HIV VIRAL LOAD REBOUND AT DELIVERY IN WOMEN ON ART WITH PREVIOUSLY SUPPRESSED VIRAL LOADS DURING THE SAME PREGNANCY

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Medicine

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Abbreviations and acronyms

ART	Antiretroviral Therapy
AZT	Zidovudine
CHBAH	Chris Hani Baragwanath Academic Hospital
DHHS	Department of Health and Human Services
eMTCT	elimination of Mother-To-Child Transmission of HIV
GA	Gestational Age
HIV	Human Immunodeficiency Virus
NVP	Nevirapine
PMTCT	Prevention of mother-to-child transmission of HIV
PWLHIV	Pregnant Women Living with HIV
REDCap	Research Electronic Data Capture
TB	Tuberculosis
UNAIDS	Joint United Nations Programme on HIV/AIDS
VL	Viral Load
VTP	Vertical Transmission Prevention
WHO	World Health Organization
WLHIV	Women living with HIV

DECLARATION

I, Siseko Mzendana declare that this research report is my own, unaided work. It is being submitted for the Degree of Master of Science in the branch of Obstetrics at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

Signature:……..

20 day of March 2025 in Johannesburg

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ABSTRACT

Background

HIV viral load (VL) non-suppression can lead to adverse pregnancy outcomes, including vertical transmission (VT). Therefore, it is crucial to achieve and maintain viral suppression during pregnancy.

Objectives

The objectives of this study were to investigate the prevalence of HIV VL rebound at delivery in women with previously suppressed VLs in the same pregnancy, and also evaluate adherence to the 2019 PMTCT guidelines on VL testing.

Methods

This was a retrospective record review of pregnant women living with HIV (PWLHIV) and on antiretroviral therapy (ART) who delivered at Chris Hani Baragwanath Academic Hospital during the period 01 January to 31 December 2021. Patient files were randomly selected and data on demographics, timing and history of HIV diagnosis and treatment, VL testing during pregnancy and delivery, and infant outcomes were extracted.

Results

A total of 362 PWLHIV were included in the study and the majority (85.5%) were diagnosed with HIV prior to the index pregnancy and almost all were on ART at the first antenatal visit. HIV VL rebound was diagnosed in 11 women (3.6%), and of these, nine (82%) had a VL

between 50 and 1000 copies per ml, and two (18%) had a VL >1000 copies per ml. Overall, 56 (15.5%) women had no VLs done at delivery. Age was the only variable significantly associated with VL rebound at the time of delivery. No cases of VT were identified.

Conclusion

The low rate of HIV VL rebound at delivery is reassuring. While there was evidence of adherence to PMTCT guidelines in terms of ART initiation and monitoring, there are still gaps with regards to VL monitoring.

Key words: HIV, pregnant women living with HIV, viral load, vertical transmission

Introduction

Human immunodeficiency virus (HIV) infection is persistently a challenge for public health in South Africa, where in 2022 there were an estimated 7.5 million people living with HIV (PLHIV), with 27.5% of women attending for antenatal care having a positive HIV status, representing the greatest disease burden in the world.[1] Pregnant women are more likely to contract HIV than non-pregnant women, and if untreated, HIV can lead to negative pregnancy outcomes such as stillbirths, low birth weight, mother-to-child transmission (MTCT), and maternal mortality.[2]

High maternal viral load (VL) is closely associated with the risk of vertical transmission (VT) and maternal HIV- associated complications.[2] Antiretroviral treatment (ART) use and adherence among pregnant women on ART are the primary drivers of changes in VL in the absence of drug resistance. Suboptimal ART adherence, disengagement from care and elevated VL have been widely documented among pregnant and postpartum women living with HIV[3]... Therefore, frequent and timely viral load testing of pregnant women living with HIV (PWLHIV) for rapid detection of elevated VL and intervention is critical to prevent vertical transmission and prevent maternal HIV-associated complications.

There are different strategies employed by different countries and organizations for HIV VL monitoring in pregnant and breastfeeding women. The World Health Organization (WHO) recommends VL testing at first antenatal care (ANC) visit for PWLHIV already on ART at the start of ANC, and at three months for women who are newly diagnosed, and newly initiated on ART. It further recommends a repeat VL at 34-36 weeks' gestation for all PWLHIV.[4] The US Department of Health and Human Services (DHHS) guidelines recommend a VL at booking, then at two to four weeks after ART initiation for newly diagnosed women. The guidelines also recommend a VL every three months for all pregnant WLHIV on ART (if VL<50 copies/ml)

and at 34-36 weeks gestation.[5] At the other extreme, Malawi (2016) guidelines recommend a first VL test at six months for newly diagnosed women and then annually. Women already on ART at booking only continue with annual VL monitoring.[6]

The South African prevention of mother-to-child transmission of HIV (PMTCT) programme was developed to allow for widespread HIV testing and ART coverage in the public sector. Since 2015, regardless of when the most recent VL was performed, the PMTCT guidelines have advised a VL test for WLHIV already on ART at the initial ANC visit to assess treatment response. A VL is advised for WLHIV newly diagnosed with HIV during pregnancy, after three months of ART.[7] The guidelines were updated in November 2019 to include a VL test at delivery for all PWLHIV on ART.[8]

Meticulous VL monitoring in pregnancy is necessary if we are to achieve the Joint United Nations Programme on HIV and AIDS (UNAIDS) 95-95-95 and elimination of MTCT (EMTCT) targets.[9] A study conducted in four Gauteng tertiary obstetric units by Moyo et al, between June 2018 and March 2019, found that 20% of WLHIV had a VL of more than 1000 copies/ml, and 36.4% had a VL of more than 50 copies/ml, around the time of delivery.[10] These are indeed significant and worrying numbers. Lesosky et al did a simulation study looking at optimal timing of VL monitoring during pregnancy, to predict viraemia at delivery in PWLHIV initiating ART in South Africa. They found that the best-performing monitoring schedule was a single VL test at 36 weeks gestation. However, they also found that only 91% of all HIV-infected women would be tested at this time due to preterm deliveries.[11]

Onoya et al, in a study done at Midwife Obstetric Units (MOUs) in peri-urban townships of the Tshwane, Ekurhuleni and Johannesburg Metropolitan districts in the Gauteng Province of South Africa found that women who initiated ART prior to pregnancy had higher rates of viral suppression at delivery than women who initiated ART during pregnancy. The findings of the

study demonstrated that in comparison to women who were ART-naive at the start of ANC, PWLHIV with pre-pregnancy ART are better able to preserve immunologic status and virologic control in pregnancy.[12] According to Langwenya et al., in their study done in Cape Town, South Africa, at a primary care facility, the duration of ART prior to delivery and viral load at the first ANC visit are both significant predictors of viral load suppression at delivery.[13] Women who accessed ANC earlier and had lower VLs and higher CD4 cell counts at their initial ANC visit were more likely to deliver with suppressed VLs.[13] While there are data on factors associated with viral suppression at delivery, there is limited information on the prevalence of peripartum VL rebound, as defined by a VL of 50 copies/ml or more in patients with a previously suppressed VL (VL less than 50 copies/ml). Hence the aim of this study was to investigate the prevalence of HIV VL rebound at delivery in women who delivered at Chris Hani Baragwanath Academic Hospital (CHBAH), and had previously suppressed VLs during the same pregnancy.

Methods

Setting

This study was conducted in the obstetrics unit at CHBAH, in Soweto, Johannesburg, South Africa. The obstetrics unit at CHBAH sees high risk pregnancies referred from the surrounding primary healthcare facilities, and district and regional hospitals. At the time of the study, the recorded prevalence of HIV in pregnant women was 24% in the City of Johannesburg district, which was lower than the national average of 27.5%. [14]

Study Design and Study Population

This was a retrospective record review of PWLHIV on ART who delivered at CHBAH, in the period from 01 January to 31 December 2021. During the study period, the 2019 PMTCT guidelines were being used and included in these was guidance on VL monitoring during the antenatal period, and peripartum – Table 1. The standard practice during this period included

HIV viral load testing at booking for all women entering antenatal care with a known positive HIV status and already on ART, a viral load at 3 months after diagnosis for those newly initiated on ART, and a viral load test for all PWLHIV on ART at delivery. Antenatal viral load tests were done at the National Health Laboratory Service (NHLS) laboratories serving the corresponding healthcare centres where the individual patients attended ANC. All VL tests at delivery were done at the CHBAH NHLS laboratory. Viral load suppression was defined as a VL of less than 50 copies/ml, and VL rebound was defined as VL of 50 copies/ml or more in patients with a previously suppressed VL.

Table 1: HIV viral load monitoring schedule according to the 2019 South African PMTCT guidelines.[8]

Newly initiating ART or re-initiating on a DTG-based regimen (before 28 weeks' gestation)	**Already on ART at pregnancy diagnosis**	**Late presentation for ANC after 28 weeks, or at delivery**
First VL at 3 months on ART	VL at ANC first visit	First VL at delivery
All women get a VL at delivery (results must be checked at postnatal visit before 6 days)		

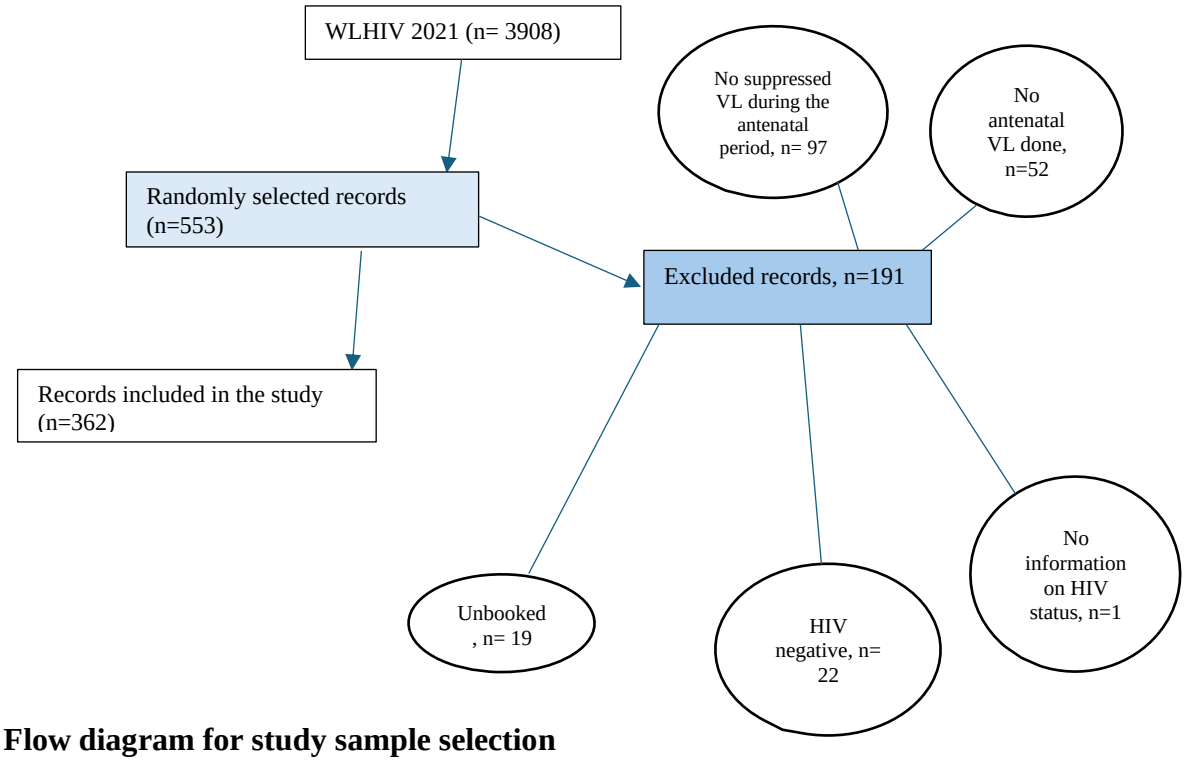
ART=antiretroviral treatment; DTG=dolutegravir; ANC=antenatal care; VL=viral load; PMTCT=prevention of mother-to-child transmission of HIV

Inclusion criteria: PWLHIV who were on ART during the index pregnancy and had at least one suppressed VL during the antenatal period and delivered at CHBAH during the study period. Exclusion criteria: Pregnant WLHIV who were unbooked and presented for the first time in labour, and were not on ART during pregnancy were excluded. Also excluded were patients with no VL tests done during the antenatal period, and those that had VLs done during the antenatal period but never had suppressed VLs at any point.

There were 3 908 pregnant WLHIV who delivered at CHBAH during the study period. Using the Yamane equation, with the population of 3 908 at a confidence level of 95% and a margin

of error of 0.05, the relevant sample size was calculated at 362. PWLHIV and on ART were identified from admission and delivery registers and names were selected randomly by numbering all the 3908 names, then used a random number generator to get random numbers. Names and/or file numbers that corresponded to each of those random numbers were then selected to form part of the sample. A total of 553 files were retrieved from the records department and 191 were excluded for various reasons, leading to 362 files that met the inclusion criteria – Figure 1.

Data were extracted from the files using a standardised data collection tool and information was collected on demographics; timing and history of HIV diagnosis and ART initiation; history of any ART regimen change; VL testing during pregnancy and peripartum; and infant outcomes, including birth PCR testing. Results that were not in the files were checked from the NHLS database using the NHLS-labtrak system. Laboratory barcodes were used to access patients' results and where barcodes were not available, patients' file numbers, names and surnames were used.



<u>Figure 1</u>: Flow diagram for study sample selection

Data analysis

Data were recorded on Research Electronic Data Capture (REDCap),[15] and Stata version 18 was used for data analysis (Stata Corporation, College Station, USA). To identify risk factors associated with the likelihood of VL rebound at the time of delivery, demographic and clinical factors were analysed using descriptive statistics and bivariate logistic regressions. By using likelihood ratio tests, the significance of the bivariate associations was assessed. Statistical significance was recognized as being indicated by P values lower than 0.05.

Ethical considerations

Ethics clearance was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (No. M230124 MED11-10-116). Permission to conduct the study was obtained from the Chief Executive Officer and the head of obstetrics and gynaecology department at CHBAH. Confidentiality was strictly maintained. No personal data, i.e. patient names, surnames and address, were included in the data collection tools. Names and surnames were kept separately and used in cases where laboratory results needed to be accessed from the NHLS system.

Results

A total of 362 patients were included in the study. The mean maternal age was 31.4 years (standard deviation (SD) 5.9), with 273 (75.4%) in the age group 16 to 35 years, and 89 (24.6%) older than 35 years – Table 2. A total of 201 (55.5%) were employed, 102 (28.2%) unemployed, and the employment status was unknown for 59 (16.3%). All patients had

accessed ANC, and the mean gestational age at the first antenatal visit was 18.4 weeks, SD: 7.4. A total of 17 (4.7%) participants were on chronic medication – 12 (70.6%) were on antihypertensives, 2 (11.8%) were on hypoglycaemics, and one each (5.9%) on medication for epilepsy, asthma and cardiac disease. Antenatal ultrasound was done for 338 patients (93.4%) and there was no record of any antenatal ultrasound for 24 (6.6%).

Table 2: Demographic and clinical characteristics, n=362

Characteristic	**n (%)**
Age – years Mean (SD) – 31.4 (5.9)	
Age categories – years	
16-35	273 (75.4)
>35	89 (24.6)
Body mass index	
Underweight	2 (0.7)
Normal	80 (26.1)
Overweight	86 (28.1)
Obese	
• class 1	65 (21.2)
• class 2	41 (13.4)
• class 3	32 (10.46)

Parity Median (IQR) – 2 (1 – 2)	
Parity categories	
Nullipara (0)	49 (13.5)
Primipara (1)	120 (33.2)
Multipara (2-5)	192 (53.0)
Grand multipara	1 (0.3)
Gravidity Median (IQR) – 2 (1 -3)	
Gravidity categories	
Primi-gravida (Gravida 1)	40 (11.0)
Multipara (2-5)	309 (85.4)
Grand multipara (>5)	13 (3.6)
ANC booking Yes	362 (100)
Total number of ANC visits Median (IQR) 6 (5 – 8)	
GA at booking categories - weeks	
Early (<20 weeks)	208 (57.5)
Late (≥20 weeks)	154 (42.5)

GA determination method	
LNMP	195 (53.9)
Palpation	31 (8.6)
Early ultrasound (≤24 weeks)	111 (30.7)
Late ultrasound	25 (6.9)
ANC facility	
PHC	164 (45.3)
CHC	155 (42.8)
District hospital	21 (5.8)
Tertiary Hospital	18 (5.0)
Regional Hospital	4 (1.1)
Medical conditions	
None	343 (94.8)
Chronic hypertension	10 (2.8)
Hypertensive disorders of pregnancy	2 (0.6)
Diabetes	2 (0.6)
Cardiac disease	1 (0.3)
Asthma	1 (0.3)
Epilepsy	1 (0.3)

ANC=antenatal care; PHC=primary health care; CHC=community health centre

There were 10 (2.8%) patients that had a positive syphilis test, and five received three doses of benzathine penicillin G (Bicillin) and for the other five, no treatment was recorded.

Overall, 359 (99.1%) patients had records of when HIV diagnosis was made – 307 (85.5%) prior to the index pregnancy, 52 (14.5%) were diagnosed during the index pregnancy, with a mean gestational age (GA) at HIV diagnosis of 15.9 weeks (SD 6.3) – Table 3. The mean GA at first HIV VL testing was 20.4 weeks (SD 7.9) – 296 (81.8%) had a VL of either lower than detectable limit (LTDL) or less than 50 copies per ml; 36 (9.9%) had a VL of more than 50 copies per ml, and 30 (8.3%) had a VL of more than 1000 copies/ml.

Among the 52 women who were diagnosed during the index pregnancy, 48.1% (n=25) had their first VL done at 3 months after diagnosis and ART initiation, 10 (19.2%) were done at diagnosis, 8 (15.4%) at one month, 7 (13.5%) at 2 months and 4 months respectively, and 2 (3.8%) were done at 5 months after diagnosis and ART initiation. All (n=307) of the women that were diagnosed prior to the index pregnancy had their first VLs done at booking. The mean GA at first suppressed VL for both patients already on ART and those newly initiated in the index pregnancy combined was 22.1 weeks (SD 8.4).

Table 3: Details of HIV diagnosis and ART initiation, n=362

Description	**n (%), or mean (SD), or median (IQR, range)**
Timing of HIV diagnosis (n=362)*	
Pre-pregnancy	307 (85.0)
During pregnancy	52 (14.4)

Unknown	3 (0.8)
GA (weeks) at HIV diagnosis for those diagnosed during pregnancy (n=52)	15.9 (6.3); 16 (11.5-20, 6-33)
Baseline CD4 count – cells/mm^3 (n=322)*	532.9 (237.6); 511 (381-678, 24-1477)
Timing of ART initiation (n=358)*	
Pre-conception	303 (84.6)
During pregnancy	55 (15. 4)
GA at ART initiation – weeks (n=55)	16.1 (6.7) or 16 (11-20, 6-34)
ART Regimen	
TLD	82 (22.6)
TEE	181 (50.0)
Other	1 (0.3)
Not specified	98 (27.1)
History of ART defaulting	
No	335 (92.5)
Yes	21 (5.8)
Unknown	6 (1.7)
History of ART regimen change (n=361) *	

Yes	27 (7.5)
No	164 (45.4)
Unknown	170 (47.1)
ART regimen change (n=27)	
TEE to TLD	26 (96.3)
TEE to [Atazanavir + Ritonavir + Truvada]	1 (3.7)

Abbreviations: ART – antiretroviral therapy, GA – gestational age, VL – viral load

*Total sum less than the cohorts sample size (due to missing data)

Overall, 306 patients (84.5%) had a VL done at delivery, and 295 patients (81.5%) had either a LTDL VL or less than 50 copies per ml at delivery. There were 11 incidences of VL rebound at delivery – 9 (2.5%) had more than 50 copies per ml and 2 (0.6%) had more than 1000 copies per ml. Table 5 illustrates the relationship between viral load rebound at delivery and demographic and clinical variables. Age was the only variable where there was a statistically significant association with VL rebound at delivery, with women older than 35 more likely to have a rebound.

Table 4: Details of viral load testing

Description	**n (%) or mean (SD) or median (IQR, range)**
1st VL result – copies/ml	
Lower than detectable limit	204 (56.4)
< 50 copies/ml	92 (25.4)

50 to 999 copies/ml 1000 and more copies/ml	36 (9.9) 30 (8.3)
GA at 1st VL suppression – weeks	22.1 (8.4); 22 (14-28, 6-40)
VL result at suppression – copies/ml Lower than detectable limit < 50 copies/ml	 245 (67.7) 117 (32.3)
VL at delivery – copies/ml Lower than detectable limit < 50 copies/ml 50 to 999 copies/ml 1000 and more copies/ml VL testing not done	 245 (67.7) 50 (13.8) 9 (2.5) 2 (0.6) 56 (15.5)

Table 5: The relationship between demographic and clinical characteristics in women who achieved HIV viral suppression at booking or during pregnancy, and viral load rebound at delivery

Variable	N** or Median (IQR)	No Viral Load Rebound median (IQR)	Viral Load Rebound median (IQR)	OR (95% CI)	P-value*
Demographic characteristics					
Age – years	32 (27-36)	31 (27-35)	39 (32- 40)	1.18 (1.04-1.33)	**0.049**
Age categories - years					
16-35	229	226 (76.6)	3 (27.3)	8.73 (2.26-33.83)	**0.001**
>35	77	69 (23.4)	8 (72.7)		
Parity	2 (1-2)	2 (1-2)	2 (1-2)	1.06 (0.63-1.78)	0.915
Parity categories					
Nullipara (0)	44 (14.4)	42 (14.2)	2(18.2)	0.99 (0.44-2.24)	0.777
Primipara (1)	107 (35.0)	104 (35.3)	3 (27.3)		

Multipara (2-5)	154 (50.3)	148 (50.2)	6 (54.5)		
Grand multipara	1 (0.3)	1 (0.3)	0 (0)		
Antenatal care (ANC) booking characteristics					
Gestational age (GA) at booking	17 (12-24)	17 (12-24)	20 (12-22)	0.99 (0.92-1.08)	0.957
GA at booking categories - weeks					
Early (<20 weeks)	176 (57.5)	171 (58.0)	5 (45.4)	1.6 (0.49-5.54)	0.537
Late (≥20 weeks)	130 (42.5)	124 (42.0)	6 (54.6)		
Total number of ANC visits	6 (5-8)	6 (5- 8)	7 (6- 8)	1.19 (0.87-1.62)	0.279
Clinical characteristics					
On chronic medication					
Yes	13 (4.2)	12 (4.1)	1 (9.09)	2.36 (0.28-19.95)	0.385
No	293 (95.8)	283 (95.9)	10 (90.9)		
Timing of HIV diagnosis (n=305) [ł]					
Pre-pregnancy	255 (83.6)	245 (83.3)	10 (90.9)	0.50 (0.06-3.90)	1.000
During pregnancy	49 (16.1)	48 (16.3)	1 (9.1)		

Unknown	1 (0.3)	1 (0.34)	0 (0)		
GA at HIV diagnosis – weeks (n=49)	16 (11-20)	16 (11-19.5)	26 (26-26)	1.27 (0.89-1.81)	-
Timing of ART initiation (n=302) [ł]					0.697
Pre-conception	250 (82.8)	240 (82.5)	10 (90.9)	0.47 (0.06-3.76)	
During pregnancy	52 (17.2)	51 (17.5)	1 (9.1)		
GA at ART initiation – weeks (n=52)	16 (11-20)	16 (11-20)	26 (26-26)	1.21 (0.91-1.61)	0.150
History of ART defaulting					
Yes	6 (2.0)	6 (2.0)	0 (0)	1.26 (0.422-3.78)	0.566
No	284 (92.8)	274 (92.9)	10 (90.9)		
Unknown	16 (5.2)	15 (5.1)	1 (9.1)		
History of ART regimen change (n=305) [ł]					
Yes	23 (7.54)	22 (7.5)	1 (9.09)	0.62 (0.24-1.58)	0.421
No	147 (48.2)	140 (47.6)	7 (63.6)		
Unknown	135 (44.3)	132(44.9)	3 (27.3)		

CD4 count – cells/mm^3 (n=280) [ł]	519 (379.5-679)	510 (373-673)	637 (471-691)	1.001 (1.00-1.00)	0.116
GA at 1st Viral Load (VL) testing - weeks	20 (13-26)	21 (13-27)	20 (12-22)	0.98 (0.90-1.05)	0.448
1st VL result – copies/ml					
Lower than detectable limit	170 (55.6)	163 (55.3)	7 (63.6)	1.04 (0.65- 1.66)	0.508
< 50 copies/ml	74 (24.2)	70 (23.7)	4 (36.4)		
> 50 copies/ml	32 (10.5)	32 (10.9)	0 (0)		
> 1000 copies/ml	30 (9.8)	30 (10.2)	0 (0)		
GA at 1st VL suppression - weeks	23 (14-29)	24 (14-29)	20 (12-22)	0.95 (0.89-1.02)	0.139
VL result at suppression – copies/ml					
Lower than detectable limit	207 (67.6)	200 (67.8)	7 (95)	1.20 (0.34-4.21)	0.751
< 50 copies/ml	99 (32.4)	95 (32.2)	4 (63.6)		

GA=gestational age; HIV=human immunodeficiency virus; VL=viral load; ANC=antenatal care; ART=antiretroviral therapy

The mean gestational age at delivery was 38.0 weeks (SD 3.1) and 98.1% (355) had a live birth – Table 6. Birth PCR was done for 337 neonates (93.1%), and all were negative.

Table 6: Delivery outcomes and PCR testing at birth, n=362

Description	n (%) or mean (SD) or median (IQR, range)
GA at delivery - weeks	38.0 (3.1) or 39 (37-40, 25-42)
Neonatal delivery outcome	
Alive	355 (98.0)
FSB	1 (0.3)
MSB	6 (1.7)
Birth weight - grams (n=352) *	2847.3 (630.8) or 2930 (2570-3245, 498-4495)
Adverse maternal/neonatal outcome condition (n=12)	
Abruptio placentae/FSB	1 (8.3)
Early neonatal death (END)	3 (25)
Low Apgar score	1 (8.3)
FSB and MSB	7 (58.3)
Birth PCR	
Done	337 (93.1)
Not recorded	18 (5.0)
Not done (stillbirths)	7 (1.9)
Birth PCR results (n=337)	
Negative	337 (100)

FSB=fresh stillbirth, MSB=macerated stillbirth PCR=polymerase chain reaction

Discussion

In this study, the majority of pregnant women (85.5%) were diagnosed with HIV prior to the index pregnancy and almost all of them were already on ART at the first antenatal visit. Of the women diagnosed in pregnancy, the diagnosis was made early in pregnancy at a mean gestational age of 15.9 weeks. In cases where the ART regimen was specified, less than a quarter were on TLD at the time of the study. While there were a few cases where there was deviation from guidelines with regards to the baseline VL done during pregnancy, over 80% of the PWLHIV were virally suppressed. There were gaps identified with regards to VL testing at the time of delivery with 56 women having no record of testing. The incidence of HIV VL rebound was low, with only 11 (3.6%) patients meeting the criteria for VL rebound. Age was the only variable significantly associated with VL rebound at the time of delivery. There were also gaps in infant HIV PCR testing with 18 of the live births having no recorded testing. Of the infants that were tested, all were negative.

Our finding that the majority of PWLHIV knew their HIV status, and were already on ART, prior to pregnancy is reassuring. In a study by Woldesenbet et al, done in South Africa, with data obtained from the South African national antenatal HIV sentinel surveys, they also found that 97.6% of pregnant women knew their HIV-positive status; 96.0% of those who knew their HIV status were on ART; and 66.0% of those on ART were virally suppressed.[16] While at the time of our study, less than a quarter of the women were on TLD, clinical evidence shows that TLD is now the first line regimen for PWLHIV. Overall, 89.0% of the women had a baseline CD4 count, and the median was high at 511 cell/mm^3. This finding is similar to that reported by Naicker et al, in a study done in KwaZulu Natal, South Africa, which found a baseline CD4 count of 543 cells/mm^3. [17]

There was consistency with the guidelines in doing VLs at booking for all known PWLHIV already on ART. This is reassuring and shows an improvement in baseline VL testing during pregnancy compared to what was reported by Moyo et al in their study, done at four tertiary obstetric units in Gauteng Province, South Africa, during the period between June 2018 and March 2019, they found a baseline VL testing rate of 18.4%. [18] With pregnant women newly diagnosed with HIV in our study, VL testing was not consistent with the guidelines, with a significant number of VLs done at diagnosis, and some before or long after the three months on ART mark stipulated in the guidelines. There were gaps in VL testing at the time of delivery with 56 (15.5%) PWLHIV with no record of VLs being done at delivery. These were known PWLHIV in the antenatal period, with their VLs done, and suppressed at some point during the antenatal period, who came to deliver at CHBAH. It is likely that some of the VLs were not recorded, but done, as attempts were made to trace the results in the laboratory system. There were several results that were not recorded on the files but were retrieved from the NHLS system during our data collection. In a study by Moyo et al, done in KwaZulu Natal Province, South Africa, in 2018 the rate of viral load testing at delivery was found to be only 30%. [19]

While there were gaps in VL testing, in those that were tested there was a high rate of VL suppression with only 11 (3.6%) of PWLHIV with evidence of viral rebound. Of the 11 women, nine had a VL of 50 copies/ml or greater, but less than a 1000 copies/ml, and only two had a viral load of 1000 copies/ml or more. Only maternal age was significantly associated with VL rebound at delivery, with women older than 35 years more likely to have a rebound. Our study was a retrospective record review, hence not possible to assess adherence and the impact on VL rebound. In a number of studies poor adherence has been cited as the biggest factor responsible for VL rebound.[20] Even though there are currently no published

studies in South Africa specifically looking at HIV VL rebound at delivery, the study by Onoya et al[12], done at Midwife Obstetric Units (MOUs) in peri-urban townships of the Tshwane, Ekurhuleni and Johannesburg Metropolitan districts in the Gauteng Province, South Africa, suggests a similar trend of low prevalence of rebound. In this study they found VL suppression rate of 43.5 % at ANC start and 69.3% at delivery for women with in-pregnancy ART, and 77.1% and 87.2% at ANC start and at delivery, respectively, for women with pre-pregnancy ART, suggesting a low rate of VL rebound.

With routine VL testing at delivery, a large number of PWLHIV are tested at delivery to reach the number needed to treat with extended infant prophylaxis to prevent one case of vertical transmission of HIV. However, what constitutes an important number needed to treat magnitude depends on disease severity and side effects of treatment. The benefit of preventing one single HIV transmission over the child's lifetime, and the minor side effects associated with AZT and NVP prophylaxis continue to justify routine HIV VL testing at delivery for all cases, including those with previously suppressed VLs in the same pregnancy. In our study, it is reassuring to note that in the infants who had a birth HIV PCR, there were no cases of vertical transmission.

The gaps identified in adherence to the guidelines need to be addressed if we are to achieve the HIV targets of 95-95-95. There is a need for continued professional development in the management of HIV in pregnancy, with regular quality improvement programmes and regular clinical audits. The PMTCT guidelines have since been updated after the study period and are now called the Vertical Transmission Prevention (VTP) guidelines. In the 2023 VTP guidelines there were no changes to the VL monitoring schedule.

While this is a retrospective record review with recognised limitations, the strength of the

study lies in the large sample size. The main limitation is that patient records may have been incomplete, with some tests being done but not recorded. The study was also done in a referral hospital and some patient information may have been retained at the referring facilities.

Conclusion

In conclusion, the majority of patients in our study remained virally suppressed at the time of delivery, with only a few cases of HIV VL rebound identified. However, VL testing at delivery, for all PWLHIV on ART is still justified to be able to identify those patients that are not suppressed and manage them accordingly. More effort is required to ensure health worker adherence to HIV management guidelines, a gap noted in the findings of this study.

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Appendix A: Approved Protocol

HIV viral load rebound at delivery in women on ART with previously suppressed viral load during the same pregnancy.

DR S MZENDANA

Registrar in Department of Obstetrics and Gynaecology, University of the Witwatersrand

MMed O&G

SUPERVISOR: DR CN Mnyani

District Clinical Specialist Team, Johannesburg Health District, and Department of Obstetrics and Gynaecology, School of Clinical Medicine, University of the Witwatersrand

Background and literature review

Human immunodeficiency virus (HIV) infection is persistently a problem for public health in poor nations, particularly in South Africa, where 4.7 million of the country's over 7.5 million HIV-positive people are women beyond the age of 19, reflecting the greatest disease burden in the world (1). Pregnant women are more likely to contract HIV than non-pregnant women, and if untreated, HIV can lead to negative pregnancy outcomes such as stillbirths, low birth weight, mother-to-child transmission (MTCT), and maternal mortality (2).

High maternal viral load (VL) is closely associated with the risk of MTCT and maternal HIV-associated complications (3). Antiretroviral treatment (ART) use and adherence among pregnant women on ART are the primary drivers of changes in VL in the absence of drug resistance. Unfortunately high levels of suboptimal ART adherence, disengagement from care and elevated VL have been widely documented among pregnant and postpartum women living

with HIV(WLHIV) globally (4). Therefore, frequent and timely viral load testing of pregnant WLHIV for rapid detection of elevated VL and intervention is critical to prevent MTCT and prevent maternal HIV-associated complications.

There are different strategies employed by different countries and organizations for HIV VL monitoring in pregnant and breastfeeding women. The World Health Organization (WHO) recommends VL testing at first antenatal care (ANC) visit for pregnant WLHIV already on ART, and at three months for newly diagnosed women initiated on ART. It further recommends a repeat VL at 34-36 weeks' gestation for all pregnant WLHIV(5). The US Department of Health and Human Services (DHHS) guidelines recommend a VL at booking, then at two to four weeks after ART initiation for newly diagnosed women. The guidelines also recommend a VL every three months for all pregnant WLHIV on ART (if VL<50 copies/ml) and at 34-36 weeks' gestation (6). At the other extreme, Malawi (2016) guidelines recommend a first VL test at six months for newly diagnosed women and then annually. Women already on ART at booking only continue with annual VL monitoring (7).

The South African prevention of mother-to-child transmission of HIV (PMTCT) program was developed to allow for widespread HIV testing and antiretroviral therapy (ART) coverage in the public sector. Since 2015, regardless of when the most recent VL was performed, the PMTCT guidelines have advised a VL test for WLHIV already on ART at the initial ANC visit to assess treatment response. A VL is advised for newly diagnosed HIV positive pregnant patients after three months of ART therapy (8). The recommendations were updated in November 2019 to require a VL test at delivery for all pregnant WLHIV (9).

It is without a doubt that meticulous VL monitoring in pregnancy is necessary if we are to achieve the Joint United Nations Programme on HIV and AIDS (UNAIDS) 90-90-90 and EMTCT targets (1). A study conducted in four Gauteng tertiary obstetric units by Moyo et al between June 2018 and March 2019 found that 20% of WLHIV had a VL of more than 1000 copies/ml and 36.4% had a VL of more than 50 copies/ml around the time of delivery(10). These are indeed significant and worrying numbers. In a retrospective cohort study by Boucoiran et al (11), done in the province of British Columbia, Canada, between the year 1997 and 2015, they found that 6% of women with previously suppressed VL had VL rebound near delivery, and 1.9% of these had VLs greater than 1000copies/ml (11).

Lesosky et al (12) did a simulation study looking at optimal timing of VL monitoring during pregnancy to predict viraemia at delivery in HIV- infected women initiating ART in South Africa. They found that the best-performing monitoring schedule was a single VL test at 36 weeks gestation. However, they also found that only 91% of all HIV-infected women would be tested at this time due to preterm deliveries(12).

Onoya, et al found that women who received ART prior to becoming pregnant had higher rates of viral suppression at delivery than women who received ART during pregnancy. The findings of the study demonstrated that, in comparison to women who were ART-naive at the start of ANC, pregnant WLHIV with pre-pregnancy ART are better able to preserve excellent immunological status and virological control in pregnancy. Additionally, they discovered that multiparity reduced the chance of viral suppression at delivery (13). Women who access ANC earlier and have fewer VLs and a higher CD4 cell count at their initial ANC visit are more likely to deliver with suppressed VLs (14). According to Langwenya et al (14), the duration of ART prior to delivery and viral load at the first ANC visit are both significant predictors of viral load

suppression at delivery.

When it comes to cost of HIV VL monitoring, there was a study conducted in 2019 (15) looking at comparative cost analysis of point-of-care versus laboratory-based testing to initiate and monitor HIV treatment in South Africa. The study showed that when considering clinic medical consumables, lab consumables and clinic staff costs, per-patient costs for HIV VL testing was found to be US$26 when performed at a laboratory (15), which is the current practice in our institutions. This amounts to about R410.00 per test per person at the current Rand to the U.S. dollar exchange rate.

Problem statement

Looking at the significant number of cases with VL rebound at delivery in women with previously suppressed VLs in other studies, and the risk of complications associated with VL non-suppression, especially risk of MTCT, it is worthwhile to investigate the scale of rebound in our setting. Knowing the scale of HIV VL rebound at delivery in pregnant WLHIV with previously suppressed VLs will help us answer the question of whether the current approach on VL monitoring is adequate, or whether we might need a different monitoring schedule that will ensure that all women with previously suppressed VLs remain suppressed at the critical time of delivery.

Hence the aim of this study is to investigate the prevalence of VL rebound at delivery in pregnant WLHIV with previously supressed VLs during the same pregnancy. As noted earlier, the current South African PMTCT guidelines recommend a repeat VL only at delivery for all women with a previously supressed VL at any point during the same pregnancy. This study will

give some indication of whether this is adequate practice or whether it might be associated with a high number of women with unsuppressed VL at delivery, with a missed opportunity for earlier intervention and high risk of MTCT. Another challenge is that the results of this VL done at delivery are mostly only available after the patients have been discharged from the hospital, and follow-up of such results might also be another potential drawback.

Objectives

1. To assess adherence to the 2019 PMTCT guidelines on VL testing during pregnancy, labour and postpartum.
2. To determine the prevalence of HIV VL rebound at delivery in women on ART with previously suppressed viral loads in the same pregnancy.
3. To identify risk factors associated with the likelihood of VL rebound at the time of delivery.

Setting

This study will be conducted in the obstetrics unit at Chris Hani Baragwanath Academic Hospital (CHBAH), in Soweto, Johannesburg.

Study design and study population

This will be a retrospective record review of PWLHIV on ART who delivered at CHBAH, in the period from 01 January to 31 December 2021. Viral load suppression will be defined as a VL of less than 50 copies/ml and VL rebound will be defined as VL of 50 copies/ml or more in patients with a previously suppressed VL.

Exclusion criteria

Pregnant WLHIV:

- who were not on ART during pregnancy
- with no VL tests done during the antenatal period
- with no suppressed VL during the antenatal period
- who were unbooked and presented for the first time in labour

Sample size

There were 3 908 pregnant WLHIV who delivered at CHBAH during the study period. It would therefore be impractical to include the whole population for this study due to constraints in time and human resources. Rather a sample will be drawn from this population using the simple random sampling technique, meaning the files will be selected randomly, collecting about 8 files per week. Using the Yamane equation, with the population of 3 908 at a confidence level of 95% and a margin of error of 0.05, the relevant sample size is calculated at 362.

Data collection

Firstly, all registers from various areas in the Department of Obstetrics and Gynaecology, namely admissions, first stage, high care area, Caesarian section theatre and postnatal wards, will be requested and utilised to identify WLHIV who delivered within the study period. Then using the details found in the registers, their files will be requested from the filing department. Data will be extracted from the files using a standardised data collection tool – Appendix A. Results that are not in the files will be checked from the National Health Laboratory Service (NHLS) database using the NHLS-labtrak system. Available laboratory barcodes and/ or patient

file numbers, names and surnames will be used to access patients' information via this system.

Variables to be collected

Demographics; timing and history of HIV diagnosis and ART initiation; history of any ART regimen change; VL testing during pregnancy and peripartum; and infant outcomes, including birth PCR testing.

Data analysis

Data will be recorded on REDCap, and Stata version 16.1 will be used for data analysis (Stata Corporation, College Station, USA). To investigate links between virologic suppression at delivery and demographic and clinical factors, descriptive statistics and bivariate logistic regressions will be used. By using likelihood ratio tests, the significance of the bivariate associations will be assessed. Statistical significance will be recognized as being indicated by P values lower than 0.05.

Ethics

Confidentiality will be strictly maintained. No personal data like patient names, surnames and address will be included in the data collection tools. Names and surnames of patients included in the study will be kept separately and used in cases where laboratory results need to be accessed from the NHLS system. Files will formally be requested for, counted, only handle and returned by the researcher. Formal ethics application will be made to the University of the Witwatersrand Human Ethics Research Committee. Permission to conduct the study will be sought from the Chief Executive Officer at CHBAH.

Funding

No external funding will be sought for this study. Any necessary costs will be incurred by the researcher.

Limitations

It might not be possible to access all the files needed due to missing records. Also, crucial information might be missed as only the information in the files will be relied on, with no interviews conducted.

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Appendix B: Data collection tool

File number: _____ Study number: ☐☐☐☐

Antenatal details

Age: ____ years Parity: ____ Gravidity: ____

Booked: Y/N Gestational age at booking: ____ weeks

Date of first antenatal visit:

Gestational age determined by: LNMP/palpation/ultrasound

Facility where antenatal care accessed: ☐ CHC ☐ PHC ☐ District Hospital ☐ Regional Hospital ☐ Private practitioner ☐ other, specify _____

Total number of antenatal visits:

Medical history:

☐ Hypertension ☐ Diabetes ☐ Asthma ☐ Epilepsy ☐ TB ☐ other, specify _____

On chronic medication: Y/N If yes, specify _____

_____

Social history:

Use during pregnancy: smoking/ alcohol/ drugs/ nil/unknown

Employed: Y/N/unknown

Tests done:

Rhesus: positive/ negative/ unknown

Syphilis test: positive/ negative/ unknown

If syphilis test positive, was treatment completed: Y/N

Weight: _____ Height: _____ Body mass index: _____ MUAC: _____

Details on HIV testing

Timing of HIV diagnosis: prepregnancy/ during pregnancy/ unknown

If during pregnancy, gestational age at HIV diagnosis:

ART regimen: TEE/ TLD/ other, specify _____

When ART initiated: preconception/ during pregnancy

If ART initiated during pregnancy, gestational age at ART initiation: _____ weeks

If ART initiated prepregnancy, date of ART initiation _____

Any history of defaulting ART: Yes/No/not documented

Any ART regimen change: Yes/No

If yes, specify: _____

CD4 count (last done in pregnancy): date and value: _____

Viral load testing:

Timing of VL	Yes/No	Date	Barcode	Result
During pregnancy				
During labour				
Postpartum				

Antenatal ultrasound(s) done: Y/N If yes, any abnormal ultrasound findings: Y/N

If abnormal findings, was it: ☐ IUGR ☐ oligohydramnios ☐ polyhydramnios ☐ abnormal UARI

Other, specify
_____

Medical condition diagnosed in pregnancy:

nil/ hypertension/ diabetes/ cardiac disease/ asthma/ epilepsy/ autoimmune disease/ TB/ other, specify _____

Medication started during pregnancy:
_____

_____
_____

Comments: _____

_____

Delivery details

Date of delivery: ___/___/___ Place of delivery: CHBAH BBA ☐

Alive/Fresh stillbirth/ macerated stillbirth Birth weight: _____ g

Birth PCR done: Yes/No/unknown

Birth PCR result: negative/positive/indeterminate/unknown

Barcode if done:

Comments:
_____

_____
_____

_____
_____

Appendix C: permission letters to conduct the Study

GAUTENG PROVINCE

REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 29th November 2022

TITLE OF PROJECT:

HIV viral load rebound at delivery in women on ART with previously suppressed viral load during the same pregnancy.

UNIVERSITY: Witwatersrand

Principal Investigator: Dr S Mzendana

Department: Obstetrics & Gynaecology

Supervisor : Dr C N Mnyani

Permission Head Department (where research conducted): Yes

NHRD No. GP_202211_059

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- **Permission having been granted by the Committee for Research on Human Subjects of the University of Witwatersrand.**
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval.

Recommended
(On behalf of the MAC)
Date: 29/11/2022

Approved/~~Not Approved~~
Hospital Management
Date: 30/11/2022

COST TO HOSPITAL AND OR PATIENTS? No

SOURCE OF FUNDING: Application will be made to the Wits School Of clinical Medicine (SOCM) MMed fund for the conference registration fee. Other costs will be incurred by the researcher.

APPROVAL OF HOD Y/N

Academic Department of Obstetrics + Gynaecology
Chris Hani Baragwanath Academic Hospital

Date: 03-11-2022

Signed:

SIGNATURE	NAME IN PRINT+ DESIGNATION	OFFICAL STAMP+ DATE
	Tasnim Adam HOD	

Appendix D: Ethics Certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr Siseko Mzendana

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M230124 MED22-10-116

NAME: (Principal Investigator)	Dr Siseko Mzendana
DEPARTMENT:	Obstetrics and Gynaecology Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Human immunodeficiency virus (HIV) viral load rebound at delivery in women on antiretroviral therapy, with previously suppressed viral load during the same pregnancy
DATE CONSIDERED:	27/01/2023
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Coceka Mnyani and Dr Vuyelwa Baba
APPROVED BY:	Dr C Penpy, Chairperson, HREC (Medical)
DATE OF APPROVAL:	15/03/2023 **EXPIRY DATE:** 15/03/2028

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report** in January each year until study is closed. Failure to submit annual report will result in ethics clearance certificate suspension. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed January and will therefore be due in the month of January each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical). Login to upload signed copy of this ethics clearance certificate prior to commencing with the study https://www.witsethics.co.za/login.aspx

Principal Investigator Signature

11/08/2023
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix E: Turnitin plagiarism report

HIV VIRAL LOAD REBOUND AT DELIVERY IN WOMEN ON ART WITH PREVIOUSLY SUPPRESSED VIRAL LOADS

DURING THE SAME PREGNANCY.docx

by Siseko Mzendana

Submission date: 22-Oct-2024 03:09PM (UTC+0200) **Submission ID:** 2493546368 **File name:** HIV_VIRAL_LOAD_REBOUND_AT_DELIVERY_IN_WOMEN_ON_ART_WITH_PREVIOUSLY_SUPPRESSED_VIRAL_LOADS_DURING_THE_SAME_PREGNANCY.docx (91.84K)

Word count: 4569

Character count: 22958

HIV VIRAL LOAD REBOUND AT DELIVERY IN WOMEN ON ART WITH PREVIOUSLY SUPPRESSED VIRAL LOADS DURING THE SAME PREGNANCY.docx

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HIV VIRAL LOAD REBOUND AT DELIVERY IN WOMEN ON ART WITH PREVIOUSLY SUPPRESSED VIRAL LOADS DURING THE SAME PREGNANCY

Siseko Mzendana

ABSTRACT

Background

HIV viral load (VL) non-suppression can lead to adverse pregnancy outcomes, including vertical transmission (VT). Therefore, it is crucial to achieve and maintain viral suppression during pregnancy.

Objectives

The objectives of this study were to investigate the prevalence of HIV VL rebound at delivery in women with previously suppressed VLs in the same pregnancy, and also evaluate adherence to the 2019 PMTCT guidelines on VL testing.

Methods

This was a retrospective record review of pregnant women living with HIV (PWLHIV) and on antiretroviral therapy (ART) who delivered at Chris Hani Baragwanath Academic Hospital during the period 01 January to 31 December 2021. Participants were randomly selected and data on demographics, timing and history of HIV diagnosis and treatment, VL testing during pregnancy and delivery, and infant outcomes were extracted.

Results

A total of 362 PWLHIV were included in the study and the majority (85.5%) were diagnosed with HIV prior to the index pregnancy and almost all were on ART at the first antenatal visit. HIV VL rebound was diagnosed in 11 women (3.1%), and of these, nine (82%) had a VL between 50 and 1000 copies per ml, and two (18%) had a VL >1000 copies per ml. Overall, 56 (15.5%) women had no VLs done at delivery. Age was the only variable significantly associated with VL rebound at the time of delivery. No cases of VT were identified.

Conclusion

The low rate of HIV VL rebound at delivery is reassuring. While there was evidence of adherence to PMTCT guidelines in terms ART initiation and monitoring, there are still gaps

Introduction

Human immunodeficiency virus (HIV) infection is persistently a challenge for public health in South Africa, where in 2022 there were an estimated 7.5 million people living with HIV (PLHIV), with 27.5% of women attending antenatal care having a positive HIV status, representing the greatest disease burden in the world.[1] Pregnant women are more likely to contract HIV than non-pregnant women, and if untreated, HIV can lead to negative pregnancy outcomes such as stillbirths, low birth weight, mother-to-child transmission (MTCT), and maternal mortality.[2]

High maternal viral load (VL) is closely associated with the risk of vertical transmission (VT) and maternal HIV- associated complications.[2] Antiretroviral treatment (ART) use and adherence among pregnant women on ART are the primary drivers of changes in VL in the absence of drug resistance. Suboptimal ART adherence, disengagement from care and elevated VL have been widely documented among pregnant and postpartum women living with HIV.[3] Therefore, frequent and timely viral load testing of pregnant women living with HIV (PWLHIV) for rapid detection of elevated VL and intervention is critical to prevent vertical transmission and prevent maternal HIV-associated complications.

There are different strategies employed by different countries and organizations for HIV monitoring in pregnant and breastfeeding women. The World Health Organization (WHO) recommends VL testing at first antenatal care (ANC) visit for PWLHIV already on ART at ANC start, and at three months for newly diagnosed women initiated on ART. It further recommends a repeat VL at 34-36 weeks' gestation for all PWLHIV.[4] The US Department of Health and Human Services (DHHS) guidelines recommend a VL at booking, then at two to

four weeks after ART initiation for newly diagnosed women. The guidelines also recommend a VL every three months for all pregnant WLHIV on ART (if VL<50 copies/ml) and at 34-36 weeks gestation.[5] At the other extreme, Malawi (2016) guidelines recommend a first VL test at six months for newly diagnosed women and then annually. Women already on ART at booking only continue with annual VL monitoring.[6]

The South African prevention of mother-to-child transmission of HIV (PMTCT) programme has developed to allow for widespread HIV testing and ART coverage in the public sector. Since 2015, regardless of when the most recent VL was performed, the PMTCT guidelines have advised a VL test for WLHIV already on ART at the initial ANC visit to assess treatment response. A VL is advised for WLHIV newly diagnosed with HIV during pregnancy, after three months of ART.[7] The guidelines were updated in November 2019 to include a VL test at delivery for all PWLHIV on ART.[8]

Meticulous VL monitoring in pregnancy is necessary if we are to achieve the Joint United Nations Programme on HIV and AIDS (UNAIDS) 95-95-95 and elimination of (MTCT) eMTCT targets.[9] A study conducted in four Gauteng tertiary obstetric units by Moyo et al, between June 2018 and March 2019, found that 20% of WLHIV had a VL of more than 1000 copies/ml, and 36.4% had a VL of more than 50 copies/ml, around the time of delivery.[10] These are indeed significant and worrying numbers. Lesosky et al did a simulation study looking at optimal timing of VL monitoring during pregnancy, to predict viraemia at delivery in PWLHIV initiating ART in South Africa. They found that the best-performing monitoring schedule was a single VL test at 36 weeks gestation. However, they also found that only 91% of all HIV-infected women would be tested at this time due to preterm deliveries.[11]

Onoya et al, in a study done at Midwife Obstetric Units (MOUs) in peri-urban townships of the Tshwane, Ekurhuleni and Johannesburg Metropolitan districts in the Gauteng Province of

South Africa found that women who initiated ART prior to pregnancy had higher rates of viral suppression at delivery than women who initiated ART during pregnancy. The findings of the study demonstrated that in comparison to women who were ART-naive at the start of ANC, PWLHIV with pre-pregnancy ART are better able to preserve immunologic status and virologic control in pregnancy.[12] According to Langwenya et al., in their study done in Cape Town, South Africa, at a primary care facility, the duration of ART prior to delivery and viral load at the first ANC visit are both significant predictors of viral load suppression at delivery.[13] Women who accessed ANC earlier and had lower VLs and higher CD4 cell counts at their initial ANC visit were more likely to deliver with suppressed VLs.[13] While there are data on factors associated with viral suppression at delivery, there is limited information on the prevalence of peripartum VL rebound. Hence the aim of this study was to investigate the prevalence of HIV VL rebound at delivery in women who delivered at Chris Hani Baragwanath Academic Hospital (CHBAH), and had previously supressed VLs during the same pregnancy.

Methods

Setting

This study was conducted in the obstetrics unit at CHBAH, in Soweto, Johannesburg, South Africa. The obstetrics unit at CHBAH sees high risk pregnancies referred from the surrounding primary healthcare facilities, and district and regional hospitals. At the time of the study, the recorded prevalence of HIV in pregnant women was 24% in the City of Johannesburg district, which was lower than the national average of 27.5%. [14]

Study Design And Study Population

This was a retrospective record review of PWLHIV on ART who delivered at CHBAH, in the period from 01 January to 31 December 2021. During the study period, the 2019 PMTCT guidelines were being used and included in these was guidance on VL monitoring during the

antenatal period, and peripartum – Table 1. The standard practice during this period included HIV viral load testing at booking for all women entering antenatal care with a known positive HIV status and already on ART, a viral load at 3 months after diagnosis for those newly initiated on ART, and a viral load test for all PWLHIV on ART at delivery. Antenatal viral load tests were done at the National Health Laboratory Service (NHLS) laboratories serving the corresponding healthcare centres where the individual patients attended ANC. All VL tests at delivery were done at the CHBAH NHLS laboratory. Viral load suppression was defined as a VL of less than 50 copies/ml, and VL rebound was defined as VL of 50 copies/ml or more in patients with a previously suppressed VL.

Table 1: 2019 HIV viral load monitoring schedule.[8]

Newly initiating ART or re-initiating on a DTG-based regimen (before 28 weeks' gestation)	**Already on ART at pregnancy diagnosis**	**Late presentation for ANC after 28 weeks, or at delivery**
First [redacted] at 3 [redacted] on ART	VL at ANC first visit	First VL at delivery
All women get a VL at delivery (results must be checked at postnatal visit before 6 days)		

ART=antiretroviral treatment; DTG=dolutegravir; ANC=antenatal care; VL=viral load

Inclusion criteria: PWLHIV who were on ART during the index pregnancy and had at least one suppressed VL during the antenatal period, and delivered at CHBAH during the study period. Exclusion criteria: Pregnant WLHIV who were unbooked and presented for the first time in labour, and were not on ART during pregnancy were excluded. Also excluded were patients with no VL tests done during the antenatal period, and those that had VLs done during the antenatal period but were unsuppressed.

There were 3 908 pregnant WLHIV who delivered at CHBAH during the study period. Using the Yamane equation, with the population of 3 908 at a confidence level of 95% and a margin

of error of 0.05, the relevant sample size was calculated at 362. PWLHIV and on ART were identified from admission and delivery registers and names were selected randomly by numbering all the 3908 names, then used a random number generator to get random numbers. Names and/or file numbers that corresponded to each of those random numbers were then selected to form part of the sample. A total of 553 files were retrieved from the records department and 191 were excluded for various reasons, leading to 362 files that met the inclusion criteria – Figure 1.

Data were extracted from the files using a standardised data collection tool and information was collected on demographics; timing and history of HIV diagnosis and ART initiation; history of any ART regimen change; VL testing during pregnancy and peripartum; and infant outcomes, including birth PCR testing. Results that were not in the files were checked from the NHLS database using the NHLS-labtrak system. Laboratory barcodes were used to access patients' results and where barcodes were not available, patients' file numbers, names and surnames were used.

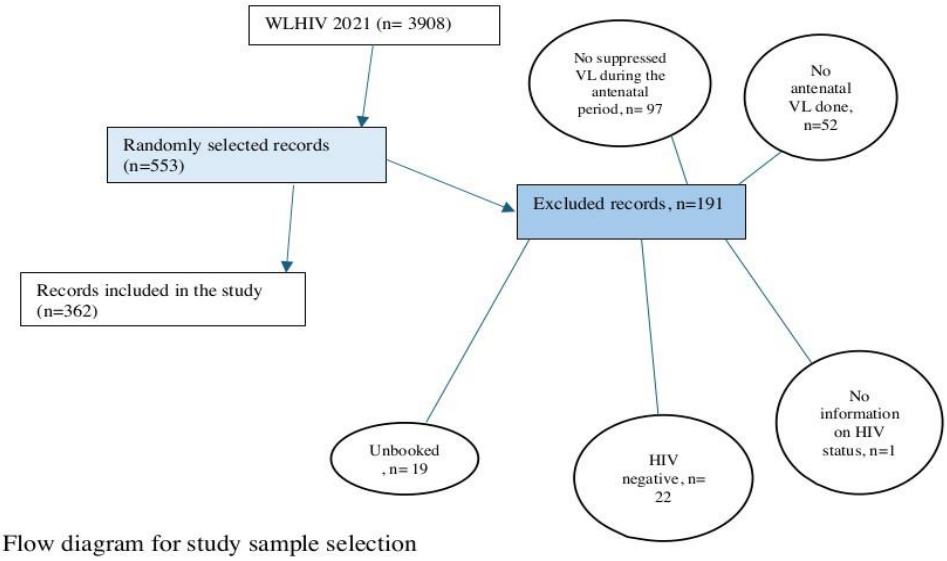

Figure 1. Flow diagram for study sample selection

Data analysis

Data were recorded on Research Electronic Data Capture (REDCap),[15] and Stata version 18 was used for data analysis (Stata Corporation, College Station, USA). To identify risk factors associated with the likelihood of VL rebound at the time of delivery, demographic and clinical factors were analysed using descriptive statistics and bivariate logistic regressions. By using likelihood ratio tests, the significance of the bivariate associations was assessed. Statistical significance was recognized as being indicated by P values lower than 0.05.

Ethical considerations

Ethics clearance was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (No. M230124 MED11-10-116). Permission to conduct the study was obtained from the Chief Executive Officer and the head of obstetrics and gynaecology department at CHBAH. Confidentiality was strictly maintained. No personal data, i.e. patient names, surnames and address, were included in the data collection tools. Names and surnames were kept separately and used in cases where laboratory results needed to be accessed from the NHLS system.

RESULTS

A total of 362 patients were included in the study. The mean maternal age was 31.4 years (standard deviation (SD) 5.9), with 273 (75.4%) in the age group 16 to 35 years, and 89 (24.6%) older than 35 years – Table 2. A total of 201 (55.5%) were employed, 102 (28.2%) unemployed, and the employment status was unknown for 59 (16.3%). All patients had accessed ANC, and the mean gestational age at the first antenatal visit was 18.4 weeks, SD: 7.4. A total of 17 (4.7%) participants were on chronic medication – 12 (70.6%) were on antihypertensives, 2 (11.8%) were on hypoglycaemics, and one each (5.9%) on medication for epilepsy, asthma and cardiac disease. Antenatal ultrasound was done for 338 patients (93.4%) and there was no record of any antenatal ultrasound for 24 (6.6%).

Table 2: Demographic and clinical characteristics, n=362)

Characteristic	n (%)
Age – years Mean (SD) – 31.4 (5.9)	
Age categories – years 16-35 >35	 273 (75.4) 89 (24.6)
Body mass index Underweight Normal Overweight Obese ▪ class 1 ▪ class 2 ▪ class 3	 2 (0.7) 80 (26.1) 86 (28.1) 65 (21.2) 41 (13.4) 32 (10.46)
Parity Median (IQR) – 2 (1 – 2)	
Parity categories Nullipara (0) Primipara (1) Multipara (2-5) Grand multipara	 49 (13.5) 120 (33.2) 192 (53.0) 1 (0.3)
Gravidity Median (IQR) – 2 (1 -3)	
Gravidity categories Primi-gravida (Gravida 1) Multipara (2-5) Grand multipara (>5)	 40 (11.0) 309 (85.4) 13 (3.6)
ANC booking Yes	 362 (100)
Total number of ANC visits Median (IQR) – 6 (5 – 8)	
GA at booking categories - weeks Early (<20 weeks) Late (≥20 weeks)	 208 (57.5) 154 (42.5)
GA determination method LNMP Palpation Early ultrasound (≤24 weeks) Late ultrasound	 195 (53.9) 31 (8.6) 111 (30.7) 25 (6.9)

ANC facility	
PHC	164 (45.3)
CHC	155 (42.8)
District hospital	21 (5.8)
Tertiary Hospital	18 (5.0)
Regional Hospital	4 (1.1)
Medical conditions	
None	343 (94.8)
Chronic hypertension	10 (2.8)
Hypertensive disorders of pregnancy	2 (0.6)
Diabetes	2 (0.6)
Cardiac disease	1 (0.3)
Asthma	1 (0.3)
Epilepsy	1 (0.3)

ANC=antenatal care; PHC=primary health care; CHC=community health centre

There were 10 (2.8%) patients that had a positive syphilis test, and five received three doses of bicillin, and for the other five, no treatment was recorded.

Overall, 359 (99.1%) patients had records of when HIV diagnosis was made – 307 (85.5%) prior to the index pregnancy, 52 (14.5%) were diagnosed during the index pregnancy, with a mean gestational age (GA) at HIV diagnosis of 15.9 weeks (SD 6.3) – Table 3. The mean GA at first HIV VL testing was 20.4 weeks (SD 7.9) – 296 (81.8%) had a VL of either lower than detectable limit (LTDL) or less than 50 copies per ml; 36 (9.9%) had a VL of more than 50 copies per ml, and 30 (8.3%) had a VL of more than 1000 copies/ml.

Among the 52 women who were diagnosed during the index pregnancy, 44.2% (n=23) had their first VL done at 3 months after diagnosis and ART initiation, 8 (15.4%) were done at diagnosis, 7 (13.5%) at one month, 6 (11.5%) at 2 months and 4 months respectively, and 2 (3.8%) were done at 5 months after diagnosis and ART initiation. All (n=307) of the women that were diagnosed prior to the index pregnancy had their first VLs done at booking. The mean GA at first suppressed VL for both patients already on ART and those newly initiated in the index pregnancy combined was 22.1 weeks (SD 8.4).

Table 3: Details of HIV diagnosis and ART initiation, n=362

Description	**n (%), or mean (SD), or median (IQR, range)**
Timing of HIV diagnosis (n=362)*	

Pre-pregnancy During pregnancy Unknown	307 (85.0) 52 (14.4) 3 (0.8)
GA (weeks) at HIV diagnosis for those diagnosed during pregnancy (n=52)	15.9 (6.3); 16 (11.5-20, 6-33)
Baseline CD4 count – cells/mm^3 (n=322)*	532.9 (237.6); 511 (381-678, 24-1477)
Timing of ART initiation (n=358)* Pre-conception During pregnancy	 303 (84.6) 55 (15. 4)
GA at ART initiation – weeks (n=55)	16.1 (6.7) or 16 (11-20, 6-34)
ART Regimen TLD TEE Other Not specified	 82 (22.6) 181 (50.0) 1 (0.3) 98 (27.1)
History of ART defaulting No Yes Unknown	 335 (92.5) 21 (5.8) 6 (1.7)
History of ART regimen change (n=361) * Yes No Unknown	 27 (7.5) 164 (45.4) 170 (47.1)
ART regimen change (n=27) TEE to TLD TEE to [Atazanavir + Ritonavir + Truvada]	 26 (96.3) 1 (3.7)

Abbreviations: ART – antiretroviral therapy, GA – gestational age, VL – viral load

*Total sum less than the cohorts sample size (due to missing data)

Overall, 306 patients (84.5%) had a VL done at delivery, and 295 patients (81.5%) had either a LTDL VL or less than 50 copies per ml at delivery. There were 11 incidences of VL rebound at delivery – 9 (2.5%) had more than 50 copies per ml and 2 (0.6%) had more than 1000 copies per ml. Table 5 illustrates the relationship between viral load rebound at delivery and demographic and clinical variables. Age was the only variable where there was a statistically significant association with VL rebound at delivery, with women older than 35 more likely to have a rebound.

Table 4 : **Details of viral load testing**

Description	**n (%) or mean (SD) or median (IQR, range)**
1st VL result – copies/ml	
Lower than detectable limit	204 (56.4)
< 50 copies/ml	92 (25.4)
50 to 999 copies/ml	36 (9.9)
1000 and more copies/ml	30 (8.3)
GA at 1st VL suppression – weeks	22.1 (8.4); 22 (14-28, 6-40)
VL result at suppression – copies/ml	
Lower than detectable limit	245 (67.7)
< 50 copies/ml	117 (32.3)
VL at delivery – copies/ml	
Lower than detectable limit	245 (67.7)
< 50 copies/ml	50 (13.8)
50 to 999 copies/ml	9 (2.5)
1000 and more copies/ml	2 (0.6)
VL testing not done	56 (15.5)

Table 5 1: **The relationship between demographic and clinical characteristics in women who achieved HIV viral suppression at booking or during pregnancy, and viral load rebound at delivery.**

Variable	N** or Median (IQR)	No Viral Load Rebound median (IQR)	Viral Load Rebound median (IQR)	OR (95% CI)	P-value*
Demographic characteristics					
Age – years	32 (27-36)	31 (27-35)	39 (32- 40)	1.18 (1.04-1.33)	**0.049**
Age categories - years 16-35 >35	 229 77	 226 (76.6) 69 (23.4)	 3 (27.3) 8 (72.7)	8.73 (2.26-33.83)	**0.001**
Parity	2 (1-2)	2 (1-2)	2 (1-2)	1.06 (0.63-1.78)	0.915
Parity categories Nullipara (0) Primipara (1) Multipara (2-5) Grand multipara	 44 (14.4) 107 (35.0) 154 (50.3) 1 (0.3)	 42 (14.2) 104 (35.3) 148 (50.2) 1 (0.3)	 2(18.2) 3 (27.3) 6 (54.5) 0 (0)	0.99 (0.44-2.24)	0.777
Antenatal care (ANC) booking characteristics					
Gestational age (GA) at booking	17 (12-24)	17 (12-24)	20 (12-22)	0.99 (0.92-1.08)	0.957
GA at booking categories - weeks Early (<20 weeks) Late (≥20 weeks)	 176 (57.5) 130 (42.5)	 171 (58.0) 124 (42.0)	 5 (45.4) 6 (54.6)	1.6 (0.49-5.54)	0.537
Total number of ANC visits	6 (5-8)	6 (5- 8)	7 (6- 8)	1.19 (0.87-1.62)	0.279
Clinical characteristics					
On chronic medication Yes No	 13 (4.2) 293 (95.8)	 12 (4.1) 283 (95.9)	 1 (9.09) 10 (90.9)	2.36 (0.28-19.95)	0.385

Timing of HIV diagnosis (n=305) [1] Pre-pregnancy During pregnancy Unknown	 255 (83.6) 49 (16.1) 1 (0.3)	 245 (83.3) 48 (16.3) 1 (0.34)	 10 (90.9) 1 (9.1) 0 (0)	0.50 (0.06-3.90)	1.000
GA at HIV diagnosis – weeks (n=49)	16 (11-20)	16 (11-19.5)	26 (26-26)	1.27 (0.89-1.81)	-
Timing of ART initiation (n=302) [1] Pre-conception During pregnancy	 250 (82.8) 52 (17.2)	 240 (82.5) 51 (17.5)	 10 (90.9) 1 (9.1)	0.47 (0.06-3.76)	0.697
GA at ART initiation – weeks (n=52)	16 (11-20)	16 (11-20)	26 (26-26)	1.21 (0.91-1.61)	0.150
History of ART defaulting Yes No Unknown	 6 (2.0) 284 (92.8) 16 (5.2)	 6 (2.0) 274 (92.9) 15 (5.1)	 0 (0) 10 (90.9) 1 (9.1)	1.26 (0.422-3.78)	0.566
History of ART regimen change (n=305) [1] Yes No Unknown	 23 (7.54) 147 (48.2) 135 (44.3)	 22 (7.5) 140 (47.6) 132(44.9)	 1 (9.09) 7 (63.6) 3 (27.3)	0.62 (0.24-1.58)	0.421
CD4 count – cells/mm^3 (n=280) [1]	519 (379.5-679)	510 (373-673)	637 (471-691)	1.001 (1.00-1.00)	0.116
GA at 1st Viral Load (VL) testing - weeks	20 (13-26)	21 (13-27)	20 (12-22)	0.98 (0.90-1.05)	0.448
1st VL result – copies/ml Lower than detectable limit < 50 copies/ml > 50 copies/ml > 1000 copies/ml	 170 (55.6) 74 (24.2) 32 (10.5) 30 (9.8)	 163 (55.3) 70 (23.7) 32 (10.9) 30 (10.2)	 7 (63.6) 4 (36.4) 0 (0) 0 (0)	1.04 (0.65- 1.66)	0.508
GA at 1st VL suppression - weeks	23 (14-29)	24 (14-29)	20 (12-22)	0.95 (0.89-1.02)	0.139

VL result at suppression – copies/ml Lower than detectable limit < 50 copies/ml	207 (67.6) 99 (32.4)	200 (67.8) 95 (32.2)	7 (95) 4 (63.6)	1.20 (0.34-4.21)	0.751

GA=gestational age; HIV=human immunodeficiency virus; VL=viral load; ANC=antenatal care; ART=antiretroviral therapy

The mean gestational age at delivery was 38.0 weeks (SD 3.1) and 98.1% (355) had a live birth – Table 6. Birth PRC was done for 337 neonates (93.1%), and all were negative.

Table 6 1 : **Delivery outcomes and PCR testing at birth, n=362**

Description	n (%) or mean (SD) or median (IQR, range)
GA at delivery - weeks	38.0 (3.1) or 39 (37-40, 25-42)
Neonatal delivery outcome	
Alive	355 (98.0)
FSB	1 (0.3)
MSB	6 (1.7)
Birth weight - grams (n=352) *	2847.3 (630.8) or 2930 (2570-3245, 498-4495)
Adverse maternal/neonatal outcome condition (n=12)	
Abruptio placentae/FSB	1 (8.3)
Early neonatal death (END)	3 (25)
Low Apgar score	1 (8.3)
FSB and MSB	7 (58.3)
Birth PCR	
Done	337 (93.1)
Not recorded	18 (5.0)
Not done (stillbirths)	7 (1.9)
Birth PCR results (n=337)	
Negative	337 (100)

FSB=fresh stillbirth, MSB=macerated stillbirth PCR=polymerase chain reaction

DISCUSSION

In this study, the majority of pregnant women (85.5%) were diagnosed with HIV prior to the index pregnancy and almost all of them were already on ART at the first antenatal visit. Of the women diagnosed in pregnancy, the diagnosis was made early in pregnancy at a mean gestational age of 15.9 weeks. In cases where the ART regimen was specified, less than a quarter were on TLD at the time of the study. While there were a few cases where there was deviation from guidelines with regards to the baseline VL done during pregnancy, over 80% of the PWLHIV were virally suppressed. There were gaps identified with regards to VL testing at the time of delivery with 56 women having no record of testing. The incidence of HIV VL rebound was low, with only 11 (3.6%) patients meeting the criteria for VL rebound. Age was the only variable significantly associated with VL rebound at the time of delivery. There were also gaps in infant HIV PCR testing with 18 of the live births having no recorded testing. Of the infants that were tested, all were negative.

Our finding that the majority of PWLHIV knew their HIV status, and were already on ART, prior to pregnancy is reassuring. In a study by Woldesenbet et al, done in South Africa, with data obtained from the South African national antenatal HIV sentinel surveys, they also found that 97.6% of pregnant women knew their HIV-positive status; 96.0% of those who knew their HIV status were on ART; and 66.0% of those on ART were virally suppressed.[16] While at the time of our study, less than a quarter of the women were on TLD, clinical evidence shows that TLD is now the first line regimen for PWLHIV. Overall, 89.0% of the women had a baseline CD4 count, and the median was high at 511 cell/mm^3. This finding is similar to that reported by Naicker et al, in a study done in KwaZulu Natal, South Africa, which found a baseline CD4 count of 543 cells/mm^3.[17]

There was consistency with the guidelines in doing VLs at booking for all known PWLHIV already on ART. This is reassuring and shows an improvement in baseline VL testing during pregnancy compared to what was reported by Moyo et al. In their study, done at four tertiary obstetric units in Gauteng Province, South Africa, during the period between June 2018 and March 2019, they found a baseline VL testing rate of 18.4%.[18] With pregnant women newly diagnosed with HIV in our study, VL testing was not consistent with the guidelines, with a significant number of VLs done at diagnosis, and some before or long after the three months on ART mark stipulated in the guidelines. There were gaps in VL testing at the time of

delivery with 56 (15.5%) PWLHIV with no record of VLs being done at delivery. These were known PWLHIV in the antenatal period, with their VLs done, and suppressed at some point during the antenatal period, who came to deliver at CHBAH. It is likely that some of the VLs were not recorded, but done, as attempts were made to trace the results in the laboratory system. There were several results that were not recorded on the files but were retrieved from the NHLS system during our data collection. In a study by Moyo et al, done in KwaZulu Natal Province, South Africa, in 2018 the rate of viral load testing at delivery was found to be only 30%. [19]

While there were gaps in VL testing, in those that were tested there was a high rate of VL suppression with only 11 (3.6%) of PWLHIV with evidence of viral rebound. Of the 11 women, nine had a VL of 50 copies/ml or greater, but less than a 1000 copies/ml, and only two had a viral load of 1000 copies/ml or more. Only maternal age was significantly associated with VL rebound at delivery, with women older than 35 years more likely to have a rebound. Our study was a retrospective record review, hence not possible to assess adherence and the impact on VL rebound. In a number of studies poor adherence has been cited as the biggest factor responsible for LV rebound.[20] Even though there are currently no published studies in South Africa specifically looking at HIV VL rebound at delivery, the study by Onoya et al[12], done at Midwife Obstetric Units (MOUs) in peri-urban townships of the Tshwane, Ekurhuleni and Johannesburg Metropolitan districts in the Gauteng Province, South Africa, suggests a similar trend of low prevalence of rebound. In this study they found VL suppression rate of 43.5 % at ANC start and 69.3% at delivery for women with in-pregnancy ART, and 77.1% and 87.2% at ANC start and at delivery, respectively, for women with pre-pregnancy ART, suggesting a low rate of VL rebound.

With routine VL testing at delivery, a large number of PWLHIV are tested at delivery to reach the number needed to treat with extended infant prophylaxis to prevent one case of vertical transmission of HIV. However, what constitutes an important number needed to treat magnitude depends on disease severity and side effects of treatment. The benefit of preventing one single HIV transmission over the child's lifetime, and the minor side effects associated with AZT and NVP prophylaxis continue to justify routine HIV VL testing at delivery for all cases, including those with previously suppressed VLs in the same pregnancy. In our study, it is reassuring to note that in the infants who had a birth HIV PCR, there were no cases of vertical transmission.

The gaps identified in adherence to the guidelines need to be addressed if we are to achieve the HIV targets of 95-95-95. There is a need for continued professional development in the management of HIV in pregnancy, with regular quality improvement programmes and regular clinical audits. The PMTCT guidelines have since been updated after the study period and are now called the Vertical Transmission Prevention (VTP) guidelines. In the 2023 VTP guidelines there were no changes to the VL monitoring schedule.

While this is a retrospective record review with recognised limitations, the strength of the study lies in the large sample size. The main limitation is that patient records may have been incomplete, with some tests being done but not recorded. The study was also done in a referral hospital and some patient information may have been retained at the referring facilities.

Conclusion

In conclusion, HIV infection remains an important public health challenge in our setting, requiring a collaborative effort between stakeholders, healthcare providers, and patients themselves in order to curb the burden of this disease. More effort, and adherence to guidelines are necessary for this vulnerable group of PWLHIV as the risk of complication is higher for them, including the additional challenge of vertical transmission.