Achieving maternal viral load suppression for elimination of mother-to-child transmission of HIV in South Africa

Moyo, Faith[a,b,c,*]; Mazanderani, Ahmad Haeri[a,d]; Murray, Tanya[a,c]; Sherman, Gayle G.[a,c,e]; Kufa, Tendesayi[a,b]

[a]Centre for HIV & STIs, National Institute for Communicable Diseases, National Health Laboratory Service

[b]School of Public Health, Faculty of Health Sciences, University of the Witwatersrand

[c]Paediatric HIV Diagnostics Division, Wits Health Consortium, Johannesburg

[d]Department of Medical Virology, Faculty of Health Sciences, University of Pretoria, Pretoria

[e]Department of Paediatrics and Child Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa.

*Correspondence to Faith Moyo, Centre for HIV & STIs, National Institute for Communicable Diseases, 1 Modderfontein Road, Sandringham, Johannesburg, South Africa. Tel: +27 11 555 0467; mobile: +27 84 596 3622; e-mail: faithmo@nicd.ac.za

Abstract

Objective: To describe changes in maternal viral control over time in South African women living with HIV (WLHIV) using surveillance data from the National Health Laboratory Service's Corporate Data Warehouse (NHLS CDW).

Design: A retrospective cohort analysis of maternal viral load during pregnancy and up to 15 months postpartum was performed amongst WLHIV (15–49 years) within the public-health sector between 2016 and 2017.

Methods: HIV and pregnancy-related test data were used to create a synthetic cohort of pregnant WLHIV from the NHLS CDW. Syphilis-screening, in association with ward type and/or postpregnancy cervical screening and/or birth HIV test and/or positive β-hCG, was used as a proxy for pregnancy. The syphilis-screening date marked the first antenatal care visit (fANC). Fractional polynomial models described viral load evolution from fANC up to 15 months postdelivery. Piecewise linear regression models determined factors associated with viral load decline.

Findings: Among 178 319 pregnant WLHIV, 345 174 viral load tests were performed [median = 2 (IQR: 2–3) per woman]. At fANC, 85 545 (48%) women were antiretroviral therapy (ART) experienced; 88 877 (49.8%) were not and 3897 (2.2%) unknown. Proportions of viraemia (viral load ≥50 copies/ml) were 39 756 (53.6%) at first viral load performed during pregnancy, 14 780 (36.9%) at delivery and 24 328 (33.5%) postpartum. Maternal age at least 25 years, $CD4^+$ cell count at least 500 cells/μl and viral load less than 50 copies/ml at baseline predicted sustained viral load suppression during follow-up.

Conclusion: Despite high-ART coverage among pregnant women in South Africa, only 63% of WLHIV achieved viral load less than 50 copies/ml at delivery. Maternal viral load monitoring requires prioritization for maternal health and eMTCT.

Keywords: mother-to-child transmission; postpartum; pregnancy; viral load HIV; viral suppression

Introduction

One in three pregnant women accessing antenatal care (ANC) in the public health sector in 2017 were living with HIV in South Africa and HIV testing and antiretroviral therapy (ART) initiation rates amongst antenatal care (ANC) clients were near universal at 97 and 98%, respectively [1]. Thus, the national prevention of mother-to-child transmission of HIV (PMTCT) programme had achieved the first and second UNAIDS 90–90–90 targets for pregnant women [2]. The early infant diagnosis programme demonstrated a national intrauterine transmission rate of less than 1% by 2017 [3]. Hence the programme focus has shifted from PMTCT to eliminating mother-to-child transmission of HIV (eMTCT), defined as fewer than 50 cases per 100 000 live births at the end of the breastfeeding period [4].

Notwithstanding past programme successes, efforts towards eMTCT are challenged by several well described factors including an extremely high maternal seroprevalence rate of 30% where a MTCT rate of 1% equates to a paediatric HIV incidence of five times the eMTCT target [4]. Additionally, suboptimal viral suppression among pregnant women living with HIV (WLHIV) [5] is common and has been associated with increased risk of perinatal transmission. Ending paediatric HIV requires virological suppression throughout the continuum of PMTCT care with HIV viral load monitoring among pregnant and breastfeeding WLHIV being central to any PMTCT programme steering towards eMTCT. Regrettably, HIV viral load monitoring among pregnant and breastfeeding WLHIV in South Africa remains poor [6].

In 2013, South Africa scaled up HIV viral load testing as a monitoring strategy for the national HIV response [7]. HIV VL monitoring was recommended at 6 and 12 months post-initiation for WLHIV initiating ART during pregnancy or breastfeeding, and at first ANC (fANC) booking for WLHIV on ART prior to pregnancy [8]. In 2015, the guidelines extended HIV viral load monitoring to 6-monthly monitoring during pregnancy and breastfeeding for all WLHIV on ART [9]. An HIV viral load 3 months post-ART initiation was recommended for WLHIV newly diagnosed during pregnancy or the breastfeeding period. For both groups, a viral load at least 1000 copies/ml prompted comprehensive adherence counselling and a repeat HIV viral load test within 1 to 2 months. In October 2019, the guidelines were revised yet again, attempting to improve HIV viral load monitoring among pregnant and breastfeeding WLHIV as follows: HIV viral load test at delivery for all pregnant WLHIV and HIV viral load suppression threshold revised from less than 1000 to less than 50 copies/ml [10]. The latter was, in part, aimed at minimizing MTCT risk associated with low-level and transient viraemia [11,12].

Despite policy provisions, there is a paucity of data on changes in maternal HIV viral load over time during pregnancy and the postpartum period in South Africa. Studies from routine settings in the Western Cape followed pregnant WLHV initiating ART from the fANC visit up to 12 months postpartum and reported HIV viral loads of less than 50 copies/ml in 70–73% of pregnant WLHIV at delivery, low-level viraemia (50 to <1000 copies/ml) in 8% and at least 1000 copies/ml in 22% of the women throughout follow-up [13,14]. As the HIV epidemic in the Western Cape differs from the rest of the country, these findings may not be

generalizable across the country. Using a national laboratory dataset, we describe changes in maternal HIV viral load over time during pregnancy, through delivery and up to 15 months postpartum among pregnant WLHIV receiving care in the public health sector in South Africa.

Methods

Setting

Approximately one million women are pregnant across South Africa annually [15]. Majority of these women access ANC in the public health sector [16]. Upon confirmation of pregnancy, all pregnant women should commence ANC at local clinics or at Midwife Obstetric Units [17]. At the fANC visit, pregnant women undergo a series of health screening checks including syphilis and HIV. Maternal syphilis testing coverage was reported at more than 96% in 2017 [1]. Current guidelines for Sexually Transmitted Infections (STIs) during ANC recommend the reverse testing algorithm for syphilis screening [18,19]. On the basis of near-universal syphilis testing coverage amongst pregnant women in the public sector, syphilis-screening tests constituted part of our criteria for identifying pregnant women from our data source.

With respect to HIV, newly diagnosed pregnant WLHIV initiate ART at the fANC visit or at confirmation of HIV infection. At ART initiation, a baseline $CD4^+$ cell count test and creatinine clearance test are performed to assess immunological profile and to evaluate kidney function respectively. HIV viral load monitoring for all pregnant WLHIV follows previously described guidelines [10].

Study design and data sources

This was a retrospective analysis of routinely collected laboratory data from the National Health Laboratory Service's Corporate Data Warehouse (NHLS CDW). The NHLS CDW is a national repository of all clinical laboratory tests performed in the public health sector, as described elsewhere [20,21]. Centralized routine data on multiple HIV, syphilis and pregnancy-related tests were used to create a synthetic cohort of pregnant WLHIV, by applying a set of criteria to HIV-related and pregnancy-related tests to identify pregnant WLHIV, because of lack of a pregnancy marker within the NHLS CDW. To test the robustness of our methodology for identifying pregnant WLHIV from the NHLS CDW, results were compared against ‘total live births to HIV-positive women’ from the South African District Health Information System (DHIS). The DHIS collates routine health data from all public health facilities in the country.

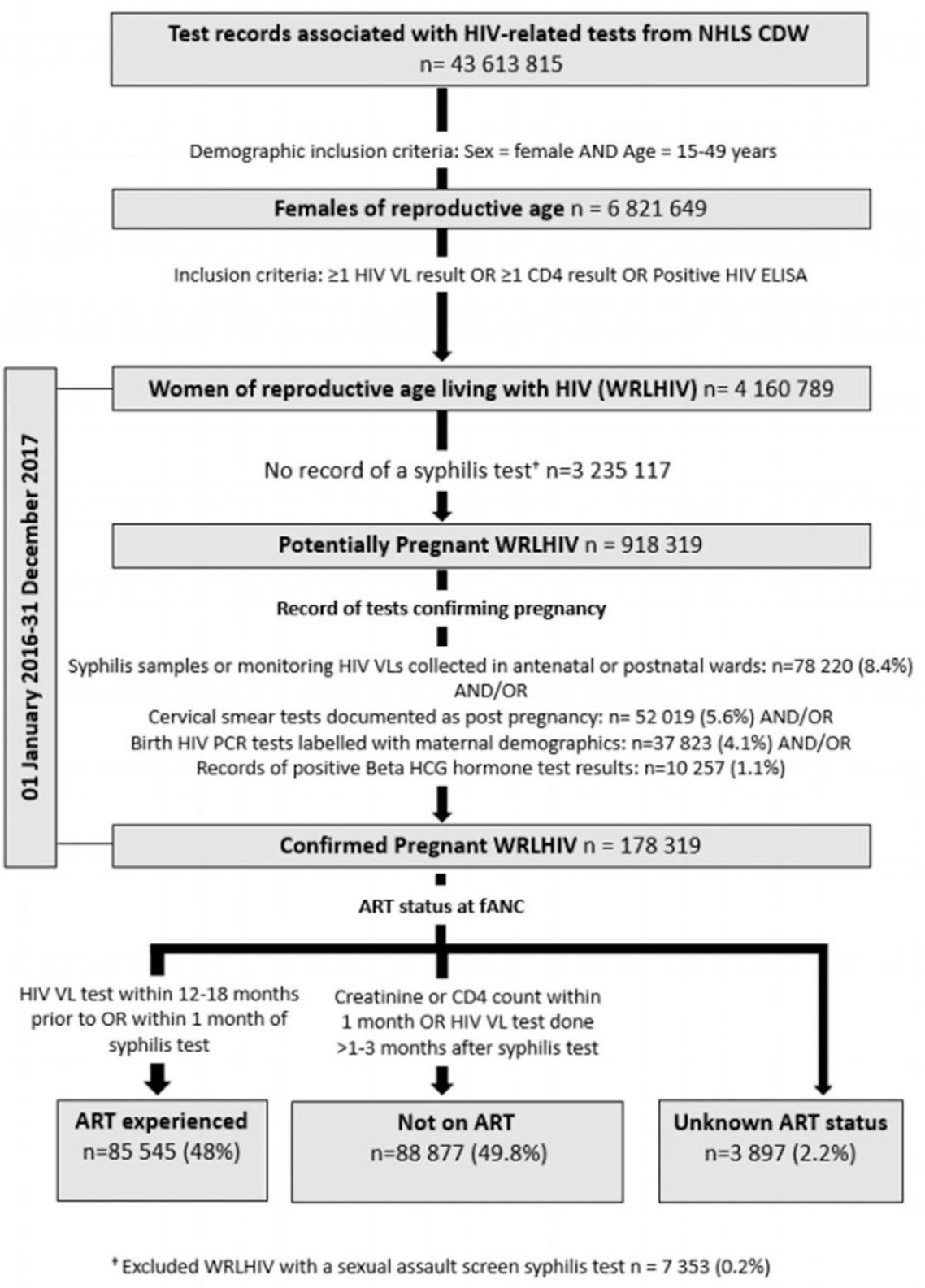

Fig. 1: Criteria for identifying HIV viral load tests performed on pregnant women living with HIV, in the National Health Laboratory Service's Corporate Data Warehouse between 1 January 2016 and 31 December 2017.

Creating the synthetic cohort

The first step involved identification of women of reproductive age with HIV-related tests between 01 April 2015 and 31 March 2019 from the NHLS CDW. This was achieved by extracting test records associated with HIV viral loads, $CD4^+$ cell counts and HIV enzyme-linked immunosorbent assay (ELISA) tests belonging to women, aged 15–49 years (Fig. 1). Data were then restricted to the study period (01 January 2016 to 31 December 2017) and syphilis screening was applied as a proxy for pregnancy by identifying women with at least one eligible syphilis test [Treponema Pallidum antibodies (TPAb)/Treponema Pallidum Haemagglutination Assay (TPHA)] or without a Rapid Plasmin Reagin (RPR) test). As syphilis screening also occurs in nonpregnant women, we applied a set of additional criteria to this cohort of potentially pregnant WLHIV to identify women with a greater likelihood of being pregnant according to Fig. 1. This subset of women constituted the eligible analytical cohort, referred to as pregnant WLHIV henceforth. Routine antenatal practice requires all pregnant women to be screened for syphilis at the fANC visit, therefore, the date of syphilis screening was used to as a proxy for the fANC visit and to mark cohort entry. Timing of HIV viral loads relative to syphilis screening, estimated delivery dates and postpartum periods for the cohort. The date of delivery was assumed to occur 5–7 months from the fANC visit, as approximately 68% of ANC clients had their fANC booking at less than 20 weeks gestation during the study period according to the DHIS. The postnatal period was up to 15 months after the estimated delivery date. Fig. 2 describes duration of follow-up for the cohort. Lastly, we determined ART status at the fANC visit, that is, the timing of ART initiation relative to the date of the first syphilis-screening test. We searched the NHLS CDW retrospectively for HIV viral loads belonging to the eligible cohort of pregnant WLHIV. All HIV viral loads performed within the previous 12–18 months from the syphilis screening date were included. An HIV viral load performed within 12–18 months prior to or within 1 month of the syphilis test defined pregnant WLHIV who were ART-experienced at fANC visit. A syphilis-screening test associated with a creatinine clearance and or $CD4^+$ cell count test performed within 1 month, or HIV viral load around 3 months after the syphilis test identified pregnant WLHIV not on ART at fANC visit.

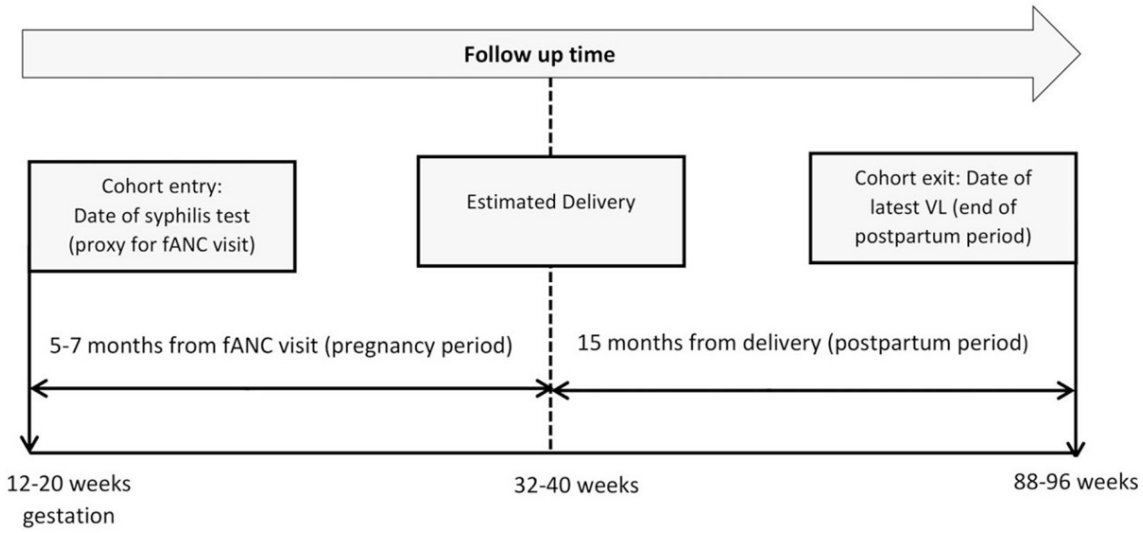

Fig. 2: Definition of study follow-up times among pregnant and postpartum women living with HIV identified from the National Health Laboratory Service's Corporate Data Warehouse.

Definition of main study variables

First HIV viral load during pregnancy

The first HIV viral load performed at fANC visit for ART-experienced pregnant WLHIV or after 3 months of ART for pregnant WLHIV not on ART at fANC visit.

Virologic response thresholds

HIV viral load results (copies/ml) were categorized into viral load suppression (viral load <50), low-level viraemia (viral load: 50 to <1000) and high viral load (viral load ≥1000).

Postpartum viral load

Any viral load performed within 15 months postpartum.

Comorbidities during pregnancy

Women who tested positive at least once for syphilis or poor kidney function or tuberculosis (TB) during the study period. Syphilis positivity was defined by any RPR-positive test excluding RPR-positive tests with discordant TPHA/TPAb. Serum creatinine values greater than 77.0 μmol/l (0.87 mg/dl) identified pregnant women with poor kidney function [22]. Tuberculosis status was determined by searching the national TB register within the NHLS CDW.

Data analysis

Performance of the study algorithm in identifying pregnant WLHIV from the NHLS CDW was assessed by determining the percentage of pregnant WLHIV in the study cohort from total live births to HIV-positive women reported in DHIS by geographic area during the study period.

Descriptive statistics were used to describe pregnant WLHIV, stratified by year of pregnancy. Analyses of maternal HIV viral load changes over time examined changes in HIV viral load values over time from the fANC visit through delivery and up to 15 months postpartum; time to HIV viral load less than 1000 copies/ml among women with an initial high HIV viral load at first HIV viral load measurement and factors associated with HIV viral load decline during follow-up.

For changes in HIV viral load over time, observed values of $\log_{10}$-transformed quantifiable viral loads were described using medians and interquartile ranges (IQR) stratified by ART status at fANC visit. Fractional polynomial models were used to predict mean $\log_{10}$ HIV viral load values among study participants during follow-up, with mean HIV viral load values and associated 95% confidence intervals (CI) reported at given time points. Time to HIV viral load less than 1000 copies/ml was determined by calculating the time difference between the date of the initial high HIV viral load and the earliest HIV viral load less than 1000 copies/ml among women with a high viral load at first HIV viral load measurement. Median times in months (IQR) were reported, stratified by ART status at fANC visit and compared using the Kruskall--Wallis test. Piecewise linear regression models with splines at 4, 8 and 12 months were used to determine factors associated with HIV viral load decline during follow-up.

Table 1 - Provincial distribution of pregnant women living with HIV in the study cohort compared with the District Health Information System indicator 'total live births to HIV-positive women' between January 2016 to December 2017 in South Africa.

	2016			2017			Total		
Province	Live births to HIV + WLHIV	Pregnant women in study	[a]%	Live births to HIV + WLHIV	Pregnant women in study	%	Live births to HIV + WLHIV	Pregnant women in study	%
Eastern Cape	29 750	10 291	34.5	31 299	8383	26.8%	61 049	18 674	30.6
Free State	13 005	2203	16.9	13 882	1520	10.9%	26 887	3723	13.8
Gauteng	55 047	28 885	52.5	55 308	23 875	43.2%	110 355	52 760	47.8
KwaZulu-Natal	67 162	21 583	32.1	74 628	20 398	27.3%	141 790	41 981	29.6
Limpopo	23 871	11 235	47.1	24 524	9007	36.7%	48 395	20 242	41.8
Mpumalanga	24 642	6990	28.4	25 662	5513	21.5%	50 304	12 503	24.9
Northern Cape	3912	1242	31.7	3756	1154	30.7%	7668	2396	31.2
North West	14 558	3588	24.6	15 235	3312	21.7%	29 793	6900	23.2
Western Cape	15 250	10 784	70.7	16 673	8356	50.1%	31 923	19 140	60.0
South Africa	247 197	96 801	39.2	260 967	81 518	31.2%	508 164	178 319	35.1

DHIS South African District Health Information System; WLHIV, women living with HIV.
[a]% represents pregnant WLHIV in the study cohort as a proportion of total live births to HIV-positive women reported in DHIS.

Splines were set at less than 4 months after the fANC visit, at delivery, 8 to less than 12 months postpartum and late (12–15 months) postpartum. The regression model adjusted for maternal age, comorbidities, geographic location, ART status, maternal HIV viral load and $CD4^+$ cell count at fANC visit. Data analysis was performed in STATA 14 (StataCorp, College Station, Texas, USA).

Ethics clearance

Ethics approval for the study was obtained from the Wits Human Research Ethics Committee (HREC no. M180854).

Results

Description of pregnant women living with HIV in the synthetic cohort

A synthetic cohort of 178 319 pregnant WLHIV was created from the NHLS CDW data. When compared with total live births to HIV-positive women from DHIS, all provinces were represented in the study cohort with some under or over-representation (Table 1). However, the provincial distribution of pregnant WLHIV in the country was comparable between DHIS and the study cohort (Supplementary Figure 1, https://links.lww.com/QAD/B894).

Among 178 319 pregnant WLHIV in the synthetic cohort, 85 545 (48%) were ART-experienced, 88 877 (49.8%) were not on ART, and ART status at fANC visit could not be determined for 3897 (2.2%) (Table 2). Median maternal age at fANC visit was 29.2 years (IQR: 24.8–33.9). Majority of women were from Gauteng and KwaZulu-Natal provinces, accounting for 29.6 and 23.5% of the cohort, respectively (Table 2). Median $CD4^+$ cell count at fANC visit was 407 (IQR: 258–579) cells/μl for the entire cohort with 19 158 (16.4%) women showing levels consistent with severe immune compromise (<200 cells/μl) and 41 662 (35.6%) having $CD4^+$ cell counts at least 500 cells/μl at fANC visit.

Table 2 - Demographic and clinical characteristics of pregnant women living with HIV in South Africa, comparison of National Health Laboratory Service's Corporate Data Warehouse dataset 2016 vs. 2017.

Characteristic	Total *N* = 178 319	2016 *N* = 96 801	2017 *N* = 81 518
	Age at fANC visit/(years)		
Median (IQR)	*29.2 (24.8–33.9)*	*29.0 (24.6–33.7)*	*29.5 (25.0–34.1)*
<25	46 653 (26.2%)	26 374 (27.3%)	20 279 (24.9%)
25 to <35	95 994 (53.8%)	51 849 (53.6%)	44 145 (54.2%)
35 to <45	34 672 (19.4%)	18 073 (18.7%)	16 599 (20.4%)
45–49	1000 (0.6%)	505 (0.5%)	495 (0.6%)
	Province		
Eastern Cape	18 674 (10.5%)	10 291 (10.6%)	8383 (10.3%)
Free State	3723 (2.1%)	2203 (2.3%)	1520 (1.9%)
Gauteng	52 760 (29.6%)	28 885 (29.8%)	23 875 (29.3%)
KwaZulu-Natal	41 981 (23.5%)	21 583 (22.3%)	20 398 (25.0%)
Limpopo	20 242 (11.4%)	11 235 (11.6%)	9007 (11.1%)
Mpumalanga	12 503 (7.0%)	6990 (7.2%)	5513 (6.7%)
Northern Cape	2396 (1.3%)	1242 (1.3%)	1154 (1.4%)
North West	6900 (3.9%)	3588 (3.7%)	3312 (4.1%)

Characteristic	Total *N* = 178 319	2016 *N* = 96 801	2017 *N* = 81 518
Western Cape	19 140 (10.7%)	10 784 (11.1%)	8356 (10.3%)
ART status at fANC visit			
ART experienced	85 545 (48.0%)	45 128 (46.6%)	40 417 (49.6%)
Not on ART	88 877 (49.8%)	48 525 (50.1%)	40 352 (49.5%)
Unknown	3897 (2.2%)	3148 (3.3%)	749 (0.9%)
$CD4^+$ cell count at fANC visit among ART-experienced WLHIV at fANC visit			
Median (IQR)	*436 (279–607)*	*420 (269–585)*	*456 (291–632)*
<500	28 827 (60.1%)	16 071 (63.0%)	12 576 (57.7%)
≥500	19 169 (39.9%)	9432 (37.0%)	9737 (43.3%)
$CD4^+$ cell count at fANC visit among WLHIV not on ART at fANC visit			
Median (IQR)	*383 (244–551)*	*383 (244–547)*	*385 (244–556)*
<500	45 613 (68.3%)	24 422 (68.7%)	21 191 (67.8%)
≥500	21 174 (31.7%)	11 129 (31.3%)	10 045 (32.2%)
First HIV viral load[a] during pregnancy among ART-experienced WLHIV at fANC visit			
Median log $_{10}$ viral load (cps/ml) *(IQR)*	*2.5 (1.7--3.8)*	*2.5 (1.7--3.9)*	*2.4 (1.7--3.8)*
<50	23 210 (57.1%)	11 227 (55.8%)	11 983 (58.4%)
50–<1000	8 999 (22.1%)	4548 (22.6%)	4451 (21.7%)
≥1000	8 451 (20.8%)	4362 (21.7%)	4089 (19.9%)
First HIV viral load[a] during pregnancy among WLHIV not on ART at fANC visit			
Median log $_{10}$ viral load (cps/ml) *(IQR)*	*3.7 (2.5--4.6)*	*3.7 (2.6–4.5)*	*3.6 (2.4--4.6)*
<50	10 757 (33.3%)	4945 (31.2%)	5812 (35.3%)
50 to <1000	6655 (20.6%)	3237 (20.4%)	3418 (20.8%)
≥1000	14 913 (46.1%)	7669 (48.4%)	7244 (44.0%)
HIV viral load[a] at delivery			
Median log $_{10}$ viral load (cps/ml) *(IQR)*	*2.1 (1.5--3.2)*	*2.2 (1.6--3.2)*	*2.0 (1.5–3.1)*
<50	25 236 (63.1%)	13 301 (61.0%)	11 935 (65.5%)
50 to <1000	9047 (22.6%)	5214 (23.9%)	3833 (21.0%)
≥1000	5733 (14.3%)	3280 (15.1%)	2453 (13.5%)
Comorbidities during pregnancy[b]			
None	162744 (91.3%)	88 355 (91.3%)	74 389 (91.3%)
Present	15575 (87%)	8446 (8.7%)	7129 (8.8%)

ART, antiretroviral therapy; cps/ml, copies per millilitre; fANC, first antenatal care visit; IQR, interquartile range; NHLS CDW National Health Laboratory Service's Corporate Data Warehouse; VL, viral load.
[a]Observed HIV viral loads.
[b]Comorbidities defined by positive test for at least one of the following conditions: syphilis, poor kidney function or tuberculosis.

Syphilis seropositivity was 3.3% (*n* = 5 943) for the entire cohort and ranged from 1 to 5% by province. A total of 7936 (4.5%) pregnant WLHIV had a serum creatinine value greater than 77.0 µmol/l (0.87 mg/dl) and 2364 (1.3%) tested positive for TB during the current pregnancy. In total, 15 575 (8.7%) pregnant WLHIV had evidence of ≥1 comorbidity.

Changes in HIV viral load values over time

The cohort contributed 345 174 HIV viral load measurements, median = 2.2 (IQR: 2–3) HIV viral loads per woman during follow-up. The first HIV viral load performed during pregnancy (n = 47 631/74 066) had a mean predicted viral load of 3.06 $\log_{10}$ viral load copies/ml [95% CI: 3.05–3.08] decreasing to 2.55 [2.53–2.58] at delivery (n = 20 773/40 016) and 2.52 [2.51–2.54] postpartum (n = 34 881/72 673). Overall, proportions of observed viraemia (viral load ≥50 copies/ml) were 39 756 (53.6%) at first HIV viral load measurement during pregnancy, 14 780 (36.9%) at delivery and 24 328 (33.5%) postpartum.

Among 40 660 (47.5%) ART-experienced pregnant WLHIV with an HIV viral load at fANC visit, 17 450 (42.9%) had a viral load at least 50 copies/ml and 8451 (20.8%) had a viral load at least 1000 copies/ml, with a median $\log_{10}$ viral loads copies/ml of 2.5 (IQR: 1.7–3.8) among women with quantifiable HIV viral load at fANC visit. Among 32 325 (36.4%) pregnant WLHIV not on ART at fANC visit with an HIV viral load after the first 3 months of ART, 21 568 (66.7%) had a viral load at least 50 copies/ml and 14 913 (46.1%) had a viral load at least 1000 copies/ml (Table 2) after a median of 3.9 (2.2–5.8) months. Overall, 72 702 (40.8%) women received at least one HIV viral load during the postpartum period. Viraemia at the time of delivery and postpartum were similar in pregnant WLHIV regardless of ART status at fANC. Figure 3 describes maternal HIV viral load decline during follow-up stratified by maternal ART status at fANC visit, overall (Fig. 3a) and for women with quantifiable HIV viral load (Fig. 3b). Provincial differences in HIV viral load decline during follow-up were observed, Supplementary Figure 2, https://links.lww.com/QAD/B895.

Time to HIV viral load less than 1000 copies/ml among pregnant women with high viral loads

Among 23 904 (32.2%) pregnant WLHIV whose first HIV viral load during pregnancy was at least 1000 copies/ml, 16 951 (70.9%) had a subsequent viral load during pregnancy or postpartum. Of these, 8980 (53.0%) had a viral load less than 1000 copies/ml at the next HIV viral load test with a median time of 3.7 (IQR: 2.6–6.0) months between the two tests. There was no difference in median time to viral load less than 1000 copies/ml between pregnant WLHIV who were ART-experienced and those not on ART at fANC visit.

Factors associated with HIV viral load decline during follow-up

Sustained maternal HIV viral load decline during follow-up was predicted by having a $CD4^+$ cell count at least 500 cells/μl, viral load less than 50 copies/ml and absence of comorbidities at baseline (Table 3). Older maternal age (≥25 years) was also associated with HIV viral load decline, despite lack of statistical evidence for differences in virological control between the less than 25 years and at least 45 years age groups. The most significant decline in $\log_{10}$ viral load occurred between the fourth month after fANC and the time of delivery, with increased HIV viral load in the late postpartum period (Table 3).

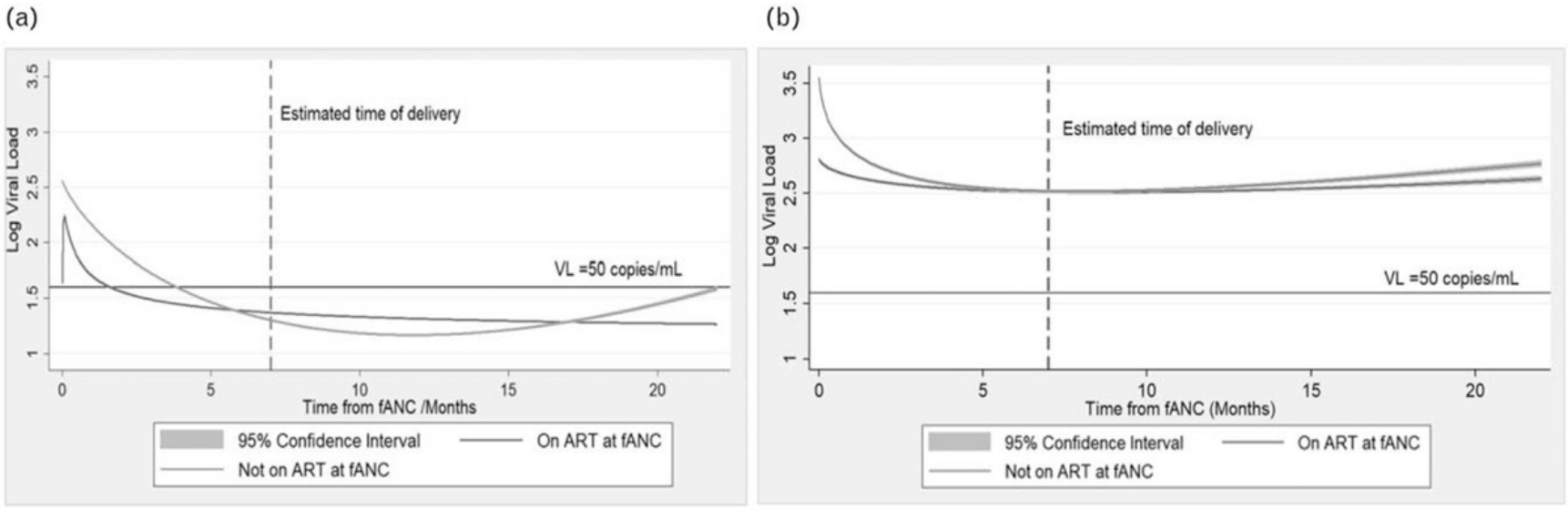

Fig. 3: Viral load decline over time by antiretroviral therapy status at first antenatal visit (a) overall: HIV viral load measurements, *n* = 338 688; observed HIV viral loads that were lower than the detectable limit of the assay were assigned a value of zero (b) among WLHIV with quantifiable viral load: HIV viral load measurements *n* = 192 140.

Table 3 - Results from a piecewise linear regression model predicting log_{10} viral load decline from the first ANC visit up to 15 months postpartum among pregnant women living with HIV in South Africa, January 2016 to December 2018.

	Number of HIV viral load measurements = 128 279[a]		
Predictors	Coefficient (log_{10} viral load)	95% CI.	*P* value
Time from fANC visit			
<4 months	1.0	*Reference*	–
4–<8 months	−0.74	−0.76 to −0.72	<0.001
8–<12 months	−0.12	−0.15 to −0.10	<0.001
12–15 months	0.27	0.24–0.30	<0.001
Maternal age at fANC visit/years			
<25	*1.0*	*Reference*	–
25–<35	−0.08	−0.09 to −0.06	<0.001
35–<45	−0.10	−0.12 to −0.07	<0.001
45–49	0.04	−0.05 to 0·14	0.390
First HIV viral load during pregnancy (cps/ml)			
<50	*1.0*	*Reference*	–
50–<1000	1.19	1.16--1.20	<0.001
≥1000	2.31	2.30-- 2.32	<0.001
$CD4^+$ count at fANC visit (cells/μl)			
<500	*1.0*	*Reference*	–
≥500	−0·28	−0.34 to −0.22	<0.001
[b]Comorbidities during pregnancy			
None	*1.0*	*Reference*	-
Present	0.12	0.09 to 0.14	<0.001
ART status at fANC visit			
ART experienced	*1.0*	*Reference*	-
Not on ART	−0.18	−0.19 to −0.16	<0.001
Province			
KwaZulu-Natal	*1.0*	*Reference*	-
Eastern Cape	*0.29*	0.26–0.31	<0.001
Free State	−0.09	−0.13 to −0.04	0.001
Gauteng	0.12	0.10 to 0.14	<0.001
Limpopo	0.31	0.29 to 0.34	<0.001
Mpumalanga	0.08	0.05 to 0.12	<0.001
Northern Cape	−0.01	−0.05 to 0.04	0.842
North West	0.05	0.01 to 0.09	0.010
Western Cape	0.01	−0.02 to 0.03	0.667

ART, antiretroviral therapy; CI, confidence interval; fANC, first antenatal care visit; VL, viral load.
[a]Missing data excluded from multivariate analysis.
[b]Comorbidities defined by having at least one of the following conditions (poor kidney function, tuberculosis or syphilis).

Discussion

We present maternal HIV viral load changes over time within the PMTCT programme at national level in South Africa. Overall, a steady decline in maternal viraemia from first presentation at ANC to delivery was demonstrated with an increase towards the end of the

postpartum period. A decreasing trend in proportions of viraemic women (viral load ≥50 copies/ml) from 54% at first HIV viral load measurement during pregnancy to 37% at delivery and 34% during the postpartum period was observed. At fANC visit, 43% of ART-experienced pregnant WLHIV had a viral load at least 50 copies/ml whereas two-thirds of pregnant WLHIV not on ART at fANC visit still had viral load at least 50 copies/ml after 3 months on ART. Provincial differences in sustaining HIV viral load suppression (VLS) into the postpartum period were noted. HIV viral load decline during follow-up was predicted by having a $CD4^+$ cell count at least 500 cells/μl, viral load less than 50 copies/ml, maternal age at least 25 years and absence of comorbidities at fANC visit.

These findings support previous reports from smaller, localized studies in South Africa [13,14,23]. A review of maternal HIV viral loads from routine care settings in the Western Cape province reported a predicted mean pre-ART HIV viral load of 4.0 $\log_{10}$ viral load copies/ml at fANC visit, decreasing to 1.7 $\log_{10}$ viral load copies/ml after approximately 3 months of ART use and 73% of the cohort achieving viral load less than 50 copies/ml at delivery [13,14]. A mean of 3.7 $\log_{10}$ viral load copies/ml after 3 months on ART was predicted for women not on ART at fANC visit in our study. We attribute the higher viral loads and lower proportion of VLS at delivery (63%) in our study to the heterogeneity of virologic control across provinces. However, the national VLS of 63% at delivery concurs with reports from cross-sectional studies examining maternal viraemia at delivery, reported at around 63–64% [1,23]. Findings suggest that despite greater than 95% coverage for the first two UNAIDS 90–90–90 targets, the third 90 target in pregnant women at delivery (and postpartum) is 63 and 86% for viral load at least 50 and at least 1000 copies/ml thresholds, respectively.

Although we observed a decreasing trend in maternal viraemia, an increase in the late postpartum period was noted. This raises concern for late postnatal transmission [13,14,24,25]. Studies from both low-income and high-income countries have reported poor virologic control during the postpartum period, particularly among WLHIV already on ART before pregnancy [26–29]. This is possibly because of social pressures (e.g. unplanned pregnancies), which facilitate poor adherence to ART and/or pregnancy-related physiological changes that predispose women to viraemia [29,30]. Alternatively, the higher proportion of viraemia among ART-experienced women may be because of misclassification error introduced by our algorithm of assigning ART status at fANC visit. However, DHIS showed that proportions of ART-experienced women at fANC visit were 45.8 and 55.7% for 2016 and 2017, respectively, suggesting that the study algorithm performed adequately in this regard. Our multivariable model showed quicker HIV viral load decline during follow-up in women not on ART at fANC visit compared with ART-experienced women. This is likely an effect of susceptibility of maternal virus to ART among women newly initiating ART during pregnancy compared with ART-experienced women. Even so, two-thirds of women not on ART at fANC visit had viral load at least 50 copies/ml after 3 months of ART use. As the NHLS CDW is not a clinical longitudinal cohort monitoring system, data on maternal ART regimens were unavailable. Hence, the effect of type or length of maternal treatment on virological control during follow-up could not be assessed.

Similar to other studies [14,26], younger maternal age (<25 years) at baseline was associated with viraemia during follow-up. A quarter of pregnant WLHIV were aged less than 25 years in this study representing a significant proportion of pregnant WLHIV who require targeted care packages to ensure viral load suppression for eMTCT. Almost 70% of $CD4^+$ cell counts at fANC visit were less than 500 cells/μl, likely reflecting the gradual transition from $CD4^+$ cell count-based ART eligibility criteria towards test and treat during the study period. Low

$CD4^+$ cell counts may also be attributed to hemodilution that occurs during pregnancy [31]. Comorbid conditions were associated with high viral loads during follow-up. Pregnant WLHIV co-infected with TB or syphilis are reported to have a 2–2.5 times higher risk of MTCT compared with their negative counterparts [32,33]. Thus, screening and treating all pregnant and postpartum WLHIV co-infected with TB or syphilis is critical for eMTCT of HIV and syphilis.

Our analysis had several strengths and limitations. We present findings based on a large sample of routinely collected surveillance data from the national PMTCT programme. The data provide insight into changes of maternal HIV viral loads over time within a routine programme setting as opposed to clinical trial study populations. Our data are reported nationally and subnationally enabling interprovincial evaluation of maternal HIV viral load changes over time, which is unique to this study.

Findings are based on a synthetic cohort created from routine NHLS CDW laboratory data. The warehouse does not have a marker for pregnancy, therefore, our results rest on the performance of criteria used to identify WLHIV as pregnant. We anticipate that our inclusion criteria were highly specific and excluded majority of nonpregnant women as well as some pregnant women but the proxy variables used to define pregnancy, delivery and postpartum periods may be inaccurate. However, our results concur with findings from similar studies [1,13,14,23] suggesting that our cohort is representative of pregnant WLHIV in South Africa. We acknowledge the uneven representation of provinces in the cohort when compared with number of live births to WLHIV from DHIS. However, this provincial distribution may reflect the extent of viral load monitoring in pregnant WLHIV across the provinces. Nonetheless, the data reveal a huge gap between the first and second UNAIDS 90–90–90s of more than 95% and a third 90 of 63% that does not bode well for achieving eMTCT. Subsequent to 2017, the third 90 may have improved and the NHLS CDW should be harnessed for more real-time reporting of HIV VLS in the antenatal, delivery and postpartum period to direct interventions.

Although South Africa's national PMTCT programme has reached the first and second UNAIDS 90–90–90 targets for pregnant women, the third 90 remains elusive. Despite high ART coverage during pregnancy, only 63% of pregnant WLHIV attained viral load less than 50 copies/ml by delivery. Among pregnant WLHIV with first HIV viral load during pregnancy at least 1000 copies/ml, a third had no evidence of subsequent viral load monitoring. Findings highlight the need for strengthening ART adherence, increased viral load monitoring and rapid reaction to high viral load. Better longitudinal data on pregnant and postpartum WLHIV, including linkage of mother--infant pairs, is required to better measure progress towards eMTCT.

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Authors’ contributions:

F.M.: Conceptualization, study design, acquisition of data, data analysis and writing the original manuscript.

A.H.M.: Conceptualization, methodology and reviewing the manuscript.

T.M.: Methodology, reviewing and editing the manuscript.

G.G.S.: Sourced funding, conceptualization, study design, acquisition of data, provided critical revision and final approval.

T.K.: Conceptualization, study design, analysis of the data and interpretation, provided critical revision and final approval.

Conflicts of interest

There are no conflicts of interest.

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