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

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**Abstract**

**Objectives**

Pregnancy and postpartum viral load (VL) suppression is critical to prevent mother-to-child HIV transmission (MTCT) 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 (OR) 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 VLs; 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, VL was ≥1000 copies/ml in 15.2%, 15.7%, 17.8%, and 16.6% respectively; VL<50 was 76.9%, 77%, 75.5% and 75.8%, respectively.

Adjusting for age, clinical and pregnancy factors, viraemia risk (VL ≥50 copies/ml) was not significantly associated with pregnancy [adjusted OR (aOR) 1.31; 95% confidence interval (CI) 0.90-1.92], six month (aOR 1.30; 95% CI 0.83-2.04), 12 month (aOR 0.96; 95% CI 0.58-1.58) and 24 month (aOR 1.40; 95% CI 0.89-2.22) postpartum period. Adjusting for ART duration-pregnancy period interaction, viraemia risk was 1.8 and two-fold higher during pregnancy and postpartum, respectively.

**Conclusions**

While undetectable VL before pregnancy through postpartum was high, the UNAIDS goal to suppress 90% of women was not met. Women on preconception ART remain vulnerable to viraemia; additional support is required to prevent MTCT and maintain maternal health.

**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 is proportional to maternal VL level 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 four-fold versus VL <50 copies/ml (9).

With expanded ART access (13–16), HIV infected women are increasingly likely to conceive on ART. Maintaining viral suppression may be particularly challenging during pregnancy and postpartum 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 UK, women on preconception ART and women starting pregnancy ART had a higher risk of postpartum 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 independent from antenatal care (24,25).

With the expanding treatment eligibility in South Africa (16), more HIV infected women will conceive on ART (27). 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 (28,29), northern KwaZulu-Natal, were eligible for inclusion. Women needed to be (i) on ART at least six months pre-pregnancy; (ii) not pregnant at ART initiation; (iii) age 15-49 years at pregnancy start; (iv) attending from 2010-2015; and (v) have at least one VL test one year pre-pregnancy to two 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 tests results weekly including CD4+ per cent/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 (28).

*Pregnancy and postpartum definition*

Pregnancy start was defined as last menstrual period date (LMP); 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 categorized 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 postpartum. The postpartum period was further categorized as: first six months postpartum (postpartum, six months); 7-12 months postpartum (postpartum, 12 months); 13-24 months postpartum (postpartum, 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 (29). VL testing was recommended six monthly until one year post-ART initiation; thereafter annually (30). Pregnancy VL testing to determine virological suppression before delivery started in 2015 (31). 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-square 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 (peri-urban, 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 (28). ART regimens were initially categorized as TDF-based, stavudine-based (d4T-based) or zidovudine-based (ZDV-based) (32,33). 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 cutoff 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) 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 postpartum (34). 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 (35,36). 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 (37). 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 the12,202 pregnancies in HIV-infected women (77.7%) (Fig. 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 was missing, and 147 women initiated on ART less than six 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*<0.001). Thus the study population was 1425 women on ART for ≥ six 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) 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 postpartum (Table 2), of whom 7.2%, 6.6% and 7.6% had VL 50-999 copies/ml, respectively. VL was ≥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 postpartum (n=150)*

There were 150 women with VL tests pre-pregnancy through six month postpartum. 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-, 22.7% during and 19.3% post-pregnancy (Table 2).

Of 45 women with unsuppressed pre-pregnancy VL, 12 (26.7%) suppressed antenally, 9 (20.0%) had VL 50-999 copies/ml, and 24 (53.3%) had pregnancy VL ≥1000. Within six months postpartum, 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 six months postpartum, 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 seven-fold and ART duration ≥3 years was marginally associated with viraemia risk. First ANC visit ≥20 weeks increased pregnancy viraemia risk to 3.37 (*p*<0.001). 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 postpartum viraemia risk non-significantly increased to 1.3 to 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 three-fold 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 postpartum period, with variables from Table 3 (Table 4), pregnancy, six and 24 month postpartum viremia risk significantly increased to 2.25, 1.81 and 2.82, respectively. Viraemia risk lowered during pregnancy and postpartum if on ART for ≥3 years (12, 24 months). Age <25 and >34 also significantly affected viraemia risk (adjusted OR 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 compared to pre-pregnancy, but the increased viraemia risk postpartum was not significant. Although the pregnancy and 12 month interaction term were significant in age >34, the aOR for other covariates were substantially altered; the age aOR lost statistical significance.

In 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 postpartum (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 postpartum 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 postpartum.

In our study, pre-pregnancy virological suppression reached 82%, narrowly missing the 90% UNAIDS goal. In prior research including South Africa, viral suppression among pregnant or breastfeeding women ranged from 27 to 78% (22,38,39). Conversely, in Malawi and Uganda, over 90% were suppressed (40,41).

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 [aHR 1.34; 95% CI 1.02 to 1.78] (42). 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 (43) or in three other studies with smaller sample sizes (44–46). 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).

Postpartum viraemia risk in our study corroborates a UK study of 19 HIV clinics where 623 women on preconception ART had higher rebound postpartum 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 postpartum VLs >400 copies/ml between 3-24 months (47). While differing designs, ART regimens and study populations complicate interpretation, a commonality between studies are postpartum issues which limit viral control (48).

We showed increased pregnancy and postpartum 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 (37). 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 postpartum 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 (49). 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 is needed to tease out the ART duration effects on the risk of viraemia, particularly adherence measures during pregnancy and postpartum (50).

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 (23,42,49). In nine Southern African countries, adolescents were more likely to have imperfect adherence versus adults, and adolescents with virologic suppression had shorter viral rebound time versus adults (aHR 2.03; 95% CI 1.31–3.13) (36).

There are several reasons for compromised viral control during the pregnancy and postpartum. Pregnancy may affect HIV-related outcomes through physiological, immunological, and hormonal changes that compromise adherence, lower drug levels to sub-therapeutic and increase ART resistance (54–56). Late antenatal attendance may also affect viral control, as observed in this study. Conversely, frequent ANC visits may improve VL control (49). 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 (30). From 2015, pregnant women received HIV care within antenatal clinics (31); 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 postpartum (26,40,57,58), a crucial period for virological control to minimise breastfeeding transmission risk. In Malawi, age <24 and poor adherence were associated with two-fold non-retention risk; patients on Option B+ had higher attrition than non-pregnant women initiating ART (26). Similar results have been observed in South African pregnant women on ART for their own health, with attrition higher postpartum than antenatally (59). Myer et al have suggested that postnatal services prioritise childcare, and women with chronic conditions such as HIV require additional support to manage their health (48). Healthcare disengagement drivers are complex and multifactorial requiring comprehensive interventions (48).

MTCT risk increases almost three-fold per log10 increase in VL (60), 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 three and six months in women initiating pregnancy ART) with results reviewed within two weeks (31). In women with VL under 1000 copies, six monthly VL testing is recommended through pregnancy and breastfeeding; VL is repeated in one month with virologic failure. As pregnancy and breastfeeding is time-sensitive, even one 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 (61). Although our study VL cutoff was stringent, viraemic risk was related mainly to those with clinical failure, with 16.8% having VL ≥1000 and 7.9% with VL 50-999 copies/ml. 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 (31).

**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 (62) and is generalisable to other rural public health programmes in sub-Saharan Africa. While South Africa recognizes the necessity for pregnancy VL monitoring (31), 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 postpartum period increase viraemia risk in women on pre-pregnancy ART.

Subgroup analysis of women with VLs pre-pregnancy through month six postpartum suggested similar pregnancy and postpartum viraemia risk. However, women without any VLs one year pre-pregnancy through two years postpartum 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 health care 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 health care engagement and follow-up. Further, detection bias in this study is possible as women had more VL tests preconception than in pregnancy or postpartum; 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 cutoff 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 (63). We received VL data directly from the laboratory suggesting information bias related to data collection is less likely. As data analysed was 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 postpartum viraemia risk. Routine VL monitoring with sustained virologic 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 postpartum MTCT.

**Abbreviations**

ANC: Antenatal clinic; aHR: Adjusted hazards ratio; aOR: Adjusted odds ratio; ART: Antiretroviral therapy; ZDV: Zidovudine; CI: Confidence interval; d4T: Stavudine; DoH: Department of Health; HIV: Human Immunodeficiency Virus; HR: Hazards ratio; LMP: Last menstrual period; MTCT: mother-to-child transmission; NHLS: National Health Laboratory Service; TDF: Tenofovir; VL: Viral load

**Declarations of interest**

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**Contributors:** TC contributed to the data collection and curation, performed the data analysis, and wrote the first draft. MLN, CT, and AC contributed to the study design, commented on the results and all subsequent drafts.

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**Competing interest:** None declared

**Ethics approval**: University of KwaZulu-Natal Biomedical Research Ethics Committee

**Data sharing statement:** Further information about the data can be obtained from the corresponding author (tchetty@africacentre.ac.za) or from the Africa Centre website ([www.africacentre.ac.za](file:///C%3A%5CUsers%5Ctchetty%5CDesktop%5CWork%20to%20do%5Cwww.africacentre.ac.za)). Access to the dataset is available with permission from the data team at the Africa Centre.

**References**

1. Duri K, Gumbo FZ, Kristiansen KI, et al. Antenatal HIV-1 RNA load and timing of mother to child transmission; a nested case-control study in a resource poor setting. Virol J. 2010 Aug 2;7(1):176.

2. Garcia PM, Kalish LA, Pitt J, et al. Maternal Levels of Plasma Human Immunodeficiency Virus Type 1 RNA and the Risk of Perinatal Transmission. N Engl J Med. 1999 Aug 5;341(6):394–402.

3. European Collaborative Study. Mother-to-child transmission of HIV infection in the era of highly active antiretroviral therapy. Clin Infect Dis. 2005;40(458–65).

4. Hoffman RM, Black V, Technau K, et al. Effects of highly active antiretroviral therapy duration and regimen on risk for mother-to-child transmission of HIV in Johannesburg, South Africa. J Acq Immune Defic Syndr. 2010 Mar 1;54(1):35–41.

5. Townsend CL, Byrne L, Cortina-Borja M, et al. Earlier initiation of ART and further decline in mother-to-child HIV transmission rates, 2000-2011. AIDS. 2014 Apr 24;28(7):1049–57.

6. Cooper ER, Charurat M, Mofenson L, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. J Acquir Immune Defic Syndr. 2002;29(5):484–94.

7. Shaffer N, Chuachoowong R, Mock PA, et al. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. Lancet. 1999 Mar;353(9155):773–80.

8. Townsend CL, Cortina-Borja M, Peckham CS, et al. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland , 2000 – 2006. AIDS. 2008;22(8):973–81.

9. Mandelbrot L, Tubiana R, Le Chenadec J, et al. No Perinatal HIV-1 Transmission From Women With Effective Antiretroviral Therapy Starting Before Conception. Clin Infect Dis. 2015 Jul 21;61(1 December):1715–25.

10. Alcantara KC, Lins J, Albuquerque M, et al. HIV-1 mother-to-child transmission and drug resistance among Brazilian pregnant women with high access to diagnosis and prophylactic measures. J Clin Virol. 2012 May;54(1):15–20.

11. Ioannidis JP, Abrams EJ, Ammann A, et al. Perinatal transmission of human immunodeficiency virus type 1 by pregnant women with RNA virus loads. J Infect Dis. 2001 Feb 15;183(4):539–45.

12. Mayaux MJ, Dussaix E, Isopet J, et al. Maternal virus load during pregnancy and mother-to-child transmission of human immunodeficiency virus type 1: the French perinatal cohort studies. SEROGEST Cohort Group. J Infect Dis. 1997 Jan;175(1):172–5.

13. World Health Organisation. WHO Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach June 2013. Geneva: World Health Organization; 2013.

14. UNAIDS. 2015 Progress Report on the Global Plan towards the elimination of new HIV infections among children and keeping their mothers alive [Internet]. 2015. Available from: http://www.unaids.org/en/resources/documents/2015/JC2774\_2015ProgressReport\_GlobalPlan

15. UNAIDS. The Gap Report [Internet]. Geneva; 2014 [cited 2016 Jun 16]. Available from: www.unaids.org/en/resources/campaigns/2014/2014gapreport/gapreport

16. South African National Department of Health. Re: Implementation of the Universal Test and Treat strategy for HIV Positive patients and differentiated care for stable patients [Internet]. 2016 [cited 2017 Mar 22]. Available from: www.sahivsoc.org/.../22 8 16 Circular UTT Decongestion...

17. Nachega JB, Uthman OA, Anderson J, et al. Adherence to antiretroviral therapy during and after pregnancy in low-income, middle-income, and high-income countries: a systematic review and meta-analysis. AIDS. NIH Public Access; 2012 Oct 23;26(16):2039–52.

18. Mepham S, Zondi Z, Mbuyazi a, Mkhwanazi N, Newell ML. Challenges in PMTCT antiretroviral adherence in northern KwaZulu-Natal, South Africa. AIDS Care. 2011;23(6):741–7.

19. El-Khatib Z, Katzenstein D, Marrone G, et al. Adherence to drug-refill is a useful early warning indicator of virologic and immunologic failure among HIV patients on first-line art in South Africa. Maartens G, editor. PLoS One. 2011 Mar 9;6(3):e17518.

20. Ramadhani HO, Thielman NM, Landman KZ, et al. Predictors of Incomplete Adherence, Virologic Failure, and Antiviral Drug Resistance among HIV-Infected Adults Receiving Antiretroviral Therapy in Tanzania. Clin Infect Dis. 2007 Dec 1;45(11):1492–8.

21. Bennett DE, Jordan MR, Bertagnolio S, et al. HIV drug resistance early warning indicators in cohorts of individuals starting antiretroviral therapy between 2004 and 2009: World Health Organization global report from 50 countries. Clin Infect Dis. Oxford University Press; 2012 May;54 Suppl 4(Suppl 4):S280-9.

22. Gill MM, Hoffman HJ, Bobrow EA, et al. Detectable Viral Load in Late Pregnancy among Women in the Rwanda Option B+ PMTCT Program: Enrollment Results from the Kabeho Study. Blackard J, editor. PLoS One. WHO Department of HIV/AIDS; 2016 Dec 22;11(12):e0168671.

23. Huntington S, Thorne C, Newell M-L, et al. The risk of viral rebound in the year after delivery in women remaining on antiretroviral therapy. AIDS. 2015;29(17):2269–78.

24. Nachega JB, Uthman OA, Anderson J, et al. Adherence to Antiretroviral Therapy During and After Pregnancy in Low-, Middle and High Income Countries: A Systematic Review and Meta-Analysis. AIDS. 2012;26(16):2039–52.

25. Haas AD, Msukwa MT, Egger M, et al. Adherence to Antiretroviral Therapy during and after Pregnancy: Cohort Study on Women Receiving Care in Malawi’s Option B+ Program. Clin Infect Dis. 2016;63(9):1227–35.

26. Haas AD, Tenthani L, Msukwa MT, et al. Retention in care during the first 3 years of antiretroviral therapy for women in Malawi’s option B+ programme: an observational cohort study. Lancet HIV. Elsevier Ltd; 2016;3(4):e175–82.

27. Benton L. Childbearing in a Time of ART: Birth Rates, Childbearing Desires and Family Planning in a Rural HIV Treatment and Care Programme in South Africa. University College London; 2015.

28. Chetty T, Thorne C, Tanser F, Bärnighausen T, Coutsoudis A. Cohort profile: the Hlabisa pregnancy cohort, KwaZulu-Natal, South Africa. BMJ Open. British Medical Journal Publishing Group; 2016 Oct 17;6(10):e012088.

29. Houlihan CF, Bland RM, Mutevedzi PC, et al. Cohort profile: Hlabisa HIV Treatment and Care Programme. Int J Epidemiol. 2011;40(2):318–26.

30. South African Department of Health. The South African Antiretroviral Treatment Guidelines [Internet]. Department of Health; 2013 [cited 2016 Jun 16]. p. 1–21. Available from: http://www.sahivsoc.org/upload/documents/2013 ART Treatment Guidelines Final 25 March 2013.pdf

31. National Department of Health South Africa. National Consolidated Guidelines For The Prevention Of Mother-to-Child Transmission of HIV (PMTCT) And The Management of HIV In Children, Adolescents And Adults [Internet]. Pretoria; 2015 [cited 2016 Jun 16]. Available from: http://www.up.ac.za/media/shared/62/ZP\_Files/art-guidelines-15052015.zp57683.pdf

32. Scarsi KK, Eisen G, Darin KM, et al. Superior Effectiveness of Zidovudine Compared With Tenofovir When Combined With Nevirapine-based Antiretroviral Therapy in a Large Nigerian Cohort. Clin Infect Dis. Oxford University Press; 2016 Feb 15;62(4):512–8.

33. Joly V, Flandre P, Meiffredy V, et al. Efficacy of zidovudine compared to stavudine, both in combination with lamivudine and indinavir, in human immunodeficiency virus-infected nucleoside-experienced patients with no prior exposure to lamivudine, stavudine, or protease inhibitors (novavir trial). Antimicrob Agents Chemother. American Society for Microbiology (ASM); 2002 Jun;46(6):1906–13.

34. Huh D, Flaherty BP, Simoni JM. Optimizing the analysis of adherence interventions using logistic generalized estimating equations. AIDS Behav. NIH Public Access; 2012 Feb;16(2):422–31.

35. Heestermans T, Browne JL, Aitken SC, Vervoort SC, Klipstein-Grobusch K. Determinants of adherence to antiretroviral therapy among HIV-positive adults in sub-Saharan Africa: a systematic review. BMJ Glob Heal. 2016;1(4):e000125.

36. Nachega JB, Hislop M, Nguyen H, et al. Antiretroviral therapy adherence, virologic and immunologic outcomes in adolescents compared with adults in southern Africa. J Acq Immune Defic Syndr. NIH Public Access; 2009 May 1;51(1):65–71.

37. Ryscavage P, Kelly S, Li JZ, Harrigan PR, Taiwo B. Significance and clinical management of persistent low-level viremia and very-low-level viremia in HIV-1-infected patients. Antimicrob Agents Chemother. American Society for Microbiology; 2014 Jul 1;58(7):3585–98.

38. Maman D, Huerga H, Etard JF, et al. Most breastfeeding women with high viral load are still undiagnosed in sub-Saharan Africa. Conf Retroviruses Opportunistic Infect. Seattle, Washington,; 2015;

39. Myer L, Phillips TK, Hsiao N-Y, et al. Plasma viraemia in HIV-positive pregnant women entering antenatal care in South Africa. J Int AIDS Soc. The International AIDS Society; 2015 Jul 6;18:20045.

40. Haas AD, Msukwa MT, Egger M, et al. Adherence to Antiretroviral Therapy during and after Pregnancy: Cohort Study on Women Receiving Care in Malawi’s Option B+ Program. Clin Infect Dis. 2016;63(9).

41. Matthews LT, Ribaudo HB, Kaida A, et al. HIV-Infected Ugandan Women on Antiretroviral Therapy Maintain HIV-1 RNA Suppression Across Periconception, Pregnancy, and Postpartum Periods. J Acq Immune Defic Syndr. 2016 Apr 1;71(4):399–406.

42. Westreich D, Cole SR, Nagar S, et al. Pregnancy and Virologic Response to Antiretroviral Therapy in South Africa. PLoS One. 2011;6(8):e22778.

43. Kourtis AP, Wiener J, King CC, et al. Effect of Pregnancy on Response to Antiretroviral Therapy in HIV-Infected African Women. J Acq Immune Defic Syndr. Wolters Kluwer Health; 2017 Jan 1;74(1):38–43.

44. Melekhin V V., Shepherd BE, Stinnette SE, et al. Antiretroviral therapy initiation before, during, or after pregnancy in HIV-1-infected women: maternal virologic, immunologic, and clinical response. Myer L, editor. PLoS One. Public Library of Science; 2009 Jan 9;4(9):e6961.

45. Mayanja BN, Shafer LA, Van der Paal L, et al. Effect of pregnancy on immunological and virological outcomes of women on ART: a prospective cohort study in rural Uganda, 2004-2009. Trop Med Int Heal. 2012 Mar;17(3):343–52.

46. Keiser O, Gayet-Ageron AA, Rudin C, et al. Antiretroviral treatment during pregnancy. AIDS. 2008 Nov 12;22(17):2323–30.

47. Ngarina M, Kilewo C, Karlsson K, et al. Virologic and immunologic failure, drug resistance and mortality during the first 24 months postpartum among HIV-infected women initiated on antiretroviral therapy for life in the Mitra plus Study, Dar es Salaam, Tanzania. BMC Infect Dis. 2015 Jan;15:175.

48. Myer L, Phillips TK. Beyond &quot; Option B+ &quot; : Understanding Antiretroviral Therapy (ART) Adherence, Retention in Care and Engagement in ART Services Among Pregnant and Postpartum Women Initiating Therapy in Sub-Saharan Africa. J Acquir Immune Defic Syndr. 2017;75:115–22.

49. Denoeud-Ndam L, Fourcade C, Ogouyemi-Hounto A, et al. Predictive factors of plasma HIV suppression during pregnancy: a prospective cohort study in Benin. Tang JW, editor. PLoS One. Public Library of Science; 2013 Jan 15;8(3):e59446.

50. Claborn KR, Meier E, Miller MB, Leffingwell TR. A systematic review of treatment fatigue among HIV-infected patients prescribed antiretroviral therapy. Psychol Heal Med. NIH Public Access; 2015;20(3):255–65.

51. Stadeli KM, Richman DD. Rates of emergence of HIV drug resistance in resource-limited settings: a systematic review. Antivir Ther. 2013;18(1):115–23.

52. Tang MW, Kanki PJ, Shafer RW. A review of the virological efficacy of the 4 World Health Organization-recommended tenofovir-containing regimens for initial HIV therapy. Clin Infect Dis. Oxford University Press; 2012 Mar;54(6):862–75.

53. Takuva S, Louwagie G, Zuma K, Okello V. Durability of First Line Antiretroviral Therapy: Reasons and Predictive Factors for Modifications in a Swaziland Cohort. J Antivir Antiretrovir. OMICS International; 2012 Jan 26;4(1):014–20.

54. van Hasselt JGC, Andrew MA, Hebert MF, et al. The Status of Pharmocometrics in Pregnancy: Highlights from the 3(rd) Conference on Pharmacometrics. Br J Clin Pharmacol. 2012;74(6):932–9.

55. Westreich D, Rosenberg M, Schwartz S, Swamy G. Representation of women and pregnant women in HIV research: a limited systematic review. PLoS One. 2013 Jan 23;8(8):e73398.

56. Chi BH, Sinkala M, Stringer EM, et al. Early clinical and immune response to NNRTI-based antiretroviral therapy among women with prior exposure to single-dose nevirapine. AIDS. 2007 May 11;21(8):957–64.

57. Sha BE, Tierney C, Cohn SE, et al. Postpartum viral load rebound in HIV-1-infected women treated with highly active antiretroviral therapy: AIDS Clinical Trials Group Protocol A5150. HIV Clin Trials. Jan;12(1):9–23.

58. Ngarina M, Popenoe R, Kilewo C, Biberfeld G, Ekstrom AM. Reasons for poor adherence to antiretroviral therapy postnatally in HIV-1 infected women treated for their own health: experiences from the Mitra Plus study in Tanzania. BMC Public Health. 2013;13:450.

59. Phillips T, Thebus E, Bekker L-G, et al. Disengagement of HIV-positive pregnant and postpartum women from antiretroviral therapy services: a cohort study. J Int AIDS Soc. 2014 Jan;17:19242.

60. Thea DM, Steketee RW, Pliner V, et al. The effect of maternal viral load on the risk of perinatal transmission of HIV-1. New York City Perinatal HIV Transmission Collaborative Study Group. AIDS. 1997 Mar 15;11(4):437–44.

61. Myer L, Essajee S, Broyles LN, et al. Pregnant and breastfeeding women: A priority population for HIV viral load monitoring. PLOS Med. 2017;14(8):e1002375.

62. Tanser F, Bärnighausen T, Grapsa E, Zaidi J, Newell M-L. High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa. Science (80- ). 2013 Feb 21;339(6122):966–71.

63. Tlou B, Sartorius B, Tanser F. Space-time patterns in maternal and mother mortality in a rural South African population with high HIV prevalence (2000-2014): results from a population-based cohort. BMC Public Health. BioMed Central; 2017 Jun 3;17(1):543.