women starting pregnancy ART had a higher risk of post-partum viral rebound than non-pregnant controls [23]. Moreover, adherence issues in women starting ART for MTCT may differ from women initiating ART for their own health independently from antenatal care [17, 24].

With the expanding treatment eligibility in South Africa [16], more HIV-infected women will conceive on ART [25]. To inform understanding of this public health programme, we explored VL and viraemia risk before, during and after pregnancy in HIV-infected women on ART before pregnancy.

Methods

Study population

HIV-infected pregnant women attending one of 17 public sector antenatal clinics (ANC) in the Hlabisa HIV Treatment and Care Programme [26, 27], northern KwaZulu-Natal, were eligible for inclusion. Women needed to be (i) on ART at least 6 months pre-pregnancy; (ii) not pregnant at ART initiation; (iii) age 15-49 years at pregnancy start; (iv) attending

from 2010 to 2015; and (v) have at least one VL test 1 year pre-pregnancy to 2 years post-delivery.

Department of Health (DoH) nurses and counsellors at ANCs and the district hospital collected routine pregnancy data. Trained data capturers then entered data into a pregnancy database at the Africa Centre for Health and Population Studies (now Africa Health Research Institute).

Data capturers also routinely collected HIV and follow-up visit data from patient files, including medications dispensed. Data were entered into an HIV database at the Africa Centre. After April 2013 (when HIV programme funding transferred to DoH), patient HIV data were collected from the Hlabisa pharmacy information system and the DoH HIV information system. The National Health Laboratory Service (NHLS) emailed laboratory test results weekly including CD4⁺ percent/count, plasma VL and HIV results; these were imported into the HIV database. Pregnancy and HIV data were linked using national identity numbers and other demographic characteristics [26].

Pregnancy and post-partum definition—Pregnancy start was defined as last menstrual period date (LMP) and pregnancy end as delivery or pregnancy loss date. Complete LMP data were available for 90% of pregnancies; for the remainder, start and end dates were estimated using reported pregnancy duration based on maternal history and either first antenatal visit date or delivery date. For women with missing birth outcomes, pregnancy end date was calculated 273 days from pregnancy start (based on median pregnancy duration). In women with additional pregnancies, subsequent pregnancies were classified as repeat pregnancies (yes, no).

'Pregnancy periods' were categorised into (i) 'pre-pregnancy', from 12 months before pregnancy to pregnancy start; (ii) 'during pregnancy' from pregnancy start to delivery; and (iii) 'after pregnancy' from the day after delivery through 24 months post-partum. The post-partum period was further categorised as: first 6 months post-partum (post-partum, 6 months); 7–12 months postpartum (post-partum, 12 months); and 13–24 months post-partum (post-partum, 24 months).

Outcome measure

The primary outcome measure was VL < 50 copies/ml. The district hospital NHLS laboratory, an accredited laboratory under national quality control, conducted routine HIV-1 VL monitoring. VLs were analysed using Nuclisens EasyQ® HIV-1 assay (BioMérieux) with a lower detection limit of 25 copies/ml [27]. VL testing was recommended 6 months until 1 year post-ART initiation, thereafter annually [28]. Pregnancy VL testing to determine virological suppression before delivery started in 2015 [29]. Patients identified with virological failure (VL >1000 copies/ml after at least 12 months on a standard first-line regimen) were referred to clinicians for further management.

Statistical analysis

Differences between women with and without viraemia were analysed using a Chi-squared or Fisher's exact test for categorical variables and Student's *t*-test for continuous variables.

For the VL descriptive analysis, VL tests closest to pregnancy start were used if there was more than one test.

Participant characteristics including clinic area (periurban, rural), prior PMTCT (no, yes), first visit gestation (<20 weeks, ≥20 weeks), delivery gestation (<37 weeks, ≥37 weeks), CD4⁺ count in the year pre-pregnancy (<350, ≥350 cells/mm³), calendar delivery year (2010, 2011, 2012, 2013, 2014, 2015) and HIV status disclosure at ART initiation (no, yes) were included as potential confounding factors.

Median ART duration was based on time on ART at pregnancy start. Tenofovir (TDF)-based ART was phased in [26]. ART regimens were initially categorised as TDF-based, stavudine-based (d4T-based) or zidovudine-based (ZDV-based) [30, 31]. As ZDV exposure was minimal, ZDV was combined with d4T-based regimens (non-TDF-based regimen) in multivariable models.

In univariable analysis, the association between each variable and viraemia risk was assessed. In model development, variables with $P < 0.2$ in univariable analyses, uncorrelated (Pearson's correlation coefficients, $r < 0.5$) and biologically plausible were considered, including maternal age, ART regimen (TDF-based, non-TDF-based) and ART regimen change from year pre-pregnancy through pregnancy end (yes, no). The ART duration cut-off was based on prior evidence of an increasing trend for viraemia and drug resistance among women on ART over 3 years [22]. ART regimen change and age (15–24, 25–34, 35–49 years) were time-varying.

We conducted multilevel logistic regression to account for random effects of each individual over time, analysing viraemia risk as the outcome variable pre-pregnancy through post-partum [32]. The appropriate model was selected using Akaike information criterion. A subgroup analysis was conducted for women with all three VLs available before, during and after pregnancy.

Ages over 35 and under 20 have been associated with better and worse ART adherence, respectively [33, 34]. To examine whether age modified pregnancy and viraemia risk, an interaction term for age (15–24, 25–34, 35–49 years) and pregnancy period was included. A separate model also explored the interaction between ART duration and pregnancy period; theoretically, as viral reservoirs tend to diminish with increasing ART duration, a longer ART duration should lower viral rebound risk [35]. Statistical analyses were conducted using Stata 13.1.

Ethics

The University of KwaZulu-Natal Biomedical Research Ethics Committee provided ethics approval for routine HIV and pregnancy data linkage within Hlabisa (E134/ 06) and for this analysis (BE002/16).

Results

By December 2015, 30 750 pregnancies were reported. HIV test results were known in 29 774 pregnancies (96.8%); 41.0% were HIV-infected (12 202/29 774). Clinical HIV data

were available for 9479 of the 12 202 pregnancies in HIV-infected women (77.7%) (Figure 1). Linkage was not possible for the remaining pregnancies due to late third-trimester attendance, with national identifying data verification and probabilistic linkage between databases challenging. Of the 9479 pregnancies, 21.6% ($n = 2046$) were on lifelong ART pre-pregnancy; 3606 started lifelong ART during pregnancy (38.0%), 2952 (31.1%) were on MTCT ART and 875 (9.2%) were not on pregnancy ART or prophylaxis.

There were 404 pregnancy and 70 repeat pregnancy exclusions from the 2046 pre-pregnancy ART pregnancies as pregnancy laboratory data were missing, and 147 women initiated on ART less than 6 months before pregnancy were excluded (621/2046; 30.4%). Pregnancies excluded were more likely to be in younger women and have a lower CD4⁺ count pre-pregnancy than pregnancies included in this analysis ($P < 0.01$). Thus, the study population comprised of 1425 women on ART for ≥ 6 months pre-pregnancy.

Maternal characteristics ($N = 1425$)

Median pregnancy start age was 31 years; 23% were 15-24 years (Table 1). Most women attended rural ANC clinics. HIV status disclosure was reported in over 60% and prior PMTCT exposure in over 50% of women. Only 1095 women (76.8%) had birth outcome data; of these, 89.0% ($n = 975$) had infants born at ≥ 37 gestational weeks (Table 1).

Median initiation CD4⁺ was 164 cells/mm³; pre-pregnancy CD4⁺ was 477 cells/mm³ (Table 1). There were 203 (14.3%) women with pre-pregnancy and antenatal ART regimen changes. Median ART duration was 2.1 years at pregnancy start. Over 50% of women received TDF-based ART, and under 42% used d4T-based regimens with either efavirenz or nevirapine; only 37 women (2.6%) used ZDV during pregnancy.

Table 1 also shows pre-pregnancy group characteristics ($N = 988$) by VL. Women with viraemia were significantly older, more likely to have disclosed their HIV status, with lower pre-pregnancy CD4⁺ counts, more likely to be on ART for ≥ 3 years and on a d4T-based regimen pre-pregnancy than those non-viraemic.

VL testing before, during and after pregnancy ($N = 1425$)

Overall, there were 3941 VL observations in 1425 women; 16.8% ($n = 660$) of VL tests were ≥ 1000 , 7.9% ($n = 312$) were 50-999 and 75.3% ($n = 2969$) were < 50 .

Of the 988 (69.3%) women with pre-pregnancy VL, 82.0%, 6.8% and 11.2% had VL < 50 , 50-999 and ≥ 1000 , respectively (Table 2). Of 854 (60%) women with pregnancy VLs, VL < 50 , 50-999 and ≥ 1000 were reported in 76.9%, 7.8% and 15.2% of women, respectively.

There were 527 (37.0%), 437 (30.7%) and 656 (46.0%) women with VL tests through six, 12 and 24 months post-partum (Table 2), of whom 7.2%, 6.6% and 7.6% had VL 50-999 copies/ml, respectively. VL ≥ 1000 in 15.7%, 17.8% and 16.6%, and virological suppression was 77%, 75.5% and 75.8% at six, 12 and 24 months, respectively.

VL distribution in women with VL tests before, during and six months post-partum ($n = 150$)

There were 150 women with VL tests pre-pregnancy through six-month post-partum. VL <50 was seen in 70.0% pre-pregnancy, 68.7% during and 71.3% after pregnancy. VL 50-999 was observed in 11.3%, 8.7% and 9.3% in the three periods, and VL was 1000 in 18.7% pre-pregnancy, 22.7% during pregnancy and 19.3% post-pregnancy (Table 2).

Of 45 women with unsuppressed pre-pregnancy VL, 12 (26.7%) suppressed antenatally, nine (20.0%) had VL 50-999 copies/ml and 24 (53.3%) had pregnancy VL 1000. Within 6 months post-partum, 13 were suppressed (28.9%), 11 (24.4%) had VL 50-999 copies/ml and 21 (46.7%) had VL 1000. Of the 47 women with pregnancy VL >50, 12 (25.5%) suppressed within 6 months post-partum, 10 (21.3%) had VL 50-999 copies/ml and 25 (53.2%) had VL 1000.

Risk factors for viraemia in women on ART for six months or longer ($N = 1425$)

Overall, there were 24.7% VL tests 50 copies/ml (972/ 3941). Crude analysis showed no significant viraemia risk by pregnancy period. Age >34 significantly reduced viraemia risk by 54%, but age <25 years did not differ from the 25–34 year group. Pre-pregnancy CD4⁺ count 350 cells/mm³ lowered viraemia risk (unadjusted odds ratio [OR] 0.04; 95% confidence interval [CI] 0.02–0.09) (Table 3). Non-TDF regimens significantly increased viraemia risk sevenfold, and ART duration 3 years was marginally associated with viraemia risk. First, ANC visit 20 weeks increased pregnancy viraemia risk to 3.37 ($P < 0.01$). Viraemia risk was reduced in 2014 and 2015.

In multivariable analyses adjusting for age, clinical and pregnancy factors (Table 3), pregnancy, six and 24-month post-partum viraemia risk non-significantly increased to 1.3-fold and 1.4-fold, respectively. Viraemia risk almost doubled compared to the univariable analysis, remaining significantly associated with age >34, but not age <25 years (95% CI 0.96-4.20).

Clinical factors remained significant for viraemia, particularly CD4⁺ count, ART regimen and ART duration. Pre-pregnancy CD4⁺ 350 cells/mm³ was protective, while non-TDF regimens significantly increased viraemia risk 3.3-fold. ART duration 3 years and late first ANC attendance significantly increased viraemia risk threefold and 2.7-fold, respectively. There was a trend towards progressively reduced risk from 2012 through 2015.

In the multivariable model assessing whether ART duration modified viraemia risk in each pregnancy and post-partum period, with variables from Table 3 (Table 4), pregnancy, 6 and 24-month post-partum viraemia risk significantly increased to 2.25, 1.81 and 2.82, respectively. Viraemia risk lowered during pregnancy and post-partum if on ART for 3 years (12, 24 months). Age <25 and >34 also significantly affected viraemia risk [adjusted (aOR) 2.19 and 0.33, respectively]. Although confidence intervals were wide, ART duration 3 years remained significant.

In the model assessing whether pregnancy start age modified the association with pregnancy period (Table 5), viraemia risk was 1.89 (95% CI 1.16-3.09) in pregnancy vs. pre-pregnancy,

but the increased viraemia risk post-partum was not significant. Although the pregnancy and 12 months interaction term were significant in age >34, the aOR for other covariates were not substantially altered; the age aOR lost statistical significance.

In a subgroup analysis of 150 women with VLs before, during and after pregnancy (Table S1), pregnancy (aOR 1.28; 95% CI 0.50-3.28) and post-partum (aOR 0.99; 95% CI 0.34-2.90) were not significantly associated with viraemia.

Discussion

In this rural setting where HIV prevalence is high, virological suppression pre-pregnancy through 24 months post-partum was relatively high. Although crude viraemia risk was not associated with pregnancy period, in the model including an ART duration–pregnancy period interaction term, viraemia risk was increased in pregnancy and post-partum.

In our study, pre-pregnancy virological suppression reached 82%, narrowly missing the 90% UNAIDS goal [14]. In South Africa, viral suppression among pregnant or breastfeeding women ranged from 27 to 78% [36, 37]. Conversely, in Malawi and Uganda, over 90% were viraemia-suppressed [24, 38].

Consistent with increased pregnancy viraemia risk in our study, in a South African study of 541 pregnancies in 5954 women, pregnancy after ART initiation modestly increased virological failure risk [adjusted hazards ratio (aHR) 1.34; 95% CI 1.02–1.78] [39]. Findings were based on observational data from one clinic without pre-initiation VL, and confounding cannot be ruled out. Pregnancy viraemia was not observed in 1041 women on pre-pregnancy ART from seven African countries [40] or in three other studies with smaller sample sizes [41–43]. Notably, these cohort studies had rigorous study procedures which may have positively affected ART adherence, follow-up and VL outcome. As our and the prior South African study were part of ongoing HIV programmes, findings may reflect more closely a real-world setting [17].

Post-partum viraemia risk in our study corroborates a UK study of 19 HIV clinics where 623 women on preconception ART had higher rebound post-partum than non-pregnant controls (<3 months: aHR 6.63; 95% CI 3.58–12.29; 3–12 months: aHR 4.05; 95% CI 2.03–8.09) [23]. Similar results were reported in Tanzanian women starting ART in late pregnancy where over 10% ($n = 73$) had post-partum VLs >400 copies/ml between 3 and 24 months [44]. While differing designs, ART regimens and study populations complicate interpretation, a commonality between studies are post-partum issues which limit viral control [45].

We showed increased pregnancy and post-partum viraemia risk only when ART duration and age were included as effect modifying covariates. Longer ART duration should reduce viraemia risk as viral reservoirs decline over time [35]. In this study, longer ART duration independently increased the risk of viraemia, consistent with the higher viraemia trend around delivery among Rwandan women on ART for >3 years [22]. However, when ART duration was combined with viraemia risk through the pregnancy period, longer ART duration in pregnancy and post-partum reduced viraemia risk in our study, confirming

diminishing VL over time and consistent with a small study in Benin where ART was started in pregnancy [46]. Selection bias with inclusion of women with VL tests who are more likely to be engaged with care, unknown confounding or measurement effect, may explain these conflicting findings. More data are needed to tease out the ART duration effects on the risk of viraemia, particularly adherence measures during pregnancy and post-partum [47].

Age was strongly associated with viraemia with risk decreasing in older women and increasing in younger women. While the younger age association lost statistical significance in the model allowing for interactions, these results relating to older age match those observed in earlier studies [23, 39, 46]. In nine Southern African countries, adolescents were more likely to have imperfect adherence vs adults, and adolescents with virological suppression had shorter viral rebound time vs adults (aHR 2.03; 95% CI 1.31–3.13) [34].

There are several reasons for compromised viral control during the pregnancy and post-partum. Pregnancy may affect HIV-related outcomes through physiological, immunological and hormonal changes that compromise adherence, lower drug levels to subtherapeutic and increase ART resistance [48–50]. Late antenatal attendance may also affect viral control, as observed in this study. Conversely, frequent ANC visits may improve VL control [46]. Unexpectedly in our study, women on pre-pregnancy ART with monthly attendance for medication were unlikely to engage early with pregnancy services as staff did not formally refer between services provided at the same location by different providers from 2010 to 2014 [28]. From 2015, pregnant women received HIV care within antenatal clinics [29]; service integration and guideline recommendations to monitor pregnancy VL may have contributed to the reduced viraemia risk trend in later years.

Several studies have demonstrated women are vulnerable to non-adherence and healthcare disengagement post-partum [24, 51–53], a crucial period for virological control to minimise breastfeeding transmission risk. In Malawi, age <24 and poor adherence were associated with twofold non-retention risk; patients on Option B+ had higher attrition than non-pregnant women initiating ART [53]. Similar results have been observed in South African pregnant women on ART for their own health, with attrition higher post-partum than antenatally [54]. Myer *et al.* have suggested that post-natal services prioritise childcare, and women with chronic conditions such as HIV require additional support to manage their health [45]. Healthcare disengagement drivers are complex and multifactorial requiring comprehensive interventions [45].

MTCT risk increases almost threefold per \log_{10} increase in VL [55], with initial rapid declines per additional week of ART, plateauing around 15 weeks [5]. The window for timely intervention of high VLs is therefore narrow. In South Africa, VL testing is recommended at the first antenatal visit in women on preconception ART (at 3 and 6 months in women initiating pregnancy ART) with results reviewed within 2 weeks [29]. In women with VL under 1000 copies, six monthly VL testing is recommended through pregnancy and breastfeeding; VL is repeated in 1 month with virological failure. As pregnancy and breastfeeding is time-sensitive, even 1 month may be too long especially in women who present late for antenatal care. Ideally, women with detectable VLs should be managed as high risk with follow-up within days for adherence support and repeat VL testing

within weeks [56]. Moreover, infants should be rapidly identified as high MTCT risk and provided with extended PMTCT prophylaxis, appropriate HIV testing and vigilant maternal monitoring to promptly manage detectable VL during breastfeeding [29].

Strengths and limitations

Our findings come from a large pregnancy cohort of HIV-infected women in a real-world setting with high-population ART coverage [57] and are generalisable to other rural public health programmes in sub-Saharan Africa. While South Africa recognises the necessity for pregnancy VL monitoring [29], few studies have evaluated programmatic viral control; this study offers additional insight into viraemia risk and identified vulnerable groups, especially younger women. Further research is required to determine the pathways through which pregnancy and post-partum period increase viraemia risk in women on pre-pregnancy ART.

Subgroup analysis of women with VLs pre-pregnancy through month six post-partum suggested similar pregnancy and post-partum viraemia risk. However, women without any VLs 1 year pre-pregnancy through 2 years post-partum were not eligible for inclusion in the study, and the VL data presented may represent a best-case scenario for women engaged with health care where plausibly there were opportunities for clinical intervention. This raises questions about the health of women who were excluded and consequences for their infants; missing VL data suggests poor healthcare engagement with late third-trimester attendance. The bias associated with incomplete data and attrition would suggest we underestimated viraemia risk. Improved ART and antenatal service linkage, support for women who may become pregnant while in ART care, patient tracing and home-based visits, may be necessary to improve healthcare engagement and follow-up. Further, detection bias in this study is possible as women had more VL tests preconception than in pregnancy or post-partum; repeat VL testing may have been indicated for women already identified as high-risk pre-pregnancy, which would have overestimated viraemia risk. Although our study VL cut-off was stringent, viraemic risk was related mainly to those with clinical failure with 16.8% having VL ≥ 1000 and 7.9% with VLs 50-999 copies/ml. We also cannot exclude mortality in this group, although in this area, maternal mortality is low [58]. We received VL data directly from the laboratory, suggesting information bias related to data collection is less likely. As data analysed were from a real-world setting, we cannot rule out residual confounding due to inaccurate or incomplete covariate measurement, and were unable to adjust for baseline VL and other demographic characteristics such as education level.

Conclusions

This study supports prior studies that identified increased pregnancy and post-partum viraemia risk. Routine VL monitoring with sustained virological suppression is crucial to minimise pregnancy and breastfeeding HIV transmission and maintain maternal health. ART adherence is a major public health concern, especially in pregnant and lactating HIV-infected women on ART. These women require additional support to ensure viral control and limit drug-resistant virus and pregnancy and post-partum MTCT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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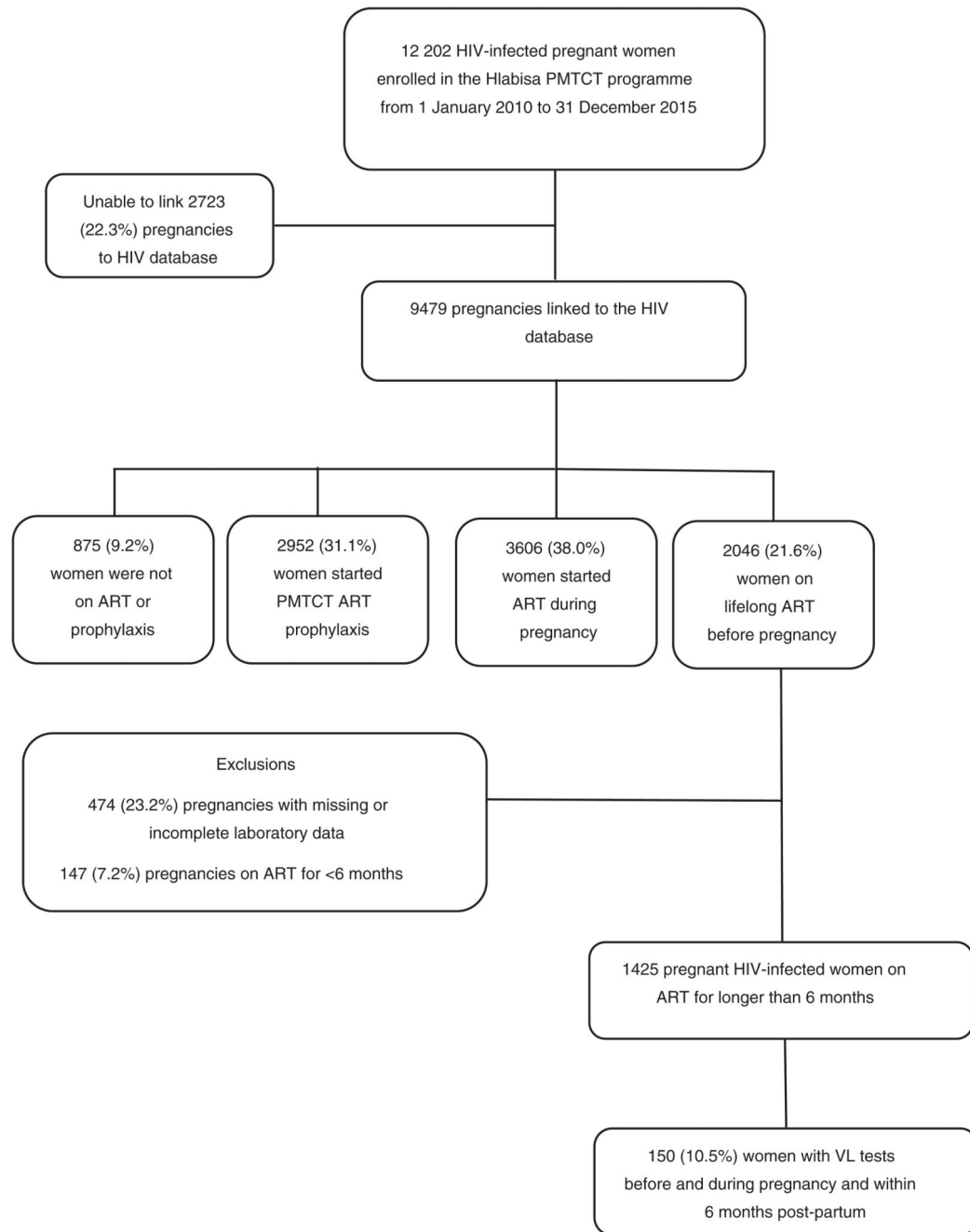


Figure 1. Study inclusions and exclusions.

Table 1

Characteristics of HIV-infected women on ART at pregnancy start ($N = 1425$) and a subgroup of women with VL tests before pregnancy start ($n = 988$), January 2010–December 2015, KwaZulu-Natal, South Africa

Characteristic	Total ($N = 1425$) n (%)	Women by detectable and undetectable VL ($n = 988$)		<i>P</i> -value
		Undetectable VL (<50 copies/ml) ($n = 623$) n (%)	Detectable VL (≥ 50 copies/ml) ($n = 365$) n (%)	
Age at first antenatal visit, median (IQR), years	31 (27–35)	30 (27–34)	32 (29–36)	<0.01
15–24	328 (23.0)	125 (20.1)	65 (17.8)	0.16
25–34	925 (64.9)	403 (64.7)	257 (70.4)	
35–49	172 (12.1)	95 (15.3)	43 (11.8)	
Place of antenatal care				
Peri-urban	370 (26.0)	177 (28.4)	87 (23.8)	0.07
Rural	987 (69.3)	415 (66.6)	267 (73.2)	
Missing	68 (4.8)	31 (5.0)	11 (3.0)	
HIV status disclosure to anyone				
No	34 (2.4)	12 (1.9)	11 (3.0)	<0.01
Yes	936 (65.7)	396 (63.6)	267 (73.2)	
Missing	455 (31.9)	215 (34.5)	87 (23.8)	
Previous PMTCT exposure				
No	425 (29.8)	186 (29.9)	105 (28.8)	0.75
Yes	764 (53.6)	339 (54.4)	196 (53.7)	
Missing	236 (16.6)	98 (15.7)	64 (17.5)	
Gestation at first visit, median (IQR), weeks	23 (16–37)	21 (16–35)	25 (16–38)	0.19
0–19	514 (36.1)	245 (39.3)	125 (34.2)	
20	859 (60.3)	358 (57.5)	231 (63.3)	
Missing	52 (3.7)	20 (3.2)	9 (2.5)	
Gestation at delivery, median (IQR), weeks	39 (38–40)	39 (38–40)	39 (38–40)	0.56
<37	120 (8.4)	50 (8.0)	33 (9.0)	
37	975 (68.4)	425 (68.2)	255 (69.9)	
Missing	330 (23.2)	148 (23.8)	77 (21.1)	
Pre-pregnancy CD4 ⁺ count, median (IQR), cells/mm ³	477 (338–641)	518 (378–671)	424 (299–601)	<0.01
<350	264 (18.5)	107 (17.2)	101 (27.7)	
350	722 (50.7)	404 (64.8)	224 (61.4)	
Missing	439 (30.8)	112 (18.0)	40 (11.0)	
Regimen change prior to or during pregnancy				
No	1222 (85.5)	604 (97.0)	359 (98.4)	0.17
Yes	203 (14.3)	19 (3.0)	6 (1.6)	
Duration on ART, median (IQR), years	2.1 (1.3–3.5)	1.9 (1.1–3.0)	3.0 (1.9–4.6)	<0.01
<3	957 (67.2)	468 (75.1)	177 (48.5)	
3	468 (32.8)	155 (24.9)	188 (51.5)	
ART regimen				

Characteristic	Total (<i>N</i> = 1425) <i>n</i> (%)	Women by detectable and undetectable VL (<i>n</i> = 988)		<i>P</i> -value
		Undetectable VL (<50 copies/ml) (<i>n</i> = 623) <i>n</i> (%)	Detectable VL (≥ 50 copies/ml) (<i>n</i> = 365) <i>n</i> (%)	
TDF-based	791 (55.5)	460 (73.8)	112 (30.7)	<0.01
d4T-based	597 (41.9)	145 (23.3)	243 (66.6)	
ZDV-based	37 (2.6)	18 (2.9)	10 (2.7)	
Calendar delivery year				<0.01
2010	58 (4.1)*	19 (3.1)	28 (7.7)	
2011	206 (14.5)	43 (6.9)	66 (18.1)	
2012	297 (20.8)	102 (16.4)	95 (26.0)	
2013	298 (20.9)	148 (23.8)	65 (17.8)	
2014	327 (23.0)	174 (27.9)	68 (18.6)	
2015	239 (16.8)	137 (22.0)	43 (11.8)	

* Due to rounding up, the percentages in the 1425 women total 100.1%.

Table 2

VL tests subsequent to ART start in 1425 women on ART before pregnancy and subgroup of 150 women with all three VL tests in pregnancy period through 6 months post-partum, 2010–2015, KwaZulu-Natal, South Africa

Viral load (copies/ml)	Overall (N = 1425)					Women with all three VL tests before and during pregnancy and within 6 months post-partum (N = 150)		
	Before pregnancy n = 988 (%)	Pregnancy n = 854 (%)	Post-partum			Before pregnancy n (%)	Pregnancy n (%)	Post-partum, 6 months n (%)
			6 months n = 527 (%)	12 months n = 437 (%)	24 months n = 656 (%)			
<50	810 (82.0)	657 (76.9)	406 (77.0)	330 (75.5)	497 (75.8)	105 (70.0)	103 (68.7)	107 (71.3)
50–999	67 (6.8)	67 (7.8)	38 (7.2)	29 (6.6)	50 (7.6)	17 (11.3)	13 (8.7)	14 (9.3)
1000	111 (11.2)	130 (15.2)	83 (15.7)	78 (17.8)	109 (16.6)	28 (18.7)	34 (22.7)	29 (19.3)

Table 3
Risk factors for viraemia subsequent to ART start between 2010 and 2015 in women who initiated ART before pregnancy ($n = 1425$)

Effect	Unadjusted OR (95% CI)	<i>P</i>	Adjusted OR (95% CI)	<i>P</i>
Pregnancy				
Before pregnancy	Ref	–	Ref	–
During pregnancy	1.29 (0.89–1.86)	0.18	1.31 (0.90–1.92)	0.16
Post-partum, 6 months	1.20 (0.77–1.86)	0.43	1.30 (0.83–2.04)	0.25
Post-partum, 12 months	0.91 (0.55–1.49)	0.70	0.96 (0.58–1.58)	0.86
Post-partum, 24 months	1.26 (0.81–1.96)	0.31	1.40 (0.89–2.22)	0.15
Age (time-varying), years				
25–34	Ref	–	Ref	–
15–24	1.10 (0.52–2.31)	0.80	2.01 (0.96–4.20)	0.06
35–49	0.46 (0.28–0.77)	<0.01	0.33 (0.19–0.55)	<0.01
Pre-pregnancy CD4 ⁺ count, cells/mm ³				
<350	Ref	–	Ref	–
350	0.04 (0.02–0.09)	<0.01	0.05 (0.02–0.11)	<0.01
Missing	0.14 (0.07–0.29)	<0.01	0.21 (0.10–0.43)	<0.01
Regimen change(time-varying)				
No	Ref	–	Ref	–
Yes	1.09 (0.49–2.44)	0.83	0.82 (0.37–1.81)	0.62
ART regimen				
TDF-based	Ref	–	Ref	–
Non-TDF-based	7.11 (3.99–12.65)	<0.01	3.31 (1.61–6.78)	<0.01
ART duration, years				
<3	Ref	–	Ref	–
3	1.74 (0.98–3.10)	0.06	3.03 (1.60–5.73)	<0.01
Gestation at first antenatal visit, weeks				
<20	Ref	–	Ref	–
20	3.37 (1.85–6.17)	<0.01	2.70 (1.50–4.86)	<0.01
Missing	0.69 (0.13–3.58)	0.66	1.21 (0.26–5.72)	0.81
Calendar year of delivery				
2010	Ref	–	Ref	–
2011	2.08 (0.56–7.73)	0.27	1.93 (0.55–6.74)	0.30
2012	0.45 (0.12–1.62)	0.22	0.74 (0.21–2.62)	0.64
2013	0.28 (0.08–1.02)	0.05	0.85 (0.22–3.34)	0.82
2014	0.16 (0.04–0.60)	<0.01	0.67 (0.17–2.71)	0.58
2015	0.10 (0.02–0.40)	<0.01	0.50 (0.11–2.33)	0.38

Antenatal clinic area, prior PMTCT exposure, birth gestation and HIV status disclosure were excluded from the model as $P > 0.2$.

Table 4

Multivariable model of viraemia risk in each pregnancy period, including an interaction term for ART duration and viraemia, between 2010 and 2015 in women who initiated ART before pregnancy ($n = 1425$)

Effect	Unadjusted OR (95% CI)	<i>P</i>	Adjusted OR (95% CI)	<i>P</i>
Pregnancy				
Before pregnancy	Ref	–	Ref	–
During pregnancy	1.29 (0.89–1.86)	0.18	2.25 (1.33–3.78)	<0.01
Post-partum, 6 months	1.20 (0.77–1.86)	0.43	1.81 (1.00–3.29)	0.05
Post-partum, 12 months	0.91 (0.55–1.49)	0.70	1.54 (0.79–3.0)	0.21
Post-partum, 24 months	1.26 (0.81–1.96)	0.31	2.82 (1.55–5.12)	<0.01
Age (time-varying), years				
25–34	Ref	–	Ref	–
15–24	1.10 (0.52–2.31)	0.80	2.19 (1.02–4.72)	0.05
35–49	0.46 (0.28–0.77)	<0.01	0.33 (0.19–0.56)	<0.01
Pregnancy and ART duration, years				
Before pregnancy, <3	Ref	–	Ref	–
During pregnancy, 3	0.28 (0.12–0.63)	<0.01	0.28 (0.12–0.64)	0.02
Post-partum 6 months, 3	0.47 (0.17–1.29)	0.15	0.47 (0.17–1.29)	0.14
Post-partum 12 months, 3	0.28 (0.09–0.90)	<0.01	0.28 (0.09–0.90)	0.03
Post-partum 24 months, 3	0.10 (0.03–0.31)	<0.01	0.11 (0.03–0.35)	<0.01
Pre-pregnancy CD4⁺ count, cells/mm³				
<350	Ref	–	Ref	–
350	0.04 (0.02–0.09)	<0.01	0.05 (0.02–0.10)	<0.01
Missing	0.14 (0.07–0.29)	<0.01	0.19 (0.09–0.41)	<0.01
Regimen change (time-varying)				
No	Ref	–	Ref	–
Yes	1.09 (0.49–2.44)	0.83	0.82 (0.36–1.84)	0.62
ART regimen				
TDF-based	Ref	–	Ref	–
Non-TDF-based	7.11 (3.99–12.65)	<0.01	3.43 (1.63–7.21)	<0.01
ART duration, years				
<3	Ref	–	Ref	–
3	1.74 (0.98–3.10)	0.06	7.11 (3.14–16.10)	<0.01
Gestation at first antenatal visit, weeks				
<20	Ref	–	Ref	–
20	3.37 (1.85–6.17)	<0.01	2.83 (1.54–5.20)	<0.01
Missing	0.69 (0.13–3.58)	0.66	1.23 (0.25–6.09)	0.80
Calendar year of delivery				
2010	Ref	–	Ref	–
2011	2.08 (0.56–7.73)	0.27	1.98 (0.55–7.15)	0.30
2012	0.45 (0.12–1.62)	0.22	0.74 (0.20–2.71)	0.65
2013	0.28 (0.08–1.02)	0.05	0.83 (0.20–3.37)	0.79

Effect	Unadjusted OR (95% CI)	<i>P</i>	Adjusted OR (95% CI)	<i>P</i>
2014	0.16 (0.04–0.60)	<0.01	0.66 (0.16–2.77)	0.57
2015	0.10 (0.02–0.40)	<0.01	0.50 (0.10–2.42)	0.39

Antenatal clinic area, prior PMTCT exposure, birth gestation and HIV status disclosure were excluded from the model as $P>0.2$.

Table 5

Multivariable model of viraemia risk in each pregnancy period, including an interaction term for age at pregnancy start and pregnancy period, in women who initiated ART before pregnancy between 2010 and 2015 ($n = 1425$)

Effect	Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Pregnancy				
Before pregnancy	Ref	–	Ref	–
During pregnancy	1.29 (0.89–1.86)	0.18	1.89 (1.16–3.09)	0.01
Post-partum, 6 months	1.20 (0.77–1.86)	0.43	1.58 (0.88–2.83)	0.13
Post-partum, 12 months	0.91 (0.55–1.49)	0.70	1.16 (0.61–2.23)	0.65
Post-partum, 24 months	1.26 (0.81–1.96)	0.31	1.36 (0.76–2.43)	0.30
Age at pregnancy start, years				
25–34	Ref	–	Ref	–
15–24	1.10 (0.52–2.31)	0.80	2.77 (0.94–8.17)	0.07
35–49	0.46 (0.28–0.77)	<0.01	0.82 (0.36–1.85)	0.63
Pregnancy period and age at pregnancy start, years				
Before pregnancy, 24–35	Ref	–	Ref	–
During pregnancy, 15–24	1.26 (0.39–4.04)	0.70	1.27 (0.39–4.11)	0.69
During pregnancy, 35–49	0.17 (0.07–0.43)	<0.01	0.17 (0.07–0.42)	<0.01
Post-partum 6 months, 15–24	0.68 (0.18–2.61)	0.58	0.65 (0.17–2.45)	0.53
Post-partum 6 months, 35–49	0.39 (0.13–1.14)	0.09	0.38 (0.13–1.11)	0.08
Post-partum 12 months, 15–24	1.28 (0.28–5.88)	0.75	0.99 (0.21–4.55)	0.99
Post-partum 12 months, 35–49	0.25 (0.07–0.83)	0.02	0.25 (0.08–0.86)	0.03
Post-partum 24 months, 15–24	2.37 (0.54–10.34)	0.25	1.66 (0.39–7.13)	0.50
Post-partum 24 months, 35–49	0.36 (0.12–1.03)	0.06	0.36 (0.12–1.03)	0.06
Pre-pregnancy CD4 ⁺ , cells/mm ³				
<350	Ref	–	Ref	–
350	0.04 (0.02–0.09)	<0.01	0.05 (0.02–0.10)	<0.01
Missing	0.14 (0.07–0.29)	<0.01	0.20 (0.09–0.42)	<0.01
Regimen change (time-varying)				
No	Ref	–	Ref	–
Yes	1.09 (0.49–2.44)	0.83	0.82 (0.36–1.84)	0.62
ART regimen				
TDF-based	Ref	–	Ref	–
Non-TDF-based	7.11 (3.99–12.65)	<0.01	3.35 (1.60–7.02)	0.01
ART duration, years				
<3	Ref	–	Ref	–
3	1.74 (0.98–3.10)	0.06	3.20 (1.65–6.21)	0.01
Gestation at first antenatal visit, weeks				
<20	Ref	–	Ref	–
20	3.37 (1.85–6.17)	<0.01	2.78 (1.52–5.10)	0.01
Missing	0.69 (0.13–3.58)	0.66	1.10 (0.22–5.46)	0.91

Effect	Unadjusted OR (95% CI)	<i>P</i>	Adjusted OR (95% CI)	<i>P</i>
Calendar year of delivery				
2010	Ref		Ref	–
2011	2.08 (0.56–7.73)	0.27	2.17 (0.60–7.87)	0.24
2012	0.45 (0.12–1.62)	0.22	0.75 (0.20–2.78)	0.67
2013	0.28 (0.08–1.02)	0.05	0.89 (0.22–3.62)	0.87
2014	0.16 (0.04–0.60)	<0.01	0.69 (0.16–2.88)	0.61
2015	0.10 (0.02–0.40)	<0.01	0.49 (0.10–2.39)	0.38

Antenatal clinic area, prior PMTCT exposure, calendar birth year, birth gestation and HIV status disclosure were excluded as $P > 0.2$.