A NATIONAL-LEVEL EVALUATION OF VIRAL LOAD OUTCOMES OF HIV-INFECTED PREGNANT WOMEN: CLOSING THE GAPS TOWARDS ELIMINATING MOTHER-TO-CHILD TRANSMISSION OF HIV IN SOUTH AFRICA

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A THESIS

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Declaration

I, Faith Moyo, student number 569935, declare that this thesis is my own, original work and that I contributed adequately towards research findings in the published articles which are included in my thesis. This thesis is being submitted for the degree of Doctor of Philosophy at the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted before for examination purposes for any degree at any University or Institution.

Signature of student…….  ……Date……02/08/2021……

Dedication

To my children

Ruvarashe Pearl and Tadiwanashe Paula Ngwenya,

May you be inspired to do more.

Acknowledgements

I would like to express my heartfelt thanks to my supervisors for their guidance and support in pursuing this work. Prof Gayle Sherman, I benefitted immensely from your vast knowledge and expertise. Special thanks to Dr Tendesayi Kufa-Chakezha for co-supervising my work. I appreciated your technical expertise in methodology and mentorship. To Dr Ahmad Haeri Mazanderani, thank you for your support all the way. I am forever indebted to you all.

Many thanks to the ELMA Foundation for funding this work.

To my family, thank you for being my biggest cheerleaders.

To God be the glory.

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List of Abbreviations

3TC	Lamivudine
AGYW	Adolescent girls and young women
ANC	Antenatal care
ART	Antiretroviral therapy
ARV	Antiretroviral
AZT	Zidovudine
DHIS	District Health Information System
DTG	Dolutegravir
EFV	Efavirenz
EGK	Electronic gate keeping
EID	Early infant diagnosis
ELISA	Enzyme-linked immunosorbent assay
eMTCT	Elimination of mother-to-child transmission of HIV
fANC	First antenatal care visit
FTC	Emtricitabine
HIV	Human immunodeficiency virus
HREC	Human Research Ethics Committee
IU	Intra-uterine
LIS	Laboratory Information System
MTCT	Mother-to-child transmission of HIV
NHLS CDW	National Health Laboratory Service's Corporate Data Warehouse
NICD SDW	National Institute for Communicable Diseases Surveillance Data Warehouse
NVP	Nevirapine
PCR	Polymerase chain reaction
PHC	Primary health care
PMTCT	Prevention of mother-to-child transmission of HIV
PoC	Point-of-care
RfA	Results for Action
RPR	Rapid Plasmin Reagin
SABSSM	South African National HIV Prevalence, Incidence, Behaviour and Communication Survey
SSA	Sub-Saharan Africa

Stats SA	Statistics South Africa
STI	Sexually Transmitted Infection
TB	Tuberculosis
TDF	Tenofovir
TOU	Tertiary obstetric unit
TPAb	Treponema Pallidum antibodies
TPHA	Treponema Pallidum Haemagglutination Assay
UNAIDS	Joint United Nations Programme on HIV/AIDS
UTT	Universal test and treat policy
UNICEF	United Nations International Children's Emergency Fund
VL	Viral load
VLS	Viral load suppression
WHO	World Health Organization
WLHIV	Women living with HIV
WRLHIV	Women of reproductive age living with HIV
β-hCG	Beta human chorionic gonadotropin hormone

Thesis Materials

Research findings emanating from this body of work were presented at various platforms and published in local and international peer-reviewed journals. Copies of articles published in peer-reviewed journals appear in Appendices 4.1-7.1

Peer-reviewed publications arising from this work:

1. Moyo F, Haeri Mazanderani A, Kufa T, Sherman GG. The geographic distribution of priority population groups for the elimination of mother-to-child transmission of HIV in South Africa. *Plos One 15(4): e0231228*.

2. Moyo F, Mazanderani Haeri A; Murray T, Sherman GG; Kufa T. Achieving maternal viral load suppression for elimination of mother-to-child transmission of HIV in South Africa. *AIDS.2021;35(2):307-306.*

3. Moyo F, Haeri Mazanderani A, Murray T, Technau K-G, Carmona S, Kufa T, Sherman GG. Characterizing Viral Load Burden Among HIV-Infected Women Around the Time of Delivery: Findings From Four Tertiary Obstetric Units in Gauteng, South Africa. *J Acquir Immune Defic Syndr. 2020;83:390–396*.

4. Moyo F, Mazanderani Haeri A, Kufa T, Sherman GG. Maternal HIV viral load testing during pregnancy and postpartum care in Gauteng Province, South Africa. S Afr Med J. 2019. (In press).

Conference presentations:

1. Moyo F, Haeri Mazanderani A, Murray T, Technau K-G, Carmona S, Kufa T, Sherman GG. Characterizing Viral Load Burden Among HIV-Infected Women Around the Time of Delivery: Findings From Four Tertiary Obstetric Units in Gauteng, South Africa. 10th International AIDS Society, Mexico City, Mexico. July 2019. ***Oral Presentation.***

IAS Lange/Van Tongeren Prizes (IAS/ANRS) Young Investigator Award 2019

2. Moyo F, Haeri Mazanderani A, Murray T, Technau K-G, Carmona S, Kufa T, Sherman GG. Characterizing Viral Load Burden Among HIV-Infected Women Around the Time of Delivery: Findings

From Four Tertiary Obstetric Units in Gauteng, South Africa. 11th International Workshop on HIV Paediatrics, Mexico City, Mexico. July 2019. ***Poster Presentation.***

3. Moyo F, Mazanderani Haeri A; Murray T, Sherman GG; Kufa T. Longitudinal evolution of maternal viral load during pregnancy and within 12 months postpartum among pregnant women living with HIV in South Africa. AIDS virtual, July 2020. ***Poster Presentation.***

4. Moyo F, Mazanderani Haeri A; Murray T, Sherman GG; Kufa T. Longitudinal evolution of maternal viral load during pregnancy and within 12 months postpartum among pregnant women living with HIV in South Africa. 12th International Workshop on HIV Paediatrics, virtual. November 2020. ***Oral Presentation***

Young Investigator Award - Best Abstract

Funding and Awards

1. The ELMA Foundation, 2018-2020
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Abstract

Background

In the words of Burton *et al.*, South Africa's prevention of mother-to-child transmission of HIV (PMTCT) programme has been an ever-changing landscape since inception in 2004. The national PMTCT programme rose from humble beginnings, fraught with delays and AIDS denialism to become the largest programme in the world. One and half decades later, the programme has documented unprecedented reduction in new paediatric HIV infections, shifting efforts from prevention to elimination of mother-to-child transmission of HIV (eMTCT). However, the road to eMTCT in South Africa is considerably challenged.

The World Health Organization defines eMTCT as the attainment of <50 new paediatric infections per 100 000 live births at the end of the breastfeeding period. By 2017, the national intra-uterine case rate alone, was five times the elimination target, with postnatal transmissions expected to contribute a further 1.5 times the intra-uterine case rate by the end of the breastfeeding period. Since maternal viral load (VL) is the strongest predictor of MTCT risk, this research project sought to provide a national description of maternal viraemia as a key driver of vertical transmission, in order to establish a baseline from which to improve virological control during pregnancy and postpartum periods to facilitate eMTCT in South Africa.

Methods

This thesis comprises of four publications conducted using data from two cohorts: a national level synthetic cohort from the National Health Laboratory Service's Corporate Data Warehouse (NHLS CDW) and a sub-national level cohort of pregnant women living with HIV (WLHIV), delivering in four tertiary obstetric units in Gauteng province (Gauteng cohort). Using the Thembisa Model and data triangulated from five HIV-related and demographic data sources, Publication 1 (Chapter 3), set the scene for the case for eMTCT by describing the provincial distribution of target populations for eMTCT (women of reproductive age, 15-49 years and adolescent girls and young women, 15-24 years; stratified by HIV status) in 2018.

In order to assess maternal VL suppression rates in the public sector, a cohort of women of reproductive age living with HIV (WRLHIV) was identified from the NHLS CDW between 2016-2017. Due to lack of a pregnancy marker within the NHLS CDW, syphilis screening in association with ward type and/or post-pregnancy cervical screening and/or infant birth HIV test and/or positive β-hCG was used to identify pregnant from non-pregnant WRLHIV. Fractional polynomial models described longitudinal changes in maternal VL during pregnancy and the postpartum periods, while spline

regression determined factors associated with maternal VL decline during follow up (Publication 2, Chapter 4). Maternal VL suppression rates observed from the national level synthetic cohort were validated against the Gauteng cohort in 2018 (Publication 3, Chapter 5). The geospatial distribution of maternal viraemia at delivery was described using ArcGIS and a negative binomial regression model assessed population-level determinants of vertical transmission within the national PMTCT programme using the national level synthetic cohort during the study period (manuscript in preparation 1, Chapter 6). Lastly, an evaluation of maternal VL testing coverage and compliance to national VL testing guidelines was assessed from the Gauteng cohort in 2018 (Publication 4, Chapter 7).

Results

In 2018, 74% of all WRLHIV were located in Gauteng, KwaZulu-Natal, Western Cape, Eastern Cape, Limpopo and Mpumalanga provinces. The same provinces also accounted for 87% of all AGYW living with HIV during the study period. These data suggested that the need for eMTCT is greatest in these six of the nine provinces in the country.

Regarding maternal viraemia (VL ≥50 copies/mL), a steady decline in viraemia was observed from presentation at the first antenatal care visit (fANC) to delivery and postpartum nationally. However, proportions with viraemia were 54% at first HIV VL measurement during pregnancy, 37% at delivery and 34% postpartum, when eMTCT requires sustained maternal VL suppression from conception through pregnancy until breastfeeding cessation. Importantly, 43% of ART-experienced pregnant WRLHIV were viraemic at fANC visit while two thirds of women not on ART at fANC visit were still viraemic after three months of ART use. At delivery, the proportion with maternal viraemia was similar to that of known pregnant WLHIV in Gauteng province, suggesting representativity of the study population to pregnant WRLHIV in the country. Notably, the community VLs of pregnant WRLHIV at all time points were higher than those of non-pregnant WRLHIV. Maternal viraemia during the postpartum period, high maternal seroprevalence, women initiating ART late in pregnancy and/or incident maternal HIV during pregnancy were significant population-level drivers of MTCT during the study period, while early booking (<20 weeks gestation) for ANC among pregnant women was associated with a decline in vertical transmission. Implementation of maternal VL monitoring guidelines during pregnancy and postpartum was poor as observed in Gauteng province. Less than 5% of pregnant WLHIV received VL monitoring according to national guidelines while >80% had no evidence of VL monitoring during the antenatal period. However, if women received VL monitoring during the antenatal period, they were more likely to be virally suppressed at delivery and receive VL monitoring postpartum. Lastly, we observed provincial differences in sustaining VL suppression into

the postpartum period, with KwaZulu-Natal, Western Cape and Free State the best performing provinces.

Conclusions

Maternal VL suppression rates during pregnancy, delivery and postpartum were poor in spite of high ART coverage during the study period. Results emphasize the need for closer monitoring of and rapid response to elevated maternal VL during pregnancy, delivery and postpartum for the attainment of eMTCT in South Africa. These findings provide baseline data on maternal virologic responses within the national PMTCT programme and have informed the development of routine surveillance reports for near real-time monitoring of VLS rates among pregnant WLHIV from the NHLS CDW. Based on these data, targeted interventions to improve PMTCT outcomes with ongoing NHLS CDW monitoring are recommended to achieve eMTCT.

Preface

"..*I hate having AIDS because I get very sick and I get very sad when I think of all the other children and babies that are sick with AIDS. I just wish that the government can start giving AZT to pregnant HIV mothers to help stop the virus being passed on to their babies*..." **Nkosi Johnson,** 13th International AIDS Conference, Durban South Africa. July 2000.

Four years after his iconic speech, part of Nkosi Johnson's dream became reality. Pressure from civil society and a court order forced the then South African government to roll out antiretroviral therapy for HIV-positive pregnant women and prophylaxis for HIV-exposed infants in the public health sector. Sadly, Nkosi did not live long enough to realize his dream, succumbing to the disease, a year after his speech. This was the dark ages of HIV in South Africa, where HIV-related deaths ravaged communities without mercy. The world was especially cruel to children infected with HIV at birth at the time. Half of all children born with HIV did not survive beyond two years, if they made it past the first three months of life. Two decades later, the tide has turned. Remarkable progress has been made in paediatric HIV response since the 2000s. Ending paediatric HIV in South Africa is no longer an illusion but a possibility. However, much work lies ahead as the country moves towards realizing the dreams of fallen giants like Nkosi Johnson and many other children who suffered a similar fate.

My path to this PhD began in 2017, under the tutelage of Professor Gayle Sherman. A year prior, I had the opportunity to work with Prof Sherman as a Project Manager for a United Nations International Children's Emergency Fund (UNICEF) funded project to investigate potential gaps in PMTCT care among HIV-positive women who transmitted HIV to their children. The project was conducted in three districts in KwaZulu-Natal province, the province with the highest maternal HIV prevalence in the country. Analysis of data from the project found that 70% of the women did not have VL monitoring during pregnancy and that 60% of these women had been diagnosed prior to conception or at the first antenatal care visit. These results triggered my interest in gaining insight into maternal virological suppression during pregnancy and the postpartum period as the country aimed for eMTCT. An extensive literature search then ensued to determine maternal VL suppression during pregnancy and postpartum among WLHIV in the country. I soon established that there was a gap in this area at the time.

Around the same time, Professor Sherman obtained a grant from the ELMA Foundation to evaluate gaps within the PMTCT treatment cascade for eMTCT in South Africa. Our stars had aligned. This provided me an opportunity to work with and to be mentored by a distinguished researcher with international recognition on a topic close to my heart. I then resolved to undertake a national project

evaluating maternal VL testing coverage and suppression rates in the public health sector to inform PMTCT policy and highlight hotspots requiring attention to fast-track eMTCT. I developed my protocol, applied for ethical clearance and access to the national laboratory database from relevant authorities. A lengthy period of data mining, data cleaning and analyses followed.

It is my hope that findings of this work will contribute towards improvement of care among women living with HIV towards ending paediatric HIV in the country.

The scope of publications emanating from this work and the outline of the thesis follows.

Scope of Publications

This PhD thesis was put together through the publication route, consisting of four peer-reviewed publications, and is presented here in the divided block format according to the University of the Witwatersrand Faculty of Health Sciences' theses and dissertations style guidelines. The thesis comprises of three main sections. ***Section 1*** is the introductory section, which consists of two chapters. Chapter *1* provides a brief background into vertical transmission of HIV and gives a narrative of the evolution of PMTCT policy and profile of vertical transmission in South Africa. The chapter also discusses literature reviewed around the study objectives and ends with a description and critique of strategies for fast-tracking eMTCT in South Africa. Chapter *2* describes the methodology, setting and data sources for this body of work. Specific details on the methods for sub-studies are described in relevant chapters in the results section.

Section 2 is the results section consisting of four published articles and one manuscript in draft, presented as five empirical chapters. Chapter *3* (Publication 1) sets the scene by providing a description of the provincial distribution of WRLHIV in relation to cases of intra-uterine transmission in South Africa. The publication utilizes the demographic profile of WRLHIV in the country to guide allocation of resources for eMTCT. Chapter *4* (Publication 2) describes the longitudinal changes in maternal viraemia during pregnancy, delivery and postpartum from a synthetic cohort of women accessing care in the national PMTCT programme. The publication also discusses factors associated with maternal viral control during pregnancy, delivery and postpartum. Chapter *5* (Publication 3) is a cross sectional review of maternal viraemia at delivery from a cohort of known, pregnant WLHIV, delivering in four tertiary facilities in the public health sector in Gauteng province (Gauteng cohort). These data were used to validate findings from the national level synthetic cohort of WRLHIV described in Chapter *4*. Chapter *6* is an ecological analysis of population-level determinants of MTCT using routine HIV test data from the synthetic cohort of women from the NHLS CDW and other routine HIV-related indicators in the era of MTCT. Chapter *7* (Publication 4) explores VL monitoring amongst pregnant and postpartum WLHIV in Gauteng province and discusses compliance to national VL testing guidelines and implications thereof on maternal VL suppression and retention in care.

Section 3 consists of a single chapter, Chapter *8*, and provides the general discussion and draws conclusions from all aspects of this work. The chapter also highlights what the study contributes to literature, recommendations for policy and next steps.

Thesis Outline

SECTION 1: INTRODUCTION

Chapter *1*: Background and Literature review

Chapter *2*: Methodology

SECTION 2: RESULTS

Chapter *3*: The geographic distribution of priority population groups for the elimination of mother-to-child transmission of HIV in South Africa

Chapter *4*: Achieving maternal viral load suppression for elimination of mother-to-child transmission of HIV in South Africa

Chapter *5*: Characterizing viral load burden among HIV-infected women around the time of delivery: Findings from four tertiary obstetric units in Gauteng, South Africa

Chapter *6*: Population-level risk factors for vertical transmission of HIV within the national prevention of mother-to-child transmission programme in South Africa: An ecological analysis

Chapter *7*: Maternal HIV viral load testing during pregnancy and postpartum care in Gauteng Province, South Africa

SECTION 3: GENERAL DISCUSSION

Chapter *8*: General Discussion and Conclusions

SECTION 1: INTRODUCTION

CHAPTER 1.

Background and Literature review

1.1 Background

Mother-to-child transmission of HIV occurs when women living with HIV (WLHIV) transmit the virus to their children *in utero*, at delivery or during the postpartum period through breastfeeding.[1-3] This type of transmission is also known as vertical transmission of HIV. Vertical transmission of HIV accounts for the bulk of paediatric HIV infections amongst children <15 years globally.[4] Almost 90% of global paediatric HIV infections are from 23 priority countries, of which 21 are in sub-Saharan Africa (SSA).[5] Providing antiretroviral therapy (ART) to pregnant and breastfeeding WLHIV is a major strategy for preventing MTCT of HIV. When ART is taken consistently prior to and during pregnancy or breastfeeding, resulting in undetectable maternal VL, the risk of MTCT is virtually eliminated.[6] Despite near universal HIV testing and expanded access to efficacious maternal ART drug regimens worldwide, some women are only diagnosed with HIV and start ART during pregnancy or the breastfeeding period. In these instances, rapid initiation onto ART is critical as each week of ART intake is associated with an 8% reduction in the risk of MTCT of HIV.[7]

South Africa is one of the 21 priority countries in SSA with a high burden of paediatric HIV infections.[5] The country provides PMTCT services largely via the public health sector.[8] Over the years, the national PMTCT programme has evolved to be a global leader, with demonstrable success in reducing new paediatric HIV infections within high burden settings. The success of the programme is attributable to a robust PMTCT policy framework and an enabling political environment, a complete antithesis of the beginning of the programme.[9] As from 2015, the national PMTCT programme has steered towards eMTCT because of an MTCT rate (percentage of HIV PCR positive children from all HIV-exposed children aged <24 months) that is below 5% at the end of the breastfeeding period.[10,11] However, the road to eMTCT is considerably challenged.

1.2 Problem statement

The World Health Organization (WHO) defines eMTCT as the reduction to fewer than 50 incident paediatric HIV infections per 100 000 live births at the end of the breastfeeding period.[12] South Africa has prioritized eMTCT on account of low MTCT rates at national level. By 2017, South Africa's national intra-uterine (IU) transmission rate approximated 1%.[13] However, this figure equates to a case rate of approximately 250 cases per 100 000 live births. This is five times in excess of the elimination target, from IU infections alone. Using data from 2012-2014, Goga *et al.* reported a cumulative MTCT rate of 4.3% at 18 months of follow up nationally, under the WHO Option B standard.[14] During this time, IU transmissions accounted for the majority of MTCT cases at 67%.[14] Analysis of routine laboratory data

shows that postnatal transmissions up to two years of age are approximately 1.5 times the IU rate (unpublished data). However, this figure likely underestimates total postnatal transmissions as it is based on HIV polymerase chain reaction (PCR) tests performed on children <2 years of age only. Regardless, in terms of implications for eMTCT, a minimum of 600 new paediatric infections were expected by the end of the breastfeeding period nationally in 2017. These data clearly show that while the low MTCT rates provide a window of opportunity for eMTCT, getting to <50 new paediatric HIV cases per 100 000 is going to be challenging.

Maternal viral load (VL) is the strongest predictor of MTCT risk[15,18], yet VL monitoring amongst pregnant and postpartum is not well described in South Africa. Maternal VL monitoring during pregnancy and the postpartum period appears to be a huge gap in PMTCT care. Prior to this research project, there was paucity of programmatic data informing maternal VL suppression rates during pregnancy and the postpartum period at national level. These data are necessary to determine whether high maternal VLs are driving MTCT in this last mile to eMTCT, that is, the period of low national MTCT rates or not. Moreover, it is unclear whether geospatial factors (hotspots) are driving MTCT in the era of eMTCT or not. Thus, a national description of maternal viraemia as a key driver of vertical transmission is critical in order to establish a baseline, from which to improve virological control during pregnancy and postpartum periods to facilitate eMTCT in South Africa. In addition, the existence of geospatial differences in the HIV epidemic across the country necessitate inter-provincial and district-level evaluation of maternal viraemia during pregnancy and postpartum periods to highlight hotspots of transmission for intervention.

1.3. Literature review

1.3.1 Evolution of the South African PMTCT programme

In the words of Burton *et al.*[9], the PMTCT programme in South Africa has been an ever-changing landscape since inception in 2004. The national PMTCT programme rose from humble beginnings, fraught with delays and AIDS denialism to become the largest programme of its kind in the world. One and half decades later, the programme has documented an unprecedented reduction in new paediatric HIV infections, shifting efforts from prevention to elimination of mother-to-child transmission of HIV (eMTCT). For example, new paediatric HIV infections decreased by 84% between 2009 and 2015.[19] In keeping with global expansion of PMTCT services, PMTCT services are available in >95% of all health facilities in the public sector and by 2017, HIV testing and ART initiation rates amongst antenatal clients had reached near universal coverage.[20,21] The rapid evolution of the PMTCT

policy has resulted in continuous changes to national guidelines around maternal antiretroviral therapy (ART) and infant prophylactic regimens.

1.3.2 Evolution of maternal ART and infant prophylactic regimens

The PMTCT policy on maternal treatment changed from single-dose nevirapine administered during labour to the mother in the early 2000s to successive implementation of World Health Organization (WHO) recommended Option A, B and B+ standards.[8] With WHO Option A, ART regimens were based on maternal immunological profile. This was later revised to triple-drug ART for all pregnant and breastfeeding WLHIV irrespective of CD4 count during pregnancy and throughout the duration of breastfeeding period (Option B) in 2013.[22,23] In 2015, the guidelines were reviewed to recommend lifelong triple ART regardless of CD4 count and WHO disease stage (Option B+).[24] With respect to maternal antiretroviral (ARV) drug regimens, the guidelines have progressively recommended more efficacious drugs in line with guidance from the WHO and emerging evidence from the field of HIV research. Since 2013, a fixed dose combination of Tenofovir (TDF) + Lamivudine (3TC)/Emtricitabine (FTC) + Efavirenz (EFV) has been the drug of choice for standard first line therapy for pregnant and postpartum WLHIV.[23,24] Pregnant and breastfeeding WLHIV were prioritized for this fixed dose combination drug formulation in order to reduce pill burden and improve adherence.[25] In 2019, the guidelines were further revised to introduce a new formulation containing Dolutegravir (DTG) in place of EFV for first line therapy.[26] Some of the benefits of DTG over EFV are that, i) it is highly effective and achieves rapid viral suppression ii) has a high barrier to resistance and iii) is well tolerated.[27,28] However, safety concerns have been raised over the risk of neural tube defects and other adverse pregnancy and infant outcomes among women becoming pregnant while taking DTG.

Reports from the Tsepamo birth outcomes surveillance study in Botswana suggested that infants born to women exposed to DTG at the time of conception or within the first trimester had a higher risk of developing neural tube defects compared to EFV exposure.[29-32] Further research from other settings went on to show a 0.2% [95% confidence interval: 0.01-0.67] higher risk of neural tube defects amongst infants born to women exposed to DTG over EFV from the time of conception.[33] However, there is general consensus that this association is also likely to be confounded by environmental factors such as folate deficiency within the first trimester.[29,32] In addition, the risk of adverse pregnancy outcomes is not unique to DTG but common to all ARVs.[34] Based on this expanded evidence, in 2019 the WHO recommended DTG as the preferred treatment option for all populations, citing that the population level benefits of DTG outweigh the risk of harm.[35]

More recently, exposure to DTG has also been linked to significant weight gain compared to EFV amongst pregnant and postpartum women in South Africa and Botswana.[36] This raises concern of increased risk of type 2 diabetes with long term use of DTG, if weight gain is not controlled. Moreover, this potential for weight gain with DTG use may lead to suboptimal adherence and limit its effectiveness in maintaining VL suppression. South Africa adopted a cautionary, patient centred approach where women of child-bearing age are counselled about the potential risks associated with DTG use and make an informed decision before switching to a DTG containing regimen.[26]

For HIV-exposed infants, early infant diagnosis and provision of effective prophylactic antiretroviral regimens were also prioritized as guidelines evolved. HIV PCR testing of all HIV-exposed infants at six weeks of age constituted routine practice prior to 2015.[24] In June of 2015, universal HIV PCR testing at birth and at 10 weeks for all HIV-exposed neonates and infants, coupled with fast-tracked ART initiation for HIV PCR positive children became standard of care.[24] In addition to 2015 recommendations, the guidelines of 2019 recommend an HIV PCR at six months of age and six weeks post breastfeeding cessation for HIV-exposed infants.[26] Furthermore, a universal HIV PCR is now recommended at 18 months of age for all children regardless of HIV exposure.[26] This recommendation was primarily made to identify children infected as a result of late maternal seroconversion during pregnancy or breastfeeding who may have escaped detection during ANC. Infant prophylactic regimens of 2015 remain standard of care. Table 1.1 describes the evolution of maternal ART and infant prophylactic regimens in the public health sector in South Africa, 2010-2019.[22-24,26]

Table 1.1 Evolution of the South African PMTCT Guidelines for pregnant WLHIV and HIV-exposed infants aged ≤18 months, 2010-2019.[22-24,26]

Year	2010	2013	2015	2019
	WHO Option A	**WHO Option B**	**WHO Option B+**	**UTT strategy***
Maternal ART	(i) If CD4 < 350 or WHO stage III or IV: initiate ART lifelong (ii) If CD4 > 350: AZT at 14 weeks' gestation Single dose NVP + AZT/3TC at onset of labour AZT/3TC daily for 7 days postpartum	All pregnant & breastfeeding WLHIV initiated on ART for duration of pregnancy and breastfeeding (i) If CD4 >350: continue ART until 1 week post cessation of breastfeeding (ii) If CD4 <350: continue ART lifelong	All pregnant and breastfeeding WLHIV initiated on lifelong ART	All persons diagnosed with HIV eligible for lifelong ART after confirmation of HIV positive diagnosis
Infant Prophylaxis	Single dose NVP daily for 6 weeks if mother is on ART or for duration of breastfeeding + 1 month post cessation of breastfeeding	Single dose NVP daily for 6 weeks	***Low Risk***: Daily dose NVP for 6 weeks ***High Risk***: -NVP for 12 weeks if mother is on cART < 4 weeks, or newly diagnosed at delivery -NVP + AZT for 6 weeks if maternal VL >1000 cps/mL -NVP + AZT if newly diagnosed whilst breastfeeding. If HIV PCR is negative, continue NVP for a total of 12 weeks	***Low Risk***: Daily dose NVP for 6 weeks ***High Risk***: -NVP for 12 weeks or until maternal VL < 1 000 cps/mL or until 1 week after breastfeeding cessation -AZT twice daily for 6 weeks

Abbreviations: PMTCT Prevention of mother-to-child transmission, WHO World Health Organization, ART Antiretroviral Therapy, UTT* universal test and treat strategy since 2016, AZT Zidovudine, NVP Nevirapine, 3TC Lamivudine, VL Viral load, PCR Polymerase chain reaction, cps/mL, copies per millilitre of blood, WLHIV women living with HIV.

1.3.3 Profile of vertical transmission in South Africa

Maternal HIV seroprevalence has plateaued at 30% for over a decade, Figure 1.1[37]. This translates into approximately 270 000 HIV-exposed neonates each year. Despite the huge burden of maternal HIV, the national PMTCT programme has documented significant advances in reducing new paediatric HIV infections. Within a decade of implementation, new paediatric infections among infants aged <24 months, MTCT rates fell from >20% in 2004 to <2% in 2014, an achievement South Africa is justifiably proud of.[38] By 2017, the national intra-uterine (IU) transmission (the MTCT rate at <7 days of life) rate was <1% based on analysis of routine laboratory HIV test data.[14] Although the MTCT rate is low nationally, rates at sub-national level vary greatly.[14,39] As a result, ending paediatric HIV in South Africa may require more than a 'one size fits all' approach.

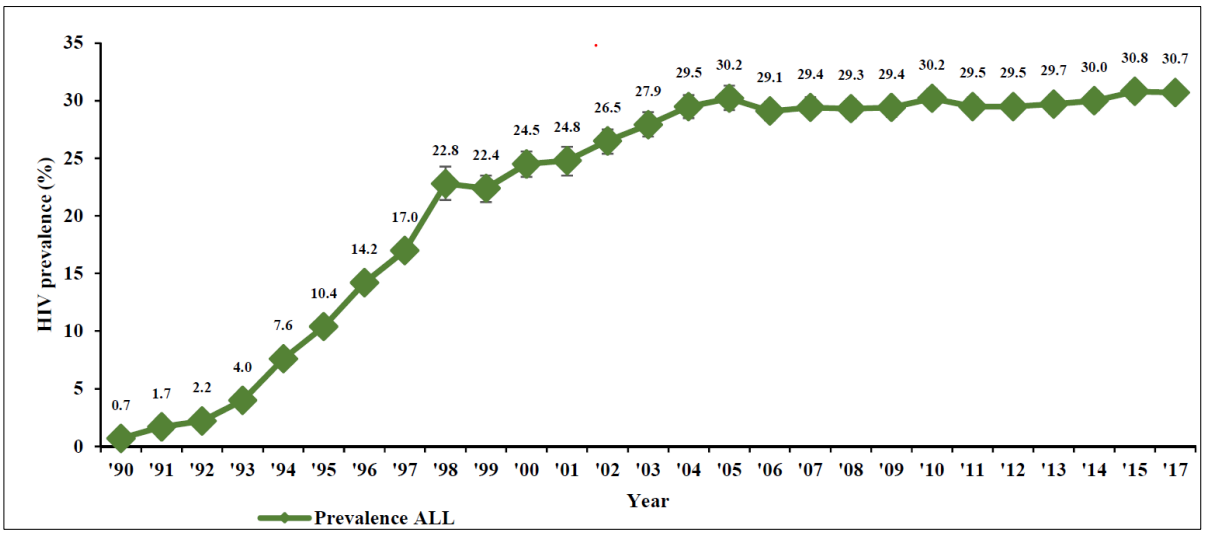

Figure 1.1 The national HIV epidemic curve for pregnant women in South Africa, 1990-2017.[37]

1.3.4 Beyond PMTCT: Towards eliminating MTCT of HIV in South Africa

In 2014, the WHO published guidance on process indicators and criteria for measuring country progress towards and validating achievement for eMTCT.[12] As of December 2019, a total of 14 countries had received validation for eMTCT[40] and none of the countries are from SSA, which has 90% of global HIV disease burden.[5] Without discrediting the effort and success of these countries, achieving eMTCT has been facilitated by several factors such as smaller HIV epidemics, access to a wide variety of ARV drugs, high coverage of elective caesarean deliveries and very low breastfeeding rates.[41] High

HIV burden and less-resourced settings such as South Africa are disadvantaged. In recognition of challenges faced by high prevalence settings, the WHO set different targets for low and high HIV prevalence settings.[42] A three-tier system was devised to provide guidance towards eMTCT for high HIV prevalence settings.[42] Table 1.2 shows WHO targets for process indicators and validation criteria for eMTCT.

Table 1.2. WHO process indicators and validation criteria for eMTCT.[42]

	Low HIV prevalence settings	**Tiers for high HIV prevalence settings**		
		Gold	**Silver**	**Bronze**
Process Indicators				
Antenatal care coverage	≥ 95%	≥ 95%	≥ 90%	
HIV testing coverage among pWLHIV	≥ 95%	≥ 95%	≥ 90%	
ART coverage among pWLHIV	≥ 95%	≥ 95%	≥ 90%	
Impact Indicators				
MTCT rate at end of breastfeeding period	<2% in non-breastfeeding populations OR <5% in breastfeeding populations			
Case rate / 100 000 live births	<50	≤250	≤500	≤750

Abbreviations: pWLHIV pregnant women living with HIV, MTCT mother-to-child transmission of HIV, WHO World Health Organization

By 2017, South Africa had reached targets for the process indicators required for eMTCT[43], the impact indicators are yet to be achieved. Even though South Africa is estimated to have an MTCT rate below 5% at the end of breastfeeding period, achieving <50 cases per 100 000 live births is unattainable in the short term. The greatest challenge towards eMTCT in South Africa remains the triple burden of a high maternal seroprevalance rate[37], extended breastfeeding duration and poor VL monitoring amongst pregnant and postpartum WLHIV.[44] Thus, albeit low, the total MTCT rate at the end of the breastfeeding period translates into an MTCT case rate that is higher than the eMTCT target due to a high maternal seroprevalence rate. In addition, breastfeeding is promoted as the infant feeding method of choice (up to 24 months of age) for WLHIV who are virally suppressed and on ART.[45-47]

Although this extends the risk period for MTCT, the risk of non-breastfed infants dying from pneumonia or diarrhoeal diseases outweighs the risk of breastmilk associated HIV transmission in these settings.[47,48] Lastly, the relationship between elevated maternal VL and continued MTCT risk is well known[15,18], yet VL monitoring among antenatal and postpartum WLHIV is not well described and may be sub-optimal in South Africa. Poor maternal VL monitoring during pregnancy and the postpartum period not only places HIV-exposed infants at a greater risk of infection but also compromises maternal health due to increased viraemia.

1.3.5 VL monitoring amongst antenatal and postpartum WLHIV

The goal of any ART programme is to achieve durable VL suppression for all users of ART to reduce morbidity, mortality and prevent transmission. In 2015, the UNAIDS adopted the 90-90-90 strategy to fast-track global efforts towards ending the AIDS epidemic by 2030.[49] The strategy aimed to have 90% of people living with HIV know their status (1st 90), 90% of people who know their HIV status to be on ART (2nd 90) and 90% of those on ART virally suppressed (3rd 90). These targets have since increased to 95-95-95 in order to accelerate country-level HIV epidemic control.[50] South Africa is yet to achieve all three 90s. For PMTCT programmes, VL monitoring amongst pregnant and postpartum WLHIV serves two purposes: 1) monitoring progress towards the UNAIDS targets and 2) ascertaining risk of MTCT for HIV-exposed children. Viral load monitoring amongst pregnant and postpartum women in SSA was neglected until 2013.[51-53] The WHO endorsed VL monitoring as a preferred method for measuring HIV disease progression to the standard practice of using clinical criteria in 2013.[51] Delays in shifting to VL monitoring within ART programmes in limited resource settings was attributed to high cost and lack of laboratory infrastructure.[52] Viral load monitoring during pregnancy in developed countries is widely accessible and part of routine care.[54]

In South Africa, VL monitoring has been scaled up in recent years. Routine centralized laboratory HIV VL testing is currently standard of care (December 2020).[48-49] This is achieved via the National Health Laboratory Service (NHLS), which has a network of approximately 260 laboratories nationwide. However, VL testing is the mandate of only 16 regional laboratories nationwide.[55,56] In 2013, VL monitoring was recommended at six and 12 months post-ART initiation for women newly diagnosed with HIV during pregnancy or the breastfeeding period.[23] For WLHIV already on ART prior to pregnancy, a VL test was recommended at the first ANC booking. In 2015, the national guidelines extended VL monitoring to six monthly during pregnancy and the breastfeeding period for all WLHIV on ART.[24] However, a VL test at three months post-ART initiation was required for WLHIV initiating ART during pregnancy or the breastfeeding period. The threshold for maternal VLs requiring

adherence-counselling intervention was set at VL ≥1 000 copies/mL. Women with VL ≥1 000 copies/mL would receive a repeat VL within two months of the elevated VL.[24] The threshold was revised to VL ≥50 copies/mL in the November 2019 guidelines.[26] This revision was in response to growing evidence of vertical transmission occurring at low-level and transient viraemia. Furthermore, a VL test at time of delivery is now recommended for all pregnant WLHIV to guide clinical management of both mother and infant during the postpartum period.

In spite of policy provisions and availability of established laboratory infrastructure, implementation of VL monitoring within the PMTCT programme was sub-optimal during the study period. The magnitude of the HIV epidemic and its associated high specimen volumes in the country, places laboratory infrastructure under strain and renders it unable to cope with demand for VL testing and returning results to patients within clinically relevant time periods.[55,56] Longer turn-around-times from testing to return of results to patients are the order of the day in some facilities, particularly remote hard to reach facilities. As a result, innovation around supplementing centralized routine HIV VL testing will be critical. Point-of-care (PoC) HIV VL testing technologies have been one such strategy. The cost of implementing PoC HIV VL testing is comparable to centralized laboratory testing[57] with added benefits of improving rates of retention in care and VL suppression rates within ART programmes. Malawi, Mozambique and Zimbabwe have reported higher maternal VL and EID testing coverage coupled with improved patient retention when using PoC technologies compared to standard of care.[58-60] Similar findings have been documented from clinical trials and donor supported projects in some parts of South Africa.[61] However, these studies may have had better systems for data collection and were better resourced for case management compared to routine testing, hence findings may not be generalizable to routine practice.

A study by Kufa *et al.*, evaluated the feasibility of implementing maternal PoC HIV VL and Early Infant Diagnosis (EID) testing at delivery within high volume tertiary obstetric units under routine settings in South Africa.[62] The study showed modest PoC coverage of 50% for maternal VL and 88% for EID testing overall, with greater variation between study sites.[62] The higher coverage for PoC EID testing was attributed to EID testing at birth being standard of care and maternal VL testing at delivery being new at the time of study implementation. The authors concluded that although PoC VL testing has potential for scale up in South Africa, successful implementation will be dependent on health system factors.

While ART programmes in other neighbouring countries (for example Malawi, Mozambique and Zimbabwe) have reported remarkable improvement in VL testing coverage and patient retention with PoC technology use,[58-60] South Africa may not achieve the same level of success within routine settings. This is because the former countries are under-resourced, with limited access to centralized laboratory

testing compared to South Africa. Therefore, the impact of PoC testing modalities is greater in these settings as VL coverage will be coming from a very low base. South Africa on the other hand, already has a functional laboratory system with reasonable VL testing coverage, albeit strained. In South Africa, 75% of people in HIV care have at least one VL test in a year.[63] Therefore, the impact of PoC VL testing in South Africa may be lower compared to neighbouring countries. Nonetheless, the utility of PoC VL testing for selected populations in South Africa (for example, pregnant WLHIV) may be useful especially where rapid response to elevated VL is necessary. Furthermore, access to laboratory HIV VL testing varies across the country therefore some geographic areas may benefit more from PoC VL testing than others.[55,56] It is in this regard that PoC VL and EID are potential game changers for eMTCT.

1.3.6 High maternal VL as a driver of MTCT

Risk factors for MTCT of HIV are well-documented[15-18,64-66] and these include high maternal VL (either in blood or breast milk), maternal sero-conversion (in pregnancy or during breastfeeding), maternal treatment duration and infant factors (low birth weight, preterm birth and inadequate infant prophylaxis). Among these, maternal VL remains the strongest predictor of MTCT of HIV from historic findings to current knowledge in this field. In 1999, using data from a modest sample of 552 HIV-infected women, Garcia *et al.* reported that MTCT risk was directly proportional to maternal plasma VL level.[64] Two decades later, consistent evidence has emerged substantiated by data from several large ART cohorts globally.[65,66] Historically, a plasma VL <1 000 copies/mL was associated with low or no risk of MTCT.[64] However, recent studies have shown lower but elevated risk of MTCT at lower plasma VL levels in the range 50-400 copies/mL compared to ≥1 000 copies/mL.[15,67-69] Mandelbrot *et al*. reported that ART started before conception, continued during pregnancy with a plasma VL <50 copies/mL eliminated MTCT risk from a French cohort of WLHIV.[6] In comparison, the risk was four times higher in women with plasma VL of 50-400 copies/mL at delivery in this cohort.[6] Albeit using different thresholds, similar trends have emerged, positively correlating higher MTCT risk with low-level viraemia from routine settings in South Africa. A study from the Western Cape Province reported an MTCT risk of 0.25%, 2.0% and 8.5% for maternal VL <50, VL 50-1 000 and VL ≥1 000 copies/mL at delivery respectively.[15] In Malawi, one in six cases of vertical transmission occurred to women with low-level viraemia (VL 40-1 000 copies/mL).[69] Low-level viraemia is reportedly associated with younger maternal age, sub-optimal adherence to ART and is likely to be transient.[68,69] However, studies on non-pregnant women show that prolonged low-level viraemia can potentially progress to virological failure.[68] These reports demonstrate that low-level viraemia is a real concern for MTCT in pregnant and postpartum WLHIV and requires urgent attention for the attainment of eMTCT.

The introduction of the UTT policy into South African ART guidelines in 2016, saw expanded access to ART to non-pregnant WLHIV irrespective of CD4 count. A progressive increase in proportions of women conceiving on ART has been observed compared to previous years when CD4 based criteria determined ART eligibility.[70] The proportion of women becoming pregnant on ART tripled between 2009-2015 from 14% to 45%.[70] By 2017, a 3:2 ratio of ART experienced WLHIV to women initiating ART in pregnancy at the fANC visit was common in the public sector.[71] While ART coverage has increased simultaneously with increased HIV testing amongst ANC clients over the years, VL monitoring in this population has remained low. This is due, in part, to the fact that VL monitoring was only introduced into national guidelines in recent years. On the other hand, poor VL monitoring may be a result of sub-optimal implementation of guidelines since the country already has a robust PMTCT policy framework. Failure to effectively monitor maternal VL elevates risk of vertical transmission amongst HIV-exposed infants. Thus, quantifying the magnitude of maternal viraemia and identifying determinants of viraemia during pregnancy and postpartum periods is critical for eMTCT.

1.3.7 Characterizing maternal VL during pregnancy and postpartum periods in SSA

A few studies have characterized maternal VL suppression rates during pregnancy and postpartum periods in SSA. The few studies which have documented maternal VL suppression among pregnant and postpartum women have reported high suppression rates using a VL <1 000 copies/mL threshold. In Rwanda, VL suppression rates of 85% (VL <1 000 copies/mL) and 50% (VL <1 000 copies/mL) were reported from women in their third trimester or within two weeks postpartum, with 76% of the cohort already on ART at fANC visit.[72] In Uganda, >90% of 111 women maintained VL <400 copies/mL across periconception, pregnancy and the postpartum period.[73] With such a small sample size and recruitment from a research site, high VL suppression rates were expected due to availability of resources for better patient management. Malawi was the first country to implement WHO Option B+ in 2011. After three to five years of implementation, 88% of the women enrolled in the donor-funded "National Evaluation of Malawi's PMTCT Programme" cohort had VL <1 000 copies/mL and 80% had VL <40 copies/mL four-six weeks postpartum.[69] The above studies reveal gaps in data on maternal VL suppression patterns within routine settings in SSA. While findings from donor-funded projects and research sites are important, they are often limited by lack of generalizability to routine settings. Relying on these findings to guide policy making carries the risk of developing policies which are insensitive to the needs of routine practice, thus compromising their efficacy.

In South Africa (2014), a Western Cape study reported that of 38% of 1 521 women fell pregnant on ART, 13% had VL >1 000 copies/mL at fANC visit in routine settings.[74] Among the remaining two thirds

of the ART naïve cohort at fANC visit, median VL was 10 000 copies/mL.[74] This finding was not surprising since the majority of pregnant WLHIV in the country were diagnosed with HIV post conception, usually at the fANC visit at the time. As a result, maternal VLs were very high at first presentation for ANC. This was the largest study in South Africa to evaluate the distribution of maternal VL amongst pregnant women presenting for care in the public sector. While this study provided useful information on extent of high maternal VLs at fANC visit, it did not provide information on maternal VL suppression rates at delivery and postpartum, the new frontiers for preventing MTCT.

In a follow up study longitudinally evaluating maternal VL (from the fANC visit, through delivery and up to 12 months postpartum) in the Western Cape, the authors reported sustained VL suppression (VL <50 copies/mL) in 70% of the women, low-level viraemia in 8% and ≥1 major viraemic episode (VL >1 000 copies/ml) in 22% of the cohort throughout follow up.[15] The majority of existing literature on maternal VL outcomes in South Africa is from the Western Cape province. However, the HIV epidemic and associated drivers differ in magnitude across the provinces in South Africa. As a result, findings may not be representative of the distribution of maternal VLs among pregnant women nationally. Studies from Gauteng and KwaZulu-Natal provinces have reported contrasting rates of maternal VL suppression at the fANC visit and delivery. A study from Gauteng province (n= 692) demonstrated overall VL suppression (VL <400 copies/mL) of 27% and 34% at the fANC visit and delivery respectively, amongst women delivering between 2016 and 2017.[75] A 40%:60% ratio of pre-pregnancy to in-pregnancy ART initiation may explain the lower rates of VL suppression amongst the cohort. However, generalizability of these results in Gauteng province or nationally is limited by the high proportions of women without VL data in the cohort which exceeded 50%. A study from KwaZulu-Natal province (n= 82) reported VL <50 copies/ml for 82% of the cohort at fANC visit.[67] This study had a very small sample size, which may explain the high rate of VL suppression at fANC visit. The authors did not report on VL outcomes at delivery. Another study from KwaZulu-Natal province reported levels of maternal VL <50 copies/mL for 82%, 77% and 76% from a cohort of pregnant WLHIV (n= 1 425) prior to pregnancy, during pregnancy and 12 months postpartum respectively.[18]

In 2016, Macleod *et al.* conducted a spatial analysis of VL suppression within the national ART programme, at facility level in South Africa.[76] The analysis provided VL outcomes among adult patients, children and adolescents, stratified by age and sex. The authors concluded that 79% of all females in the national ART programme had a suppressed VL <1 000 copies/mL.[76] However, VL suppression rates for pregnant women were not explored separately. More recently, data from the Fifth South African National HIV Prevalence, Incidence, Behaviour and Communication Survey of 2017 showed that 89.9% of females aged 15-64 years and on ART had VLs <1 000 copies/mL.[77] This was higher VL suppression than reported in Macleod *et al.*'s study. These data show that the national AIDS programme had

achieved the third 90 target for this population. However, VL suppression (VL <1 000 copies/mL) was lower among women of reproductive age and adolescent girls and young women at 66.7% and 47.1% respectively.[77] Furthermore, proportions of VL suppression are expected to be lower when a VL threshold of <50 copies/mL is used, which is required for eMTCT. Again, VL suppression rates of pregnant women were not reported in this survey. Thus, it remains to be seen whether the programme has achieved the third 90 target for pregnant WLHIV or not.

Findings from the 2017 National Antenatal Sentinel HIV Survey showed that 56% of pregnant women accessing care in routine settings had a VL <50 copies/ml during the third trimester (which can be interpreted as a proxy for VL at delivery), with 71% having initiated ART prior to pregnancy.[37] However, a quarter of women who had initiated ART prior to pregnancy failed to achieve VL suppression by the third trimester. Results of this survey provided maternal VL suppression rates around the time of delivery but failed to provide longitudinal changes in maternal VL throughout duration of pregnancy as well as postpartum. Nonetheless, findings emphasizes the importance of VL monitoring in all pregnant or postpartum women, as poor VL monitoring has the potential to reverse the gains of pre-pregnancy ART initiation. Some studies report that VL monitoring during pregnancy or postpartum is biased towards women newly initiating ART during pregnancy or postpartum, with healthcare workers neglecting ART experienced women.[78,79] These practices are based on the assumption that because they are not new on treatment, ART experienced women are adherent to their medication and do not need monitoring.[78,79] For some women this assumption is inaccurate. Research shows that some ART experienced WLHIV have poorer treatment outcomes during pregnancy compared to pre-pregnancy.[80,82] South Africa has a high rate of unplanned pregnancies regardless of HIV status. Fertility intentions among WLHIV have also increased since the adoption of the UTT policy in South Africa (as much as 45%)[83]. However a fair amount of pregnancies among WLHIV are unplanned[83-85] and unplanned pregnancies bring with them psychosocial stress which may compromise adherence to ART. Pregnancy itself is a major life event for some women and is associated with marriage in some instances. These major life events are associated with non-adherence to ART due to non-disclosure of HIV status and subsequently poor VL outcomes.[86] Hence, ART-experienced pregnant WLHIV who were clinically stable prior to pregnancy may exhibit poor clinical outcomes during pregnancy or postpartum. Thus, attainment of eMTCT will require more focused patient management for all pregnant or postpartum WLHIV regardless of duration on ART.

1.3.8 Community VL suppression: A strategy for achieving eMTCT?

Community VL is an aggregate measure of HIV plasma VLs of a defined population of HIV-infected persons over a defined period of time.[87,88.] A community VL can be used to quantify a population's exposure to ART and its effect on HIV transmission.[87,88] As ART coverage increases, community VL is expected to decrease and so should incident HIV infection. Women of reproductive age constitute the largest proportion of patients in HIV programmes worldwide.[44] Due to the scale-up of ART services and adoption of the UTT model of HIV care, many women are initiating ART prior to conception. Community VLs of women of reproductive age living with HIV can be used as a population level marker for vertical transmission risk.[87,88] Thus, to fast-track progress towards eMTCT, it is critical that community VLs of all women of reproductive age are suppressed. Given the magnitude of the epidemic, this may be the quickest way of eliminating vertical transmission during pregnancy and the breastfeeding periods. The other strategies for fast-tracking eMTCT which include adoption of elective caesarean births and avoidance of breastfeeding among WLHIV are hindered by high costs and higher risk of infant death due to diarrhoeal diseases in the absence of breastfeeding respectively in settings like South Africa.[47,48] As for the case of caesarean births, sustained maternal VL suppression during pregnancy reduces the risk of MTCT during vaginal delivery to a point where caesarean birth offers no advantage.[67,89,90] However, both the national PMTCT and Maternity Care guidelines are not clear about delivery options for women with elevated VL at time of delivery. A potential game changer for eMTCT should consider elective caesarean births amongst mothers with elevated VL, detected by PoC HIV VL testing at time of delivery.

1.3.9 Summary of literature review and research gaps

From the literature review, there is limited data describing maternal virologic responses during pregnancy and postpartum periods within routine settings, both in South Africa and across SSA. This is a clear gap that requires urgent attention, considering the region is home to approximately 90% of global paediatric HIV. Inadequate laboratory infrastructure is often blamed for poor monitoring of maternal VLs, hence the need to supplement existing laboratory systems with PoC modalities. South Africa has committed to achieving eMTCT. Without data on maternal VL responses, it is difficult to assess progress towards eMTCT as well as the UNAIDS 90-90-90 targets. A larger proportion of existing studies reviewing maternal VL during pregnancy and postpartum periods were cross sectional by design and most involved small sample sizes. Cross sectional designs do not provide adequate information on maternal VL suppression throughout the continuum of PMTCT care, that is, during pregnancy to the end of breastfeeding period. Elimination of mother-to-child transmission of HIV requires maternal VL suppression prior to and during pregnancy as well as postpartum. Small sample sizes limit the generalizability of findings, particularly beyond the populations from which studies are

drawn. Moreover, the studies which contributed to literature on maternal VL suppression were either donor-funded projects or emanating from research sites. While findings from these studies are important, they have limited generalizability to routine practice and stakeholders run the risk of developing misguided policy. This underscores the importance of using routine data to inform policy where possible. Lastly, the unit of analysis for the bulk of studies reviewed was at individual level. There may be value in determining population level factors associated with community VL among pregnant and non-pregnant WLHIV as the country moves towards eMTCT.

1.4 Rationale for this study

Despite the existence of low MTCT rates, achievement of eMTCT in South Africa is challenged by a high maternal seroprevalence rate. The PMTCT programme has been in existence for close to two decades, undergoing continuous changes aimed at setting the country on the path to eMTCT. Two of the provisions of the country's 'Last mile plan to eMTCT' is addressing bottlenecks along the PMTCT cascade and reaching out to high HIV burden areas.[91] Viral load monitoring amongst pregnant and postpartum WLHIV appears to be a neglected area in PMTCT care. Programmatic data describing VL outcomes of pregnant and postpartum WLHIV nationally is lacking, therefore maternal VL suppression rates are unknown. This has dire implications for a programme that is in pursuit of eMTCT. The burden of maternal viraemia within the national PMTCT programme is not well described. Therefore, research needs to focus on documenting maternal VL outcomes to guide interventions to improve the programme. A few studies have reviewed maternal VL suppression at sub-national level. The bulk of this research is from routine settings and research sites in the Western Cape province. It is well known that the HIV epidemic and response differs geographically in South Africa. As a result, performance of the programme in the Western Cape province may not be generalizable to the rest of the country.

This research project sought to close the above gaps by evaluating VL suppression rates among pregnant and postpartum WRLHIV. It sought to provide a baseline for maternal virologic control during pregnancy and postpartum periods nationally. Sub-national level (province and district) evaluations aimed to identify hotspots of maternal viraemia to guide interventions for eMTCT. Guiding interventions can include understanding predictors of MTCT, the timing of maternal viraemia (when are WRLHIV most viraemic- during pregnancy or the postpartum period) in the era of UTT. Lastly, the study uses routinely collected laboratory test data used for surveillance purposes. This approach is in line with principles of 'next generation surveillance', which advocates for moving away from national surveys and sentinel surveillance which are often very expensive.[92,93] Routine laboratory data from the National Health Laboratory Service's Corporate Data Warehouse (NHLS CDW) provides a cost-

effective yet robust surveillance system for monitoring the public health response to HIV at national level in near real-time.[38] This surveillance system does not require sampling, provides comprehensive coverage at all sub-national levels and requires minimal field work. The study also aims to provide insights into how to render the NHLS data user friendly to continuously improve monitoring of the eMTCT program going forward.

1.5 Thesis framework

Figure 1.2 illustrates the framework used in this study. The framework highlights critical points during pregnancy and the postpartum period for monitoring maternal VL and links unsuppressed maternal VL and paediatric HIV infection. Pregnant WLHIV are a subset of HIV-positive women of reproductive age, with some women transitioning between the two categories. Pregnant WLHIV enter the PMTCT care continuum either as newly diagnosed and ART naïve or known, ART-experienced patients. VL monitoring is essential for both groups in order to achieve virologic control. Virologic control is associated with improved health for the mother and lower risk of both horizontal and vertical transmission. While ART provision is the main strategy for controlling maternal VL during pregnancy and postpartum, there are several factors that affect maternal VL responses. For example socio-economic factors (HIV status disclosure and employment), policy environment (access to care), and other clinical factors (comorbidities, ART drug efficacy, etc.) play a role. This study focused on clinical factors such as ART status at fANC, presence of comorbidities and policy related factors such as implementation of VL testing guidelines in pregnant and postpartum WLHIV and the influence of geographical differences on maternal virologic control during pregnancy and the postpartum period. The other factors were not reviewed due to lack of data or simply because they were beyond the scope of this study.

1.6 Aim of the study

The study seeks to provide a national description of maternal viraemia as a key driver of mother-to-child transmission (MTCT) of HIV to establish a baseline from which to improve virological control during pregnancy and the postpartum period in order to facilitate elimination of MTCT in South Africa.

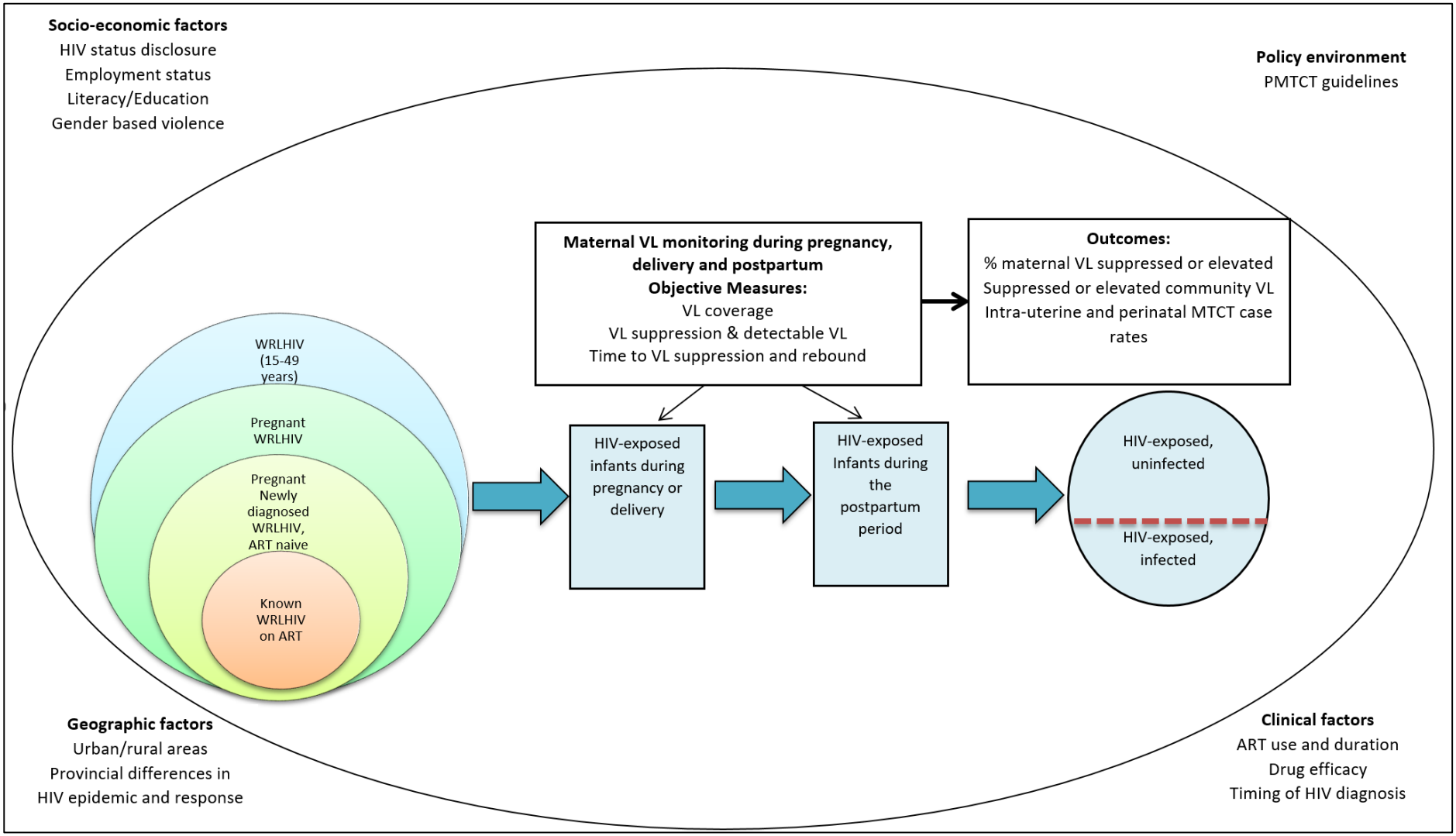
Socio-economic factors
HIV status disclosure
Employment status
Literacy/Education
Gender based violence
Policy environment
PMTCT guidelines
Maternal VL monitoring during pregnancy, delivery and postpartum
Objective Measures:
VL coverage
VL suppression & detectable VL
Time to VL suppression and rebound
Outcomes:
% maternal VL suppressed or elevated
Suppressed or elevated community VL
Intra-uterine and perinatal MTCT case rates
WRLHIV (15-49 years)
Pregnant WRLHIV
Pregnant Newly diagnosed WRLHIV, ART naive
Known WRLHIV on ART
HIV-exposed infants during pregnancy or delivery
HIV-exposed Infants during the postpartum period
HIV-exposed, uninfected
HIV-exposed, infected
Geographic factors
Urban/rural areas
Provincial differences in HIV epidemic and response
Clinical factors
ART use and duration
Drug efficacy
Timing of HIV diagnosis

Figure 1.2. Framework illustrating factors that affect maternal VL during pregnancy and postpartum periods.

Abbreviations: WRLHIV women of reproductive age living with HIV, ART antiretroviral therapy, VL viral load, PMTCT prevention of mother-to-child transmission of HIV

1.6.1 Overall objective

To define high prevalence regions (hotspots) of maternal viraemia and associated factors in pregnant and postpartum WRLHIV at district level in South Africa, to direct interventions to improve ante- and post-natal care to achieve eMTCT.

1.6.2 Specific objectives

1.6.2.1 To describe and map the burden of WRLHIV and adolescent girls and young women (AGYW) living with HIV by province in 2018 in South Africa

1.6.2.2 For three time periods (namely; at first ANC visit, around delivery and within 15 months postpartum) and among WRLHIV who were pregnant between Jan 2016-Dec 2017:

a) describe and map the burden of high maternal VL nationally and by province

b) describe the evolution of maternal VL levels nationally and by province

c) determine factors associated with high maternal VL during pregnancy and postpartum nationally

1.6.2.3 At sub-district level among WRLHIV who were pregnant between Jan 2016-Dec 2017:

d) determine population-level risk factors for MTCT

e) compare community VL of pregnant versus non-pregnant WRLHIV

e) correlate maternal VL suppression rates with *in utero* HIV MTCT rates

1.6.2. 4 Describe VL suppression at delivery and coverage of VL monitoring in pregnant and postpartum WLHIV in Gauteng province in 2018

1.7 Hypotheses and assumptions

This project assumed that pregnant WRLHIV (and their ART status) can be readily identified from non-pregnant WRLHIV of reproductive age in the centralized laboratory database using syphilis screening and other test results as a proxy for first ANC visit in pregnancy. Viral load coverage and suppression rates were hypothesized to be relatively low at ±70% compared to the UNAIDS 90-90-90 targets among pregnant and postpartum WRLHIV in anticipation of poor implementation of guidelines and other pregnancy related factors. The community VL of pregnant women was expected to be higher than that of non-pregnant WRLHIV of reproductive age in HIV care on account of poor VL monitoring during pregnancy in South Africa during the study period. It was further hypothesized that maternal VL suppression rates would be positively correlated with MTCT rates at population level and that sub-districts with low maternal VL suppression rates would have a larger burden of paediatric infection.

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CHAPTER 2.

Methodology

2.1 Study setting

2.1.1 Antenatal care in South Africa

South Africa records approximately one million live births in a given year.[1] Majority of these births occur to women who access ANC in the public health sector.[2] At the fANC visit, pregnancies are confirmed using tests such as Beta human chorionic gonadotropin hormone (β-hCG) and pregnant women are required to commence ANC at local clinics or at Midwife Obstetric Units.[3] These women subsequently undergo a series of health screening checks, including syphilis and HIV to improve maternal health and prevent adverse pregnancy outcomes.

Maternal syphilis testing coverage was reported at >96% in 2017.[4] Current guidelines for Sexually Transmitted Infections (STIs) in ANC recommend the reverse testing algorithm for syphilis screening.[5] Screening starts with a specific treponemal test such as a Treponema Pallidum antibodies (TPAb) or Treponema Pallidum Haemagglutination Assay (TPHA) followed by a Rapid Plasmin Reagin (RPR) for patients testing positive for the specific test. Since STI management in South Africa is syndromic, only a small proportion of syphilis tests are performed for clinical presentations of STIs. However, syphilis screening does constitute part of sexual assault investigation. Based on near universal syphilis testing coverage amongst pregnant women in the public health sector, syphilis-screening tests constituted part of our criteria for identifying pregnant women from our data source. Although majority of the tests for syphilis serology performed in the public sector are stored in the National Health Laboratory Service's Corporate Data Warehouse (NHLS CDW), some women are screened using rapid test kits, results of which are not captured on the NHLS CDW.

With respect to HIV, newly diagnosed pregnant women living with HIV (WLHIV) initiate ART at the fANC visit or at confirmation of HIV-infection. At ART initiation, a baseline CD4 count test and creatinine clearance test are performed to assess immunological profile and to evaluate kidney function, respectively. HIV VL monitoring for all pregnant WLHIV follows previously described guidelines.[6,7] Similar to syphilis, screening results of WLHIV diagnosed with rapid test kits are not captured on the NHLS CDW. However, HIV enzyme-linked immunosorbent assay (ELISA) results for diagnosis of HIV and longitudinal HIV test data (HIV VL and CD4 counts) are stored in the NHLS CDW.

2.1.2 Methods

This section provides an overview of methodology and data sources for the thesis by publication.

2.2. NHLS CDW synthetic cohort

The national level synthetic cohort provided data for publication 2 (Chapter 4) and the manuscript in preparation (Chapter 6).

2.2.1. Data source

The NHLS CDW is a national repository of all clinical laboratory tests performed in the public health sector and is described elsewhere.[8,9] Results of all registered specimens (including laboratory specimen numbers), patient identifying details (name, surname, date of birth, age, home address, telephone number), details of registering facility (facility name, hospital/clinic number) and geographic location (province, district, sub-district) are automatically stored in near real time in the NHLS CDW based at Sandringham, Johannesburg. No clinical data is stored. Routine longitudinal laboratory test data is linked by means of a patient linking algorithm. As the NHLS CDW lacks a national level unique identifier, the algorithm uses probabilistic matching of patient demographic information (name, surname, date of birth, facility number, etc.) to generate a unique ID and assigns it to test data belonging to same individual.[9] When the current patient linking algorithm was validated against a gold standard dataset in 2016, it was found to have a Type 1 error of 11% (over-matching probability) and Type 2 error (under-matching probability) of 15% among adults patients.[9] However, it has not been validated for record-matching in pregnant WLHIV who may differ from adult patients in that they typically receive care in multiple different facilities during ANC, delivery and postpartum, making it more complex for an algorithm to link their tests.

2.2.2 Study characteristics

2.2.2.1 Design

A retrospective cohort design based on analysis of longitudinal data of a synthetic cohort created from centralized routine laboratory surveillance data.

2.2.2.2 Study population

Women of reproductive age, 15-49 years living with HIV (WRLHIV), who were in care and receiving HIV laboratory tests at any public health facility in South Africa during the study period. Women were considered to be living with HIV by virtue of having ≥1 HIV VL or ≥1 CD4 count or a reactive HIV ELISA

and deemed pregnant and presenting at their fANC visit by virtue of a syphilis screening test, coupled with either a creatinine clearance and CD4 count or a VL to determine their HIV ART status.

2.2.2.3 Creating the synthetic cohort

Centralized routine data on multiple HIV, syphilis and pregnancy-related tests were used to create a synthetic cohort of pregnant WRLHIV. That is, a cohort that was created by applying a set of criteria to HIV- and pregnancy-related test data in order to identify pregnant WRLHIV. This was necessary due to a lack of a marker for pregnancy within the NHLS CDW. The first step involved identification of women of reproductive age using HIV-related tests conducted between 01 April 2015 to 31 March 2019 from the NHLS CDW (data extraction period). This was achieved by extracting test records associated with HIV VLs, CD4 counts and HIV ELISA tests belonging to females, aged 15-49 years during this period (Figure 2.1). Data were then restricted to the study period (01 January 2016 to 31 December 2017). The data extraction period allowed the study to evaluate patterns of HIV testing prior to pregnancy to demonstrate pre-pregnancy HIV-infection as well as to allow sufficient follow up time during the postpartum period.

WRLHIV were defined as individuals having ≥1 HIV VL or ≥1 CD4 count or a reactive HIV ELISA From this set, syphilis screening was applied as a proxy for pregnancy during the 2016/17 study period. Women with ≥1 eligible syphilis test –TPAb/ TPHA with or without an RPR test during the study period, were selected. Since syphilis screening also occurs in non-pregnant women, a set of additional criteria were applied to the cohort of potentially pregnant WRLHIV to identify women with a greater likelihood of being pregnant. Women with records of eligible syphilis and HIV VL tests requested from ANC, labour, maternity and postnatal wards were considered highly likely to be pregnant. Test records of other pregnancy-related tests such as postpartum cervical smears, infant birth HIV PCR tests submitted to the laboratory with maternal details and positive β-hCG tests performed during the study period also identified WRLHIV with a greater likelihood of being pregnant. Women with test results suggesting sexual assault were excluded from this subset (for example syphilis test results from sexual assault clinics/centres) This subset of women constituted the eligible analytical cohort, referred to as pregnant WRLHIV henceforth.

Once the cohort of pregnant WRLHIV was identified, the date of the fANC visit was determined. The date of syphilis screening was used as a proxy for the fANC visit according to routine antenatal practice, which requires all pregnant women to be screened for syphilis at the fANC visit.[3] Thus, timing of HIV VLs 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, based on the fact

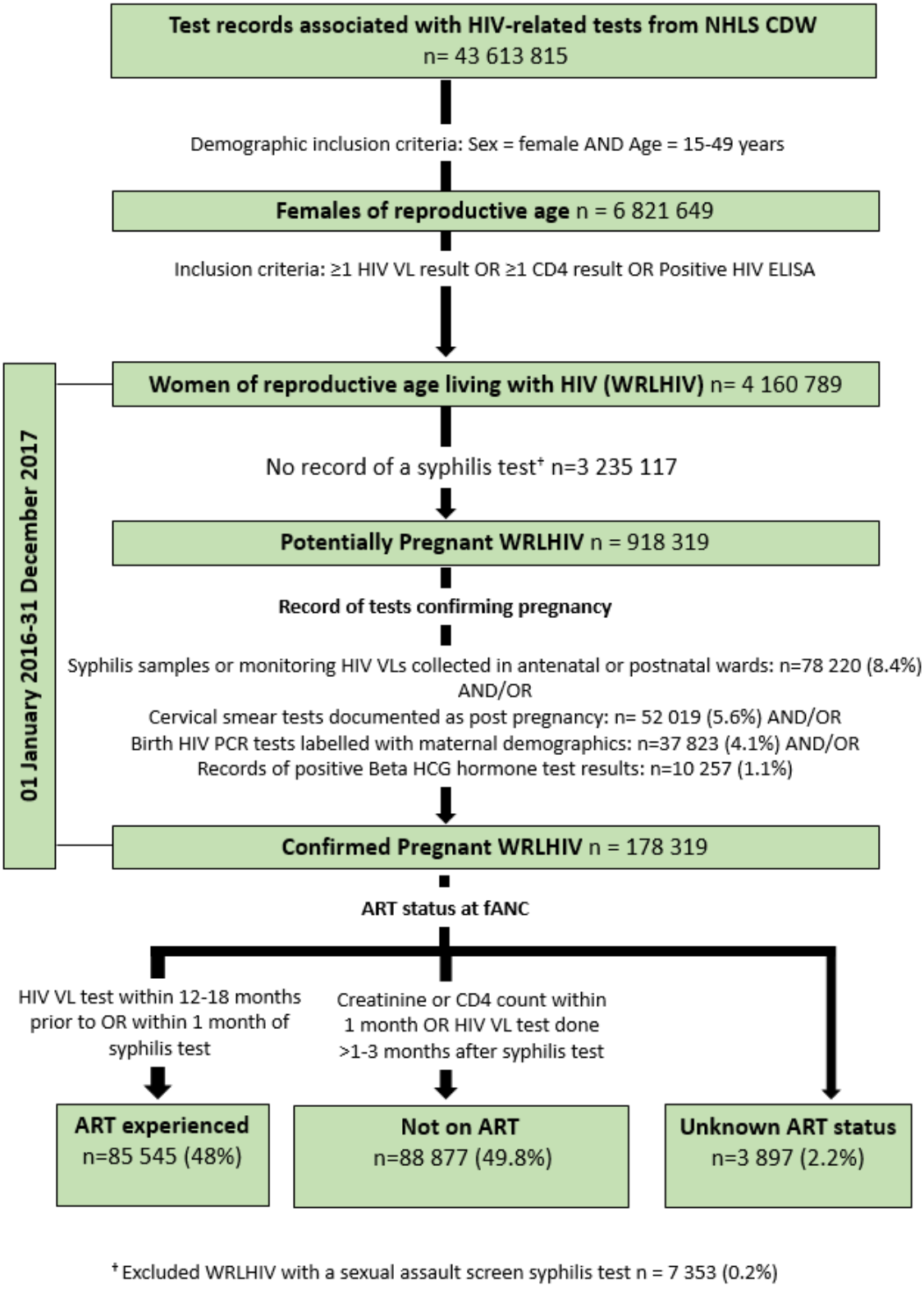

Figure 2.1. Criteria for identifying HIV viral load tests performed on pregnant women of reproductive age living with HIV, in the NHLS CDW between 1 January 2016-31 December 2017.

Abbreviations: NHLS CDW National Health Laboratory Services' Corporate Data Warehouse; fANC first antenatal care visit; VL viral load; ART antiretroviral therapy; PCR polymerase chain reaction; HCG human chorionic gonadotropin.

that approximately 68% of ANC clients had their first booking at <20 weeks gestation within routine settings during the study period according to the South African District Health Information System (DHIS). The DHIS is a repository of aggregated routine health data from all public health facilities in the country. A more detailed description of the DHIS will follow in the next chapter. The postnatal period was up to 15 months post the estimated delivery date. Figure 2.2 describes duration of follow up for the cohort.

Lastly, maternal ART status at the fANC visit was determined by the timing of ART initiation relative to the date of the first syphilis screening test. The synthetic cohort was linked to any HIV VLs performed in the 12-18 months preceding the syphilis test. An HIV VL performed within 12-18 months prior to or within 1 month of the syphilis test defined pregnant WRLHIV who were ART experienced at fANC visit. A syphilis screening test associated with a creatinine clearance and or CD4 count test performed within 1 month, or HIV VL around 3 months after the syphilis test identified pregnant WRLHIV not on ART at fANC visit.

To test the robustness of this methodological approach of identifying pregnant WRLHIV from the NHLS CDW, results were compared against 'total live births to HIV-positive women' from the DHIS to assess geographic distribution of pregnant WRLHIV selected from the NHLS CDW.

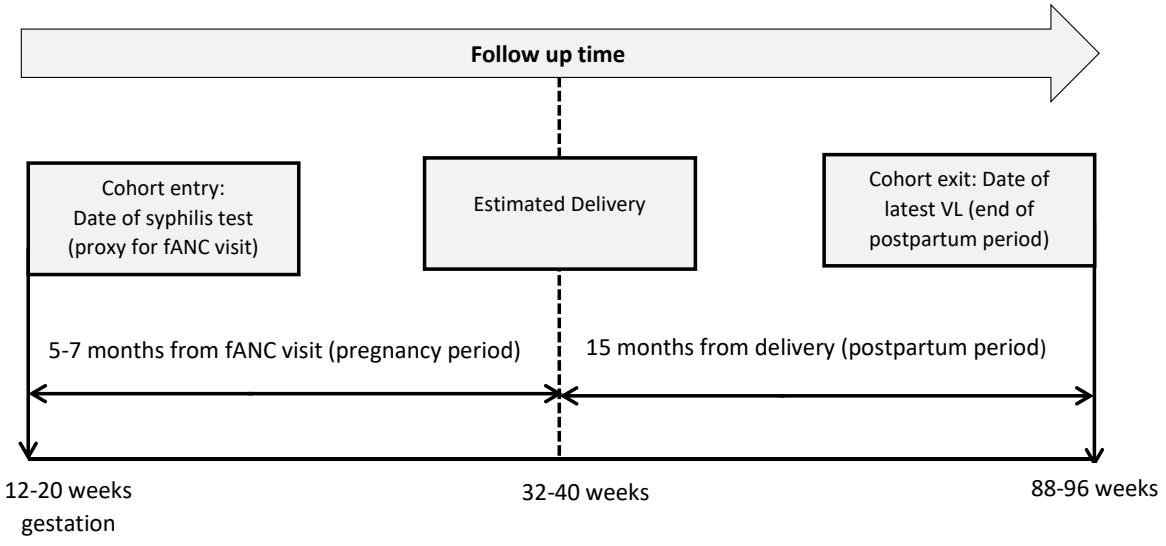

Figure 2.2. Definition of study follow up times among pregnant and postpartum WRLHIV identified from the NHLS CDW.

Abbreviations: fANC first antenatal care visit; WRLHIV women of reproductive age living with HIV; NHLS CDW National Health Laboratory Service's Corporate Data Warehouse.

2.2.2.5 Sample size

All participants that met the study's inclusion criteria were included in the analyses. However, based on a million pregnancies per annum and a maternal HIV seroprevalence rate of 30%, the project anticipated identifying ±600 000 WRLHIV from a pool of 2 million pregnant women nationally between Jan 2016-Dec 2017. Given >95% ART coverage among HIV-infected pregnant women in South Africa and the fact that >80% of all diagnostic pathology services performed in the public sector are stored at the NHLS CDW, a maximum eligible sample of ±450 000 pregnant WRLHIV nationally was anticipated during the study period. It was anticipated that laboratory monitoring according to guidelines would be less than perfectly implemented in routine settings hence the option to analyse data from a smaller sample size of WRLHIV but with a higher specificity for pregnancy was elected.

2.2.2.6 Study measures

Specific details of the measures analysed in the study are discussed per manuscript, in the relevant chapters of the results section.

2.3 Gauteng cohort

Since the main study cohort was a synthetic cohort of pregnant WRLHIV, created by applying a set of criteria to routine laboratory data, data from a known group of pregnant WLHIV (regardless of age) was analyzed to validate findings from the national level synthetic cohort and to test its representativeness. Data from the Gauteng cohort was used for the analyses presented in publications 3 (Chapter 5) and 4 (Chapter 7).

2.3.1. Data source

Data for the validation study came from a study evaluating the feasibility of integrating point-of-care (PoC) VL testing into routine settings in Gauteng, South Africa.[10]

2.3.2 Study characteristics

2.3.2.1 Study design and population

This was a prospective study of all consenting, pregnant WLHIV presenting for delivery of their babies and admitted to labour or postnatal wards at four high volume, tertiary obstetric units (TOUs) in Gauteng province between 01 June 2018 and 31 March 2019.

2.3.2.2 Study procedures

Mothers and their newborn babies were offered a PoC VL and EID test respectively, around the time of delivery. Specimen collection was performed by routine clinical staff while dedicated PoC operators conducted testing at the study sites. Point-of-care testing and centralized laboratory testing were performed in parallel. That is, for each PoC test performed, a corresponding specimen was sent to the NHLS for routine testing. Both PoC and NHLS test results were captured by a study co-ordinator into a REDCap™ database and constituted study data. Maternal VL data at time of delivery from this cohort was subsequently compared with maternal viraemia from the national, synthetic cohort of pregnant WRLHIV from the NHLS CDW. In addition, the validation cohort was used to extract longitudinal VL test data associated with patient identifiers and maternal demographics of pregnant WLHIV delivering in the study sites from the NHLS CDW to describe compliance to national VL testing guidelines.

2.3.2.3 Study measures

Further details on specific measures analysed are presented in the relevant results sections (Chapters *5* and *7*).

2.4 Other data sources used in the thesis

The Thembisa model and five other independent routine health and HIV related data sources (Statistics South Africa, DHIS, the South African National HIV Prevalence, Incidence, Behaviour and Communication Survey, the National Antenatal Sentinel HIV & Syphilis Survey Report, the National Institute for Communicable Diseases' Surveillance Data Warehouse were used to provide a cross-sectional provincial distribution of WRLHIV and AGYW living with HIV in relation to intra-uterine transmission rates in the country in 2018 (publication 1, Chapter 3). The Thembisa model, which is a mathematical model that profiles the South African HIV epidemic and the impact of the HIV response in the country, was used as the primary data source for these analyses.[12] Data from the Thembisa

model was triangulated with routine health and HIV related data for validation or to provide data in instances where data was not available from the Thembisa model. A detailed description of the routine data sources used in these analyses is presented in Chapter 3.

2.5 Data analysis plan

Table 2.1 provides the analysis plan per objective.

Table 2.1. Overview of data analysis plan

Objective	Outcome	Analysis	Chapter
1. To describe and map the burden of WRLHIV and adolescent girls and young women living with HIV by province in 2018 in South Africa	Demographic profile of WRLHIV and AGYW (15-24 years) by province	Frequencies and percentages. Hot spots analysis in ArcGIS using the Gertis-Ord Gi* statistic performed	Chapter 3, Publication 1
2.1 Among WRLHIV, pregnant and delivering between Jan 2016-Dec 2017, at first ANC visit, around delivery and within 15 months postpartum:			
a) describe and map the burden of high maternal VL nationally and by province	Proportions of maternal VL ≥50 or VL ≥ 1000 cps/mL at delivery	Frequencies and percentages. Proportions described using ArcGIS	Chapter 6, manuscript in preparation
b) describe the evolution of maternal VL levels nationally and by province	Maternal VL values; (Observed and predicted)	Fractional polynomial models	Chapter 4, Publication 2
c) determine factors associated with high maternal VL during pregnancy and postpartum period nationally	Maternal VL values (Observed and predicted)	Piecewise (spline) linear regression	Chapter 4, Publication 2
2.2 Among WRLHIV, pregnant and delivering between Jan 2016-Dec 2017, at sub-district level:			
c) determine population-level risk factors for MTCT	MTCT cases (from birth-24 months)	Negative binomial regression	Chapter 6, manuscript in preparation
d) compare community VL of pregnant vs. non pregnant WRLHIV	Median VL of aggregated VLs for	Kruskall Wallis test	Chapter 6, manuscript in preparation

	pregnant and non-pregnant WRLHIV		
e) correlate maternal VL suppression rates to total cases of MTCT	Total MTCT cases (from birth-24 months)	Negative binomial regression	Chapter 6, manuscript in preparation
3. Describe VL suppression at delivery and coverage of VL monitoring in pregnant and postpartum WLHIV in Gauteng province in 2018	Proportions of women with 1) VL test during pregnancy and postpartum 2) VL <50 cps/mL	Descriptive statistics, Pearson Chi square test	Chapter 7, Publications 3 & 4

Abbreviations: WRLHIV women of reproductive age living with HIV, WLHIV women living with HIV, AGYW adolescent girls and young women, IU intra-uterine, ANC antenatal care, VL viral load, cps/ml copies/millilitre, MTCT mother-to-child transmission.

2.4 Ethical considerations

Permission to access data from the NHLS CDW was obtained from the NHLS Director of Academic Affairs Research and Quality Assurance (Appendix 2.1). Approval from the NHLS was granted upon submission of a study protocol and ethics clearance certificate that was approved by the Human Research Ethics Committee (HREC) of the University of the Witwatersrand (Appendix 2.2). Identifiable patient data from the NHLS CDW was extracted for the purpose of matching test sets. Matched data were subsequently de-identified prior to analysis, allocated a unique identifier and stored in password protected platforms to ensure confidentiality. Data was only accessible to the research team to maximize patient protection. Ethical clearance for sub-studies have been declared in the individual chapters in the results section.

2.5 Research team and candidate's role in the study

This study was conducted by the Paediatric HIV Surveillance team within the Centre for HIV and Sexually Transmitted Infections at the National Institute for Communicable Diseases (NICD). The Centre for HIV and Sexually Transmitted Infections is a knowledge resource and expertise centre serving South Africa and the continent with surveillance and research activities, including but not limited to HIV virology and immunology, HIV/STI epidemiology and diagnostics.[11] The Paediatric HIV

Surveillance team is responsible for paediatric HIV surveillance, monitoring early infant diagnosis and linkage into care within the national PMTCT programme. This study was nested in a bigger project funded by the ELMA Foundation, which was implemented by the Paediatric HIV Surveillance team in order to evaluate gaps within the PMTCT treatment cascade for eMTCT (Part 1) as well as to evaluate South Africa's progress towards the UNAIDS 90-90-90 targets for the paediatric HIV programme at national level (Part 2). This study constituted Part 1 of the bigger project, with a focus on characterization of high maternal VL as a key driver of MTCT among pregnant and postpartum women WLHIV accessing PMTCT services in the public health sector South Africa.

The candidate was a full-time employee within the Centre for HIV and Sexually Transmitted Infections unit and was the principal investigator for this study. The candidate submitted a full research protocol and an ethics application to the HREC of the University of the Witwatersrand. The candidate, in consultation with both supervisors was responsible for study design and providing technical guidance on the specifications of the data extractions and development of software coding for extracting study data from the NHLS CDW. The NHLS CDW architecture has had to cater for changes in the laboratory information system (LIS) over time e.g. different coding for test sets and facilities and changing health district boundaries. Thus, the data required multiple data balancing exercises and reliance on institutional knowledge of several NHLS departments for accurate data extraction and representation. The candidate was responsible for data management, data cleaning, analyses and was first author for all manuscripts, publications and conference presentations emanating from this work. For the validation study involving the Gauteng cohort, the candidate was also responsible for overseeing data collection, data management (including longitudinal record linkage), data cleaning and analysis. The supervisors provided critical review of all study outputs, mentorship and guidance to ensure completion of tasks in a timely manner.

2.6 References

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SECTION 2: RESULTS & EMPIRICAL CHAPTERS

CHAPTER 3.

The geographic distribution of priority population groups for the elimination of mother-to-child transmission of HIV in South Africa.

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3.1 Introduction

Women constitute the highest proportion of people living with HIV globally.[1] In South Africa, the HIV epidemic also disproportionately affects women. In 2017, approximately two thirds of people living with HIV who were aged 15-49 years and on antiretroviral therapy (ART) were female.[2] In the same year, disparities in HIV prevalence by sex were most pronounced among young adults. HIV prevalence among 20-24 year olds was three times higher in females (15.6%) compared to males (4.8%).[2] The potential reasons for gender disparities in the profile of the HIV epidemic are both economic and sociocultural.[3] Extensive geospatial heterogeneity in the distribution of the HIV epidemic in South Africa has been reported previously.[4] In 2018, provincial HIV prevalence estimates among people living with HIV aged 15-49 years ranged from 6.7% in the Western Cape to 18.4% in KwaZulu-Natal.[4] While poorly understood, variations in provincial HIV prevalence rates have been linked to differences in the uptake of HIV prevention interventions and societal norms between provinces.[4] These provincial variations in the profile of the HIV epidemic necessitate optimized allocation of resources and targeted interventions for HIV/AIDS programmes. This is particularly pertinent for the PMTCT programme, which has prioritized eMTCT.

The national MTCT rate of 1.0% at birth in 2017 equalled just under 250 cases per 100 000 live births.[6] Sub-national level variations in MTCT rates also exist, with some districts reporting almost double the national MTCT rate at birth.[6] The foregoing supports the need for contextualized and tailored responses to maternal and paediatric HIV in South Africa.

We describe the distribution of women living with HIV of reproductive age (WRLHIV) as well as those without HIV by province in South Africa, in order to identify areas that may require additional eMTCT interventions. These may include interventions aimed at reducing the risk of HIV acquisition by HIV-negative women of reproductive age and unplanned pregnancies among WRLHIV, that is, pillars 1-2 of the South African PMTCT strategy.[7] WRLHIV and sub-groups (adolescent girls and young women-AGYW, aged 15-24 years) are priority populations for achieving eMTCT. These women can potentially become pregnant and transmit HIV to their infants. While the risk of vertical transmission of HIV is low in planned pregnancies, where WRLHIV fully access and utilize preconception and post conception PMTCT services, the contrary is true for unplanned pregnancies.[8] Pregnancies are more likely to be unplanned in AGYW compared to older women.[9] In addition, AGYW represent a sub-population that will remain in the reproductive age group for the longest time; are associated with high incident infections and where HIV positive, AGYW have poorer PMTCT outcomes compared to older WRLHIV.[9] Therefore, the risk of MTCT is higher in this population. However, an increase in number of women

conceiving on ART has been observed with the scale up of universal test and treat policy (UTT).[10] Consequently, understanding where WRLHIV, including AGYW (regardless of their HIV status) and those who are pregnant, are located in South Africa is key for eMTCT. Scaling up family planning services and ART/PMTCT services (for example, stock planning of Efavirenz based regimens and Dolutegravir rollout in relation to new ART guidelines) in geographic areas with a high burden of these groups may be beneficial for maternal HIV care and eMTCT.

Obtaining accurate estimates of vertical transmission is challenging in South Africa because of the lack of a unique patient identifier in the health system. Monitoring of early infant MTCT rates and coverage of early infant diagnosis currently relies on routine data from the DHIS and the NHLS.[11] There are no accurate, national data sources for postnatal transmission rates, breastfeeding practices and maternal virological control during pregnancy and the postpartum period. An analysis of current data sources used for tracking eMTCT, their strengths and weakness, were described elsewhere by Sherman *et al.*[11] Using six different data sources, we describe the distribution of WRLHIV in South Africa during 2018 in relation to where the intra-uterine (IU) transmissions occur.

3.2 Materials and Methods

Data for these analyses were extracted from six independent sources for HIV-related and demographic indicators from the public health sector in South Africa. These were the Thembisa Model, DHIS, Statistics South Africa (Stats SA), the South African National HIV Prevalence, Incidence, Behaviour and Communication Survey (SABSSM), the National Antenatal Sentinel HIV & Syphilis Survey Report, (herein referred to as the ANC sero-prevalence survey) and the National Institute for Communicable Diseases' Surveillance Data Warehouse (NICD SDW), a division of the NHLS. The Thembisa Model was used as the primary data source because it had most of the indicators required for the analyses. The other sources were used for triangulation purposes where applicable. The reporting period was the year 2018. Where data for 2018 was not available, available data from the most recent year were used. A brief description of each data source and indicators that were used for the analyses follows (Table 3.1).

Table 3.1 Indicators used in the analyses by data sources.

Indicators	Data Sources					
	Thembisa Model	Stats SA	DHIS	ANC sero-prevalence survey	SABSSM	NICD SDW
Total Population estimates (males and females, all ages)	✓	✓				
Total Population for females (All ages)	✓	✓				
Total Population for females 15-49 years	✓	✓				
Total Population for females 15-24 years	✓	✓				
Number of live births	✓	✓	✓			
Total births to HIV-positive women	✓		✓			
HIV prevalence in females 15-49 years	✓					
HIV prevalence in females 15-24 years	✓					
HIV prevalence in pregnant females 15-49 years				✓		
HIV prevalence in pregnant females	✓					
HIV prevalence in adults 15-49 years	✓	✓			✓	
HIV PCR tests at age <7 days (Birth HIV PCR)						✓
Total fertility rate	✓	✓				
Reporting Unit	National Province	National Province	National Province District Sub-district Facility	National Province District	National*	National Province District Sub-district Facility
Year for which data was available	2018	2018	2018	2017	2017	2018

Abbreviations: Stats SA Statistics South Africa; DHIS Demographic Health Information System; PCR polymerase chain reaction; ANC antenatal care; NICD National Institute for Communicable Diseases SDW Surveillance Data Warehouse; SABSSM South African National HIV Prevalence, Incidence, Behaviour and Communication Survey. *Data available at national level only at time of publication. Blocked out areas indicate absence of data for a specific indicator per data source.

3.2.1 Description of data sources

a) Thembisa Model

The Thembisa Model is an integrated epidemiological and demographic mathematical model developed to describe the South African HIV epidemic and to evaluate the impact of HIV prevention and treatment strategies in the country.[12] In addition, the model also provides demographic statistics and is used to evaluate the demographic impact of HIV in South Africa.[12] The model provides data at national and provincial level. Data were obtained from Thembisa 4.1, published in 2018.

b) DHIS

The DHIS collects aggregated data on health services provided by all health facilities in the public sector in South Africa since 2001. The data are collected from paper-based registers at facility level then entered electronically onto the DHIS software for collation at sub-district, district, provincial and national level on a monthly basis.[13] In some facilities, the data is collected from Tier.net, a national electronic HIV register for aggregation onto DHIS.

c) STATS SA Statistical Release P0302 and P0305

The P0302 document provides data on mid-year population estimates for South Africa and the nine provinces on an annual basis. The projections are based on the cohort component method for population estimation which has been described elsewhere.[14] The population estimates approximate the actual population as at 1 July of a given year. The P0305 document provides data on recorded live births in the public sector in South Africa. The data are based on births registered in the national birth registry system, which is collated and maintained by the Department of Home Affairs in South Africa. At the time of writing of the manuscript, the latest P0302 and P0305 documents were released in 2018 [14,15].

d) National Antenatal Sentinel HIV & Syphilis Survey Report (ANC sero-prevalence survey)

South Africa has been conducting the ANC sero-prevalence survey annually to monitor HIV & syphilis prevalence among pregnant women aged 15-49 years, attending antenatal clinics since the 1990s.[16] The survey is cross sectional by design and is conducted across the 52 health districts in South Africa. Sentinel sites are randomly selected from public sector facilities across the country using probability proportional to size sampling methods.[10] The most recent report for the 2017 survey was published in 2019.[10]

e) SABSSM Survey

The SABSSM is a population based, cross sectional survey of all households in South Africa that evaluates trends in HIV prevalence and other health indicators related to HIV across the country.

The surveys are conducted every five years. At the time of writing, only an executive summary of findings from the latest 2017 survey was available.[2]

f) National Institute for Communicable Diseases (NICD) Surveillance Data Warehouse (SDW)

All pathology tests performed in the public sector are processed by the NHLS through a network of about 260 laboratories as previously described.[17] A single Laboratory Information System (LIS) used by all laboratories stores data pertaining to test specimens (viz. patient identifiers, clinical and geographic information). These data are archived in near real-time in a central data repository called the Surveillance Data Warehouse (SDW) of the NICD. The NICD is a division of the NHLS and the NICD SDW also archives results of all pathology tests performed in the public sector in parallel to the NHLS CDW.

3.2.2. Study measures

The distribution of WRLHIV and AGYW for the year 2018 was described with respect to the following:

a) Total population estimation: Total population estimates were extracted from the Thembisa Model and Stats SA to describe: i) overall population ii) total population of women of all ages and ii) total population of WRLHIV (15- 49 years) and iii) total population of AGYW (15-24 years) and iv) total population of AGYW living with HIV nationally and by province.

b) Number of live births: The number of births (Thembisa Model), number of live births at a facility (DHIS) and number of registered live births from Stats SA were extracted nationally and by province and used to describe child-birth patterns by geographic location.

c) Number of WRLHIV: In order to estimate the number of WRLHIV in South Africa, the total population estimates for women aged 15-49 years were multiplied by the mean HIV prevalence rate amongst women aged 15-49 years. To estimate number of pregnant WRLHIV, total births to HIV-positive women were extracted from the Thembisa Model. For comparison, number of live births from Stats SA were multiplied by the HIV prevalence rate amongst pregnant women aged 15-49 years obtained from the ANC sero-prevalence survey.

d) Number of HIV-positive AGYW: The number of AGYW living with HIV were calculated by multiplying the total population of AGYW by the prevalence of HIV in females aged 15-24 years obtained from the Thembisa Model.

e) Number of live births to women living with HIV: The indicators used to provide these data were obtained from the Thembisa Model and compared to i) number of live births to women living with HIV (DHIS), number of HIV-exposed infants (obtained by multiplying the number of registered live births from Stats SA by the HIV prevalence estimates from the ANC sero-

prevalence survey) and iii) number of HIV PCR tests performed among neonates aged <7 days from the NICD SDW, considering that birth testing coverage for HIV-exposed neonates is >95%. These data were also used as a proxy for number of HIV-positive, pregnant women as explained in 3.2.2c.

f) **IU transmission rates:** These were calculated as the number of de-duplicated HIV PCR positive tests performed at birth (<7 days of life) divided by total HIV PCR tests performed at birth expressed as a percentage from the NICD SDW. The number of IU infections per 100 000 live births was also reported (IU case rates). Test data for HIV PCR positive neonates were de-duplicated by a patient-linking algorithm that uses probabilistic matching of demographics (for example name, surname, date of birth) supplemented by manual matching to account for spelling errors. Because of availability of data, IU transmission rates were also calculated to district level. Intra-partum and postnatal case rates could not be accurately calculated from the SDW because of the lack of a unique identifier to allow for longitudinal monitoring.

3.2.3 Data analysis

Frequencies and percentages were presented for indicators analysed by geographic level. Hot spot analysis using the Gertis-Ord Gi* statistic was performed to detect high burden areas of IU transmission at provincial level using districts as the unit of analysis.

3.3 Ethics clearance

Part of this work utilized routinely collected surveillance data for HIV programs under ethical clearance issued to the NICD (M160 667) by the Human Research Ethics Committee (HREC) of the University of the Witwatersrand (Appendix 3.1). This clearance waives the requirement for patient consent for studies conducted by the NICD, which audit routine programmatic data from the national HIV surveillance programme. Patient identity was protected by anonymizing the data prior to analysis.

3.4. Results

There were approximately 58 million people in South Africa in 2018 with half of the population (51%) being female (Figure. 3.1). Women of reproductive age constituted 27% of the total population, while WRLHIV (3.8 million) accounted for approximately 7% of the total population. There was a total of 4.7 million (8.1%) AGYW of which 477 798 (10.1%) were living with HIV in South Africa. Gauteng province had the highest number of females (all ages) followed by KwaZulu-Natal, the Eastern Cape and the

Western Cape (Figure. 3.2). The Northern Cape had the lowest number of females during the analysis period. A similar trend was observed for women of reproductive age (Figure. 3.3A) and AGYW (Figure. 3.3B), where 69.5% and 67.9% occurred in the four most populous provinces, respectively. However, the analysis of the geographic distribution of WRLHIV (Figure. 3.3C) and HIV-infected AGYW (Figure. 3.3D) showed that 74.4% and 86.7% respectively, of these women were located in four provinces. The latter comprised three of the four most populous provinces but included Mpumalanga instead of the Western Cape. KwaZulu-Natal and Gauteng provinces recorded the highest numbers of WRLHIV at approximately 1 million each, contributing 53.7% of the total population of WRLHIV in the country followed by the Eastern Cape, Mpumalanga and Limpopo provinces.

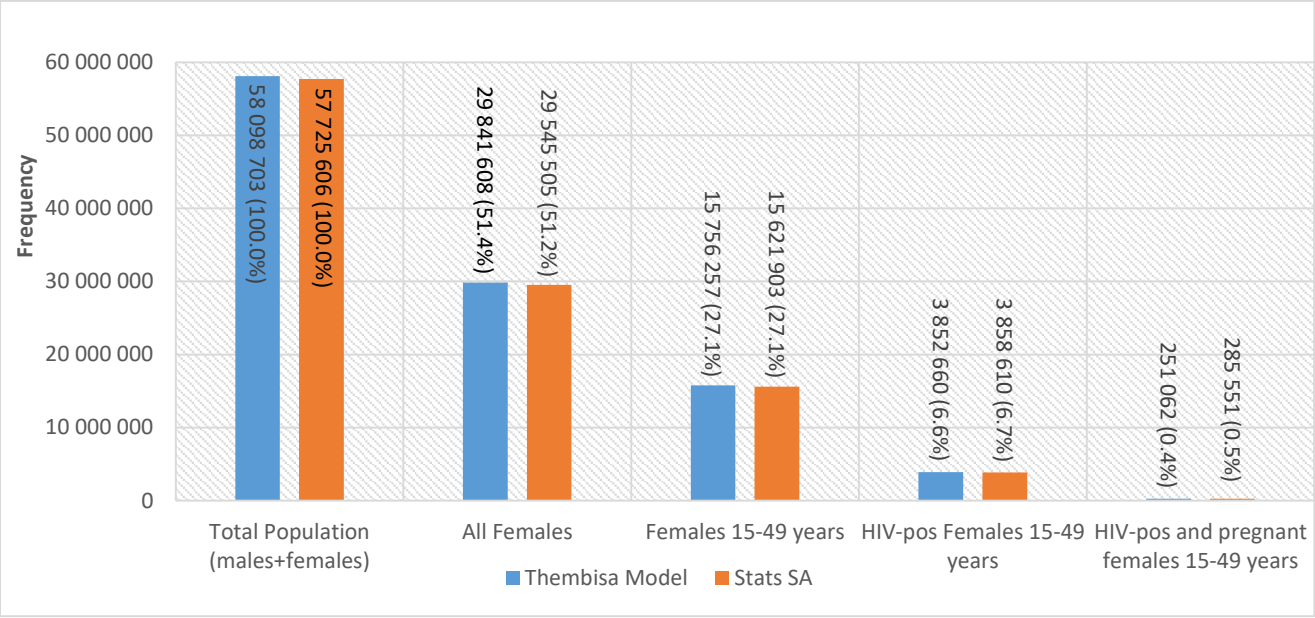


Figure 3.1: Profile of females of reproductive age in South Africa in 2018.

Abbreviation: Stats SA Statistics South Africa.

Overall, out of approximately 1 million live births in the country; between 250 000-286 000 births occurred to women living with HIV in 2018 (Table 3.2). Limpopo province had the third highest number of live births in 2018 ahead of the Eastern Cape and Western Cape provinces (Table 3.2). This was in keeping with Limpopo province having the highest fertility rate throughout the country at (3.1%) (Table 3.2). KwaZulu-Natal province recorded the highest number of live births to women living with HIV, followed by Gauteng and the Eastern Cape respectively (Table 3.2). Similarly, KwaZulu-Natal had the highest HIV prevalence rate among pregnant women (Table 3.3) followed by Mpumalanga province (Table 3.3).

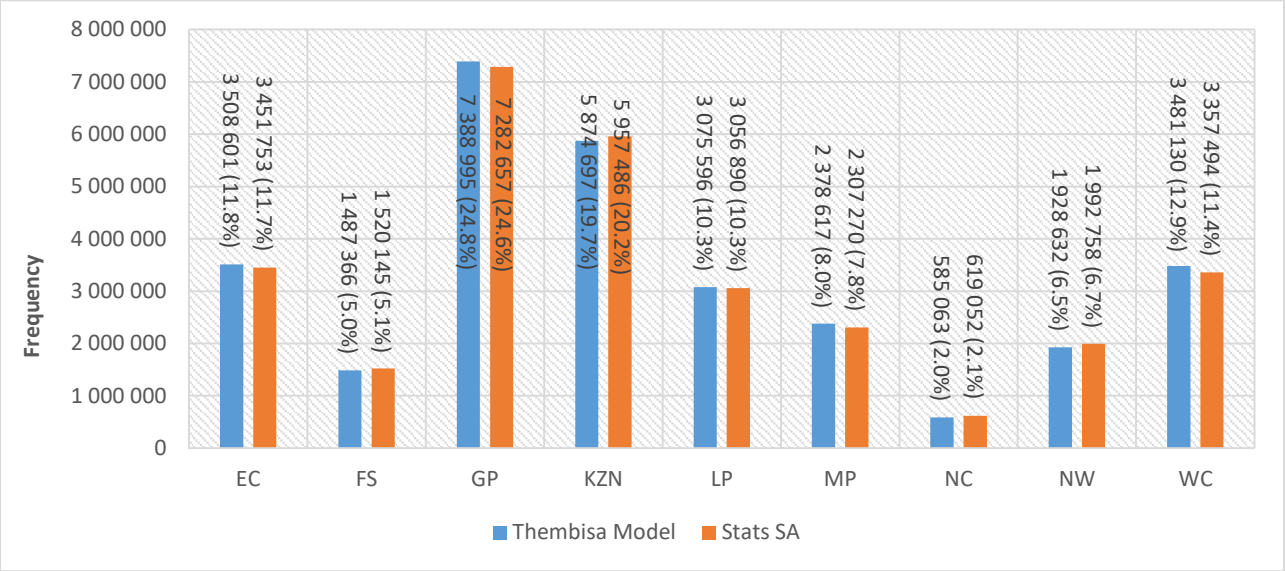


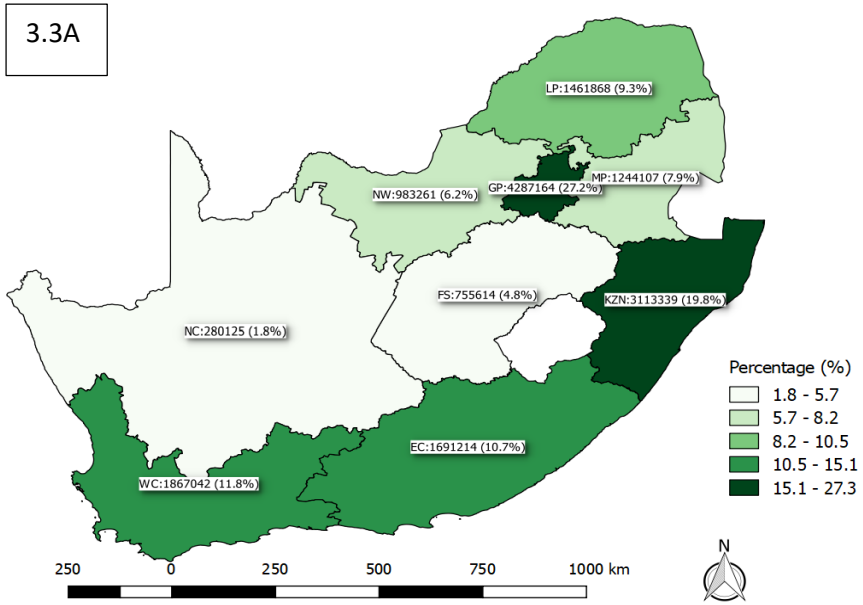
Figure 3.2: Population of females (all ages) by province in South Africa, 2018.

Abbreviations: EC Eastern Cape, FS Free State, GP Gauteng Province, KZN KwaZulu-Natal, LP Limpopo Province, NC Northern Cape, NW North West, WC Western Cape, Stats SA Statistics South Africa.

The IU transmission rate for South Africa was 0.8%, translating into 241 cases of HIV-infected neonates per 100 000 live births (Table 3.4). Provincial IU transmission rates ranged from 0.6% in KwaZulu-Natal to 1.1% in Limpopo province. Districts IU transmission rates ranged from 0.4% to 1.7% with KwaZulu-Natal districts recording IU transmission rates lower than the national average of 0.8% (Table 3.4). Provincial IU case rates were fairly similar and ranged from 179-325 cases per 100 000 live births in the Northen Cape and Mpumalanga respectively. District-level IU case rates had a greater spread, ranging from 87-415 cases per 100 00 live births (Table 3.4). Overall, the four provinces with the most WRLHIV yielded 1 417 (65.5%) of all IU infections in 2018. In addition, Limpopo's infections contributed a further 264 (12.2%). Therefore focussing eMTCT efforts in five provinces has the potential to reduce 1 681 (77.8%) of all IU infections per annum, nationally.

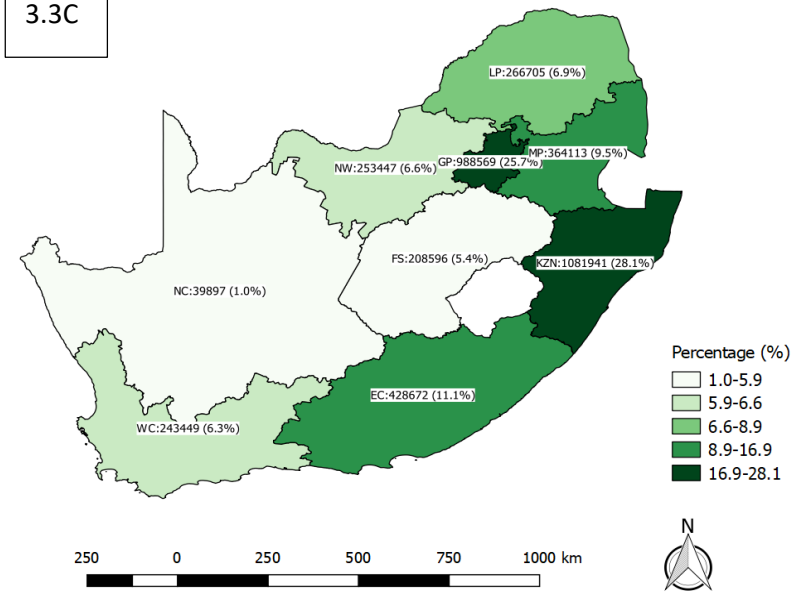
3.3A

Percentage of females of reproductive age (15-49 years) by province in South Africa, 2018



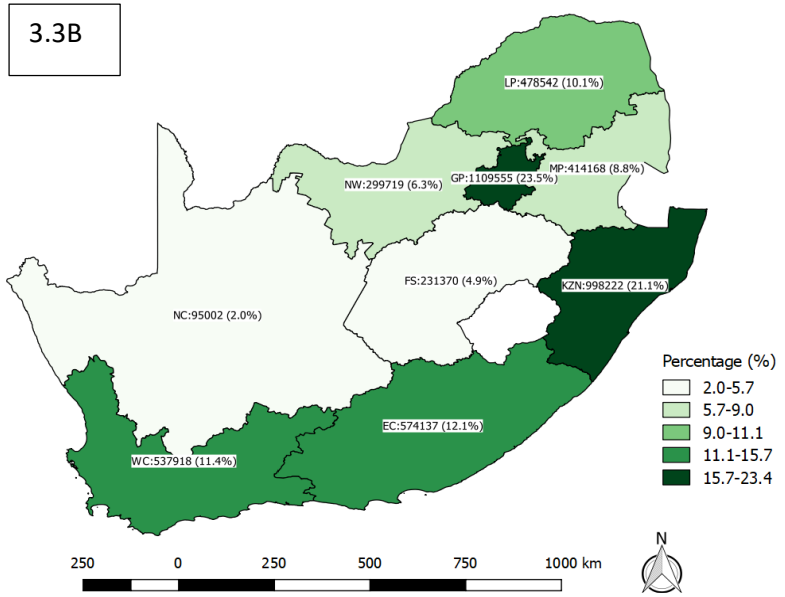
3.3C

Percentage of women of reproductive age (15-49 years) living with HIV by province in South Africa, 2018



3.3B

Percentage of adolescent girls and young women (15-24 years) by province in South Africa, 2018



3.3D

Percentage of adolescent girls and young women (15-24 years) living with HIV by province in South Africa, 2018

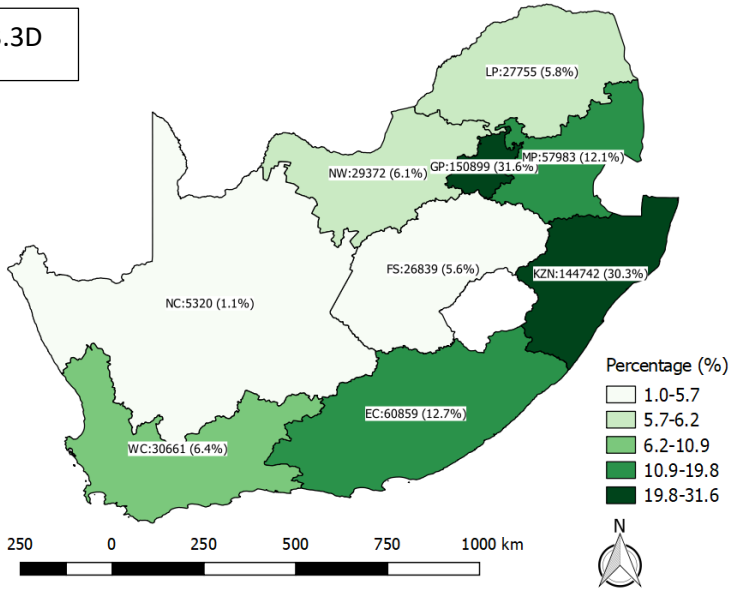


Figure 3.3 Provincial distribution of percentages of: A) females of reproductive age B) adolescent girls and young women C) women of reproductive age living with HIV D) adolescent girls and young women living with HIV in South Africa, 2018. Source: Thembisa Model 4.1.

Abbreviations: EC Eastern Cape, FS Free State, GP Gauteng Province, KZN KwaZulu-Natal, LP Limpopo Province, NC Northern Cape, NWNorth West, WC Western Cape.

Table 3.2. Number of live births (total), number of live births to women living with HIV and IU transmission rates by province in South Africa, 2018.

Prov	Total Population	Number of Live births (Total)			Live births to women living with HIV				Fertility rates		HIV PCR positive (<7 days)	IU transmission rate	IU Case rate/100 000
	Thembisa Model	Thembisa Model	Stats SA	DHIS	Thembisa Model	Stats SA	DHIS	NICD SDW	(Stats SA)	Thembisa Model	NICD SDW		
EC	6 593 566 (11.3%)	126 530 (10.8%)	105 796 (11.4%)	104 016 (11.0%)	27 448 (10.9%)	31 950 (11.9%)	32 164 (11.2%)	31 316 (11.7%)	2,8%	2,5%	248	0,8%	238
FS	2 875 955 (5.0%)	57 744 (5.0%)	47 306 (5.1%)	47 062 (5.0%)	13 553 (5.4%)	14 097 (5.3%)	14 386 (4.9%)	14 963 (5.6%)	2,6%	2,5%	106	0,7%	225
GP	14 931 713 (25.7%)	280 597 (24.1%)	205 612 (22.2%)	219 958 (23.2%)	54 976 (21.9%)	62 095 (20.6%)	55 497 (21.7%)	56 340 (21.0%)	1,9%	2,0%	471	0,8%	235
KZN	11 214 103 (19.3%)	231 742 (19.9%)	190 923 (20.6%)	195 292 (20.6%)	70 126 27.9%)	84 770 (29.2%)	78 662 (29.7%)	75 195 (28.1%)	2,6%	2,3%	453	0,6%	254
LP	5 794 578 (10.0%)	140 604 (12.1%)	123 414 (13.3%)	122 932 (13.0%)	19 885 (7.9%)	26 781 (9.4%)	25 265 (9.4%)	24 978 (9.3%)	3,1%	3,1%	264	1,1%	227

MP	4 650 305 (8.0%)	94 957 (8.1%)	77 353 (8.3%)	79 669 (8.4%)	24 708 (9.8%)	26 996 (9.8%)	26 558 (9.5%)	26 350 (9.8%)	2,7%	2,4%	245	0,9%	325
NW	3 914 669 (6.7%)	76 700 (6.6%)	55 094 (5.9%)	58 097 (6.1%)	17 119 (6.8%)	16 087 (5.8%)	15 746 (5.6%)	16 353 (6.1%)	2,7%	2,9%	157	1,0%	283
NC	1 154 340 (2.0%)	25 451 (2.2%)	24 195 (2.6%)	21 549 (2.3%)	3 024 (1.2%)	4 597 (1.5%)	3 970 (1.6%)	4 192 (1.6%)	2,6%	2,5%	42	1,0%	179
WC	6 809 913 (11.7%)	122 076 (10.5%)	97 298 (10.5%)	98 535 (10.4%)	14 389 (5.7%)	18 389 (6.5%)	17 395 (6.4%)	18 198 (6.8%)	2,0%	2,1%	176	1,0%	183
RSA	58 098 703	1 166 440	927 113	947 110	251 062	285 551	269 643	267 887	2,4%	2,4%	2 162	0,8%	241

Abbreviations: Prov province; EC Eastern Cape; FS Free State; GP Gauteng Province; KZN KwaZulu-Natal; LP Limpopo Province; MP Mpumalanga Province; NC Northern Cape; NW North West; WC Western Cape; RSA South Africa; Stats SA Statistics South Africa; DHIS District Health Information System; NICD National Institute for Communicable Diseases' Surveillance Data Warehouse.

Table 3.3 HIV prevalence rates by province in South Africa, 2018.

Province	HIV prevalence in females 15-49 years (Thembisa Model 2018)	HIV prevalence in pregnant females 15-49 years (2017 ANC survey)	HIV prevalence in pregnant females (Thembisa Model 2018)	HIV prevalence in Adults 15-49 years (males and females, SABSSM 2017)
Eastern Cape	25,4%	33,7%	22,5%	25,2%
Free State	27,7%	32,7%	24,2%	25,5%
Gauteng	23,4%	32,2%	20,2%	17,6%
KwaZulu-Natal	35,1%	41,1%	31,4%	27,0%
Limpopo	18,3%	23,4%	15,0%	17,2%
Mpumalanga	29,7%	37,3%	27,0%	22,8%
North West	26,0%	27,7%	22,8%	22,7%
Northern Cape	14,3%	17,9%	12,5%	13,9%
Western Cape	13,2%	15,9%	12,1%	12,6%
South Africa	**24,7%**	**30,7%**	**22,1%**	**20,6%**

Abbreviations: ANC antenatal care; SABSSM South African National HIV Prevalence, Incidence, Behaviour and Communication Survey.

Table 3.4 Intra-uterine transmission rates and intra-uterine case rates per 100 000 live births by geographic location in South Africa, 2018.

Geographic Area	District	ANC prevalence among pregnant women* (ANC seroprevalence survey)	Registered live births per year (Stats SA)	Total PCR <7 days	PCR Positive (<7 days)	IU transmission rate	IU Case rate/100 000
South Africa		**30,8%**	**897750**	**267 887**	**2 162**	**0,8%**	**241**
Eastern Cape	**Total**	**30,2%**	**104325**	**31 316**	**248**	**0,8%**	**238**
	Alfred Nzo	26,6%	18230	4 171	28	0,7%	154
	Amathole	28,3%	11070	3 092	23	0,7%	208
	Buffalo City Metro	31,2%	17468	4 156	30	0,7%	172
	Chris Hani	31,9%	11178	3 839	22	0,6%	197
	Joe Gqabi	28,3%	2475	1 476	9	0,6%	364
	Nelson Mandela Bay Metro	29,9%	16717	3 717	54	1,5%	323
	O R Tambo	33,3%	21847	9 068	63	0,7%	288
	Sarah Baartman	25,4%	5340	1 797	19	1,1%	356
Free State	**Total**	**29,8%**	**47047**	**14 963**	**106**	**0,7%**	**225**
	Fezile Dabi	26,5%	7353	2 570	15	0,6%	204
	Lejweleputswa	27,3%	9832	3 260	21	0,6%	214
	Mangaung Metro	31,7%	15559	4 475	29	0,6%	186
	Thabo Mofutsanyana	31,0%	12942	4 328	38	0,9%	294
	Xhariep	35,1%	1361	330	3	0,9%	220
Gauteng	**Total**	**30,2%**	**200726**	**56 340**	**471**	**0,8%**	**235**
	City of Johannesburg Metro	29,6%	57855	17 317	165	1,0%	285
	City of Tshwane Metro	25,3%	62923	12 524	109	0,9%	173

	Ekurhuleni Metro	31,6%	57406	17 761	152	0,9%	265
	Sedibeng	34,0%	14835	4 039	17	0,4%	115
	West Rand	35,5%	7707	4 699	28	0,6%	363
KwaZulu-Natal	**Total**	**44,4%**	**178456**	**75 195**	**453**	**0,6%**	**254**
	Amajuba	39,7%	8199	3 303	22	0,7%	268
	eThekwini Metro	46,2%	55992	23 409	139	0,6%	248
	Harry Gwala	39,5%	8371	3 050	18	0,6%	215
	iLembe	44,3%	9170	4 616	27	0,6%	294
	Ugu	45,9%	12595	5 659	31	0,5%	246
	uMgungundlovu	46,2%	14523	7 173	47	0,7%	324
	uMkhanyakude	46,3%	13232	6 067	26	0,4%	196
	Umzinyathi	36,7%	11867	3 640	21	0,6%	177
	uThukela	36,3%	11441	4 577	17	0,4%	149
	uThungulu	45,9%	16894	7 403	55	0,7%	326
	Zululand	48,4%	16172	6 298	50	0,8%	309
Limpopo	**Total**	**21,7%**	**116276**	**24 979**	**264**	**1,1%**	**227**
	Capricorn	21,6%	26133	5 847	61	1,0%	233
	Greater Sekhukhune	22,6%	25747	5 098	50	1,0%	194
	Mopani	24,5%	22170	5 335	53	1,0%	239
	Vhembe	16,8%	30009	4 560	54	1,2%	180
	Waterberg	25,8%	12217	4 139	46	1,1%	377
Mpumalanga	**Total**	**34,9%**	**75369**	**26 350**	**245**	**0,9%**	**325**
	Ehlanzeni	38,5%	39407	13 524	128	0,9%	325
	Gert Sibande	38,6%	15886	7 195	66	0,9%	415
	Nkangala	25,1%	20076	5 631	51	0,9%	254
North West	**Total**	**29,2%**	**55392**	**16 353**	**157**	**1,0%**	**283**
	Bojanala Platinum	33,8%	18421	6 299	54	0,9%	293
	Dr Kenneth Kaunda	30,9%	12291	3 618	37	1,0%	301

	Dr Ruth Segomotsi Mompati	22,1%	9182	2 314	24	1,0%	261
	Ngaka Modiri Molema	23,9%	15498	4 122	42	1,0%	271
Northern Cape	**Total**	**19,0%**	**23402**	**4 192**	**42**	**1,0%**	**179**
	Frances Baard	24,3%	8957	1 733	15	0,9%	167
	John Taolo Gaetsewe	21,9%	5162	1 171	7	0,6%	136
	Namakwa	2,9%	1550	113	2	1,8%	129
	Pixley Ka Seme	15,8%	2843	540	7	1,3%	246
	ZF Mgcawu	14,5%	4890	635	11	1,7%	225
Western Cape	**Total**	**18,9%**	**95997**	**18 199**	**176**	**1,0%**	**183**
	Cape Winelands	15,2%	13354	2 127	25	1,2%	187
	Central Karoo	11,8%	1156	109	1	0,9%	87
	City of Cape Town Metro	21,6%	63800	13 288	121	0,9%	190
	Eden	15,7%	9062	1 415	18	1,3%	199
	Overberg	19,8%	3855	723	6	0,8%	156
	West Coast	13,8%	4770	537	5	0,9%	105

Abbreviations: Stats SA Statistics South Africa; PCR polymerase chain reaction; ANC antenatal care; IU intra-uterine. *ANC sero-prevalence survey was used because the Thembisa Model does not provide district-level estimates.

3.5 Discussion

In 2018, South Africa's population of 58 million people was evenly distributed between males and females. Gauteng province had the highest number of females, accommodating a quarter of the total population of females (all ages). The majority of all women, 20 253 423 (68%), and women of reproductive age, 10 958 758 (70%), were located in the densely populated provinces; that is Gauteng, KwaZulu-Natal, Western Cape and Eastern Cape provinces ("the big four"). Although the distribution of WRLHIV followed a similar trend, Mpumalanga and Limpopo had the fourth [364 113 (10%)] and fifth, [266 705 (7%)] highest number of WRLHIV ahead of the Western Cape. Adolescents and young women were also mostly located in the big four provinces, 3 219 832 (68%). Ten percent (477 798) of all AGYW were living with HIV in South Africa in 2018. Gauteng, KwaZulu-Natal, Eastern Cape and Mpumalanga, had the highest percentage of AGYW living with HIV at 32%, 30%, 13% and 12% respectively. Although the national IU transmission rate was <1.0%, 241 per 100 000 neonates acquired HIV from their mothers in 2018 at birth. Mpumalanga, North West and KwaZulu-Natal had IU case rates that were above the national average at 325, 283 and 254 cases per 100 000 live births. Districts IU case rates varied greatly and ranged from as low as 87 up to 415 cases per 100 000 live births. However, even districts with the lowest IU transmission rate at birth, still had case rates higher than the eMTCT target without taking infections after birth into account.

Based on the demographic profiles of provinces, findings of these analyses suggest disparities in the need for eMTCT interventions. In this last mile to eMTCT, it may be worthwhile strengthening interventions in provinces that have the largest numbers of WRLHIV (north eastern parts of the country) as well as those regions with the highest IU transmission rates and IU case rates while maintaining current levels of support elsewhere. Although early transmission rates are below the eMTCT target of <5%, South Africa is not positioned to achieve eMTCT case rate targets because of the extremely high maternal HIV seroprevalence.[18] However, the country has a well-established PMTCT programme in place. Closing PMTCT gaps[5] and scaling up sexual and reproductive health for preventing vertical transmission of HIV could represent low hanging fruit. Sexual and reproductive health services should include intensifying family planning and contraception services amongst all women of reproductive age regardless of HIV status and providing pre-exposure prophylaxis to AGYW.

As expected, most women & AGYW were situated in the 'big four' provinces. However, we found that the burden of HIV in women and AGYW was also pronounced in Limpopo and Mpumalanga provinces. Limpopo province has the highest fertility rate in the country and a high proportion of AGYW without HIV who may benefit from family planning and pre-exposure prophylaxis initiatives. Mpumalanga also

has a significant amount of WRLHIV who may be in need of family planning services. Cross border mobility of pregnant women seeking healthcare from neighbouring countries may be a contributing factor to high WRLHIV and fertility rates in these two provinces.

The findings from our analysis of IU transmission rates did not necessarily follow the underlying population densities. We observed lower transmission rates in KwaZulu-Natal which has the highest number of WRLHIV and live births to women living with HIV. We attribute the low IU transmission rates in this province and its districts to the larger denominator (total live births, Table 3.1) and/or a more effective PMTCT programme. The converse probably explains the high IU transmission rate in the Northern Cape and its districts, where smaller denominators result in higher IU rates. Poor de-duplication of HIV PCR positive test data may also result in some provinces like the Western Cape having IU transmission rates that are above the national average. These results suggest that case rates per 100 000 may be a better indicator for monitoring programme performance at the various geographic levels[18] as it is directly linked to the performance of the PMTCT programme, for example coverage of services and attainment of viral suppression in pregnancy. Since most provincial level IU case rates were fairly similar, it is necessary to tackle the IU case rates at district level where there is considerable variation. Districts with high IU case rates deserve special attention with respect to improving PMTCT services. We attempted to perform hotspot analysis to assess whether differences in IU transmission rates between provinces were significant, using district-level data as the unit of analysis and the results were inconclusive (Appendix 3.2) because of insufficient data points. Next steps should use facility level data (which was not available to this study) to provide more data points and enable more robust results for this particular analysis.

Despite the distinct geographical differences in WRLHIV and AGYW, attainment of eMTCT will require more than understanding the geographic distribution of all WRLHIV. In order to fast-track eMTCT, it is critical to target PMTCT pillars of prevention of HIV infection[7] and family planning particularly in AGYW. The proposed School Health Programme which caters for sexual and reproductive health education and HIV testing in schools among children aged ≥12 years, has the potential to reduce maternal HIV prevalence in future and enable eMTCT. Among AGYW with HIV and other WRLHIV, the focus needs to shift towards virologic control, with specific attention to pregnant women, especially considering maternal viral load is the strongest predictor of MTCT risk.[19] Therefore, improving viral load monitoring during pregnancy, delivery and breastfeeding, and improving quality of patient management among WRLHIV and all HIV positive pregnant women may translate into improved viral load suppression rates. Achieving this in the big four provinces may fast-track eMTCT. There is urgent need to effectively track and monitor viral loads of all HIV positive pregnant women. A marker of pregnancy, delivery and the postpartum period within the NICD SDW as recommended in the 2019

National PMTCT guidelines, should allow for monitoring of viral load suppression rates at facility level in near real time to advance UNAIDS 90-90-90[20] targets in women of reproductive age, particularly in high risk areas. Such monitoring will provide information on the true picture of viral load burden during pregnancy and prompt rapid intervention. Currently this information is lacking.

3.6 Study limitations

In our analyses, the Thembisa Model was used as our primary data source because the model was specifically designed and is used for estimating HIV populations in SA. As a result it contained data for 10/12 indicators reviewed for these analyses. However, estimates may be inaccurate if underlying assumptions are incorrect. We therefore used other data sources to validate the data. Although there were differences in absolute numbers; we found that data from the other sources was generally within the upper and lower limits of the Thembisa model estimates (Appendix 3.3). This may be because the Thembisa Model uses some of the data we triangulated with it, for example Stats SA. Where there were significant differences, we attribute these to differences in (i) methodology or (ii) in reporting intervals or (iii) data quality issues for some of the data sources used for triangulation purposes. For example, the latest data for the ANC seroprevalence survey at the time of writing was 2017, while the reporting period for these analyses was 2018 (Appendix 3.3). The laboratory based data lacks unique patient identifiers therefore de-duplication may be incomplete, resulting in over-estimation of transmission rates. Intra-partum transmission rates would be anticipated to be similar to IU transmission rates however; postnatal transmissions would depend on breastfeeding practices (e.g. duration of breastfeeding), postnatal virologic control and incident maternal infections which we were not able to measure.

3.7 Conclusion

We have attempted to quantify the need for eMTCT interventions based on the demographic profile of provinces in South Africa. Our results confirm what is mostly known. The need for HIV/eMTCT resources is greatest in Gauteng, KwaZulu-Natal and Eastern Cape. Limpopo and Mpumalanga provinces also warrant attention. While advocating for allocation of interventions for eMTCT on a needs-basis; it is important not to neglect those provinces with the least need. Routine monitoring and surveillance needs to continue until the country reaches eMTCT. Ending paediatric HIV will require robust VL monitoring & intervention among WRLHIV in general, as well as pregnant and breastfeeding women. The NHLS laboratory data have the potential to provide VL monitoring service near-real time until clinical databases can assume this role.

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CHAPTER 4.

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

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4.1 Introduction

One in three pregnant women accessing antenatal care (ANC) in the public health sector in 2017 were living with HIV in South Africa (SA). 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 intra-uterine transmission rate of <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 an MTCT rate of 1% equates to a paediatric HIV incidence five times greater than 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 (VL) monitoring among pregnant and breastfeeding WLHIV being central to any PMTCT programme steering towards eMTCT. Regrettably, HIV VL monitoring among pregnant and breastfeeding WLHIV in SA remains poor.[6]

In 2013, SA scaled up HIV VL testing as a monitoring strategy for the national HIV response.[7] HIV VL monitoring was recommended at six and 12 months post initiation for WLHIV initiating ART during pregnancy or breastfeeding, and at first ANC booking for WLHIV on ART prior to pregnancy.[8] In 2015, the guidelines extended HIV VL monitoring to six monthly monitoring during pregnancy and breastfeeding for all WLHIV on ART.[9] An HIV VL three months post ART initiation was recommended for WLHIV newly diagnosed during pregnancy or the breastfeeding period. For both groups, a VL ≥1000 copies/mL prompted comprehensive adherence counselling and a repeat HIV VL test within one-two months. In October 2019, the guidelines were revised yet again, attempting to improve HIV VL monitoring among pregnant and breastfeeding WLHIV as follows: (i) HIV VL test at delivery for all pregnant WLHIV and (ii) HIV VL suppression threshold revised from <1000 to <50 copies/mL.[10] The latter was, in part, aimed at minimizing MTCT risk associated with low-level and transient viraemia.[11,12] Regarding maternal ART regimens, women received a fixed dose combination of Tenofovir, Emtricibatine and Efavirenz as first line therapy and second line therapy being a protease inhibitor based regimen.[9] These regimens did not change during the study period.

Despite policy provisions, there is a paucity of data on changes in maternal HIV VL over time during pregnancy and the postpartum period in SA. 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 VLs of <50 copies/mL in 70-73% of pregnant WLHIV at delivery, low-level viraemia (50-<1000 copies/mL) in 8% and ≥1000 copies/mL in 22% of the women throughout follow up.[13,14] Since 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 VL over time during pregnancy, through delivery and up to 15 months postpartum among pregnant WLHIV receiving care in the public health sector in SA.

4.2 Materials and methods

4.2.1 Setting

The majority of pregnant WLHIV access ANC in the public health sector in South Africa. A detail of ANC services and management of pregnant WLHIV has been described previously (Chapter 2).

4.2.2. Study design

This was a retrospective cohort analysis of maternal viral load (VL) during pregnancy and up to 15-months postpartum amongst WRLHIV (15-49 years) within the public-health sector between 2016 and 2017. A detailed explanation of the creation of the study cohort has been provided in Chapter 2.

4.2.3 Study measures

Definition of main study variables:

- *First HIV VL during pregnancy*: the first HIV VL performed at fANC visit for ART-experienced pregnant WLHIV or after three months of ART for pregnant WLHIV not on ART at fANC visit.
- *Virologic response thresholds*: HIV VL results (copies/mL) were categorized into i) VL suppression (VL <50), ii) low-level viraemia (VL: 50-<1000) and iii) high VL (VL ≥1000).
- *Postpartum VL*: Any VL performed within 15 months postpartum.
- *Comorbidities during pregnancy*: Women who tested positive ≥1 for syphilis or poor kidney function or tuberculosis (TB) during the study period. Syphilis positivity was defined by any Rapid Plasmin Reagin (RPR) positive test excluding RPR positive tests with discordant Treponema Pallidum Haemagglutination Assay or Treponema Pallidum antibodies (TPHA/TPAb). Serum creatinine values >77·0 µmol/l (0·87 mg/dl) identified pregnant women

with poor kidney function.[15] Tuberculosis status was determined by searching the national TB register within the NHLS CDW.

4.2.4 Data analysis

Performance of the study algorithm in identifying pregnant WRLHIV 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 WRLHIV, stratified by year of pregnancy. Analyses of maternal HIV VL changes over time examined i) changes in HIV VL values over time from the fANC visit through delivery and up to 15 months postpartum ii) time to HIV VL <1000 copies/mL among women with an initial high HIV VL at first HIV VL measurement and iii) factors associated with HIV VL decline during follow up.

For changes in HIV VL over time, observed values of $\log_{10}$ transformed quantifiable VLs 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 VL values among study participants during follow up, with mean HIV VL values and associated 95% confidence intervals (CI) reported at given time points. Time to HIV VL <1000 copies/mL was determined by calculating the time difference between the date of the initial high HIV VL and the earliest HIV VL <1000 copies/mL among women with a high VL at first HIV VL 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 four, eight and 12 months were used to determine factors associated with HIV VL decline during follow up. Splines were set at <4 months after the fANC visit, at delivery, 8-<12 months postpartum and late (12-15 months) postpartum. The regression model adjusted for maternal age, comorbidities, geographic location, ART status, maternal HIV VL and CD4 count at fANC visit. Data analysis was performed in STATA 14 (StataCorp, College Station, Texas, USA).

4.3 Ethics clearance

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

4.4 Results

4.4.1 Description of pregnant WLHIV in the synthetic cohort

A synthetic cohort of 178 319 pregnant WRLHIV was created from the NHLS CDW data. When compared to total live births to HIV-positive women from DHIS, all provinces were represented in the study cohort with some under or over-representation (Table 4.1). However, the provincial distribution of pregnant WRLHIV in the country was comparable between DHIS and the study cohort (Figure 4.1).

Among 178 319 pregnant WRLHIV in the synthetic cohort, 85 545 (48.0%) were ART-experienced, 88 877 (49.8%) were not on ART, and ART status at fANC visit could not be determined for 3 897 (2.2%) (Table 4.1). 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 4.1). Median CD4 count at fANC visit was 407 (IQR: 258-579) cells/mm^3 for the entire cohort with 19 158 (16.4%) women showing levels consistent with severe immune compromise (<200 cells/mm^3) and 41 662 (35.6%) having CD4 counts ≥500 cells/mm^3 at fANC visit.

Syphilis seropositivity was 3.3% (n= 5 943) for the entire cohort and ranged from 1-5% by province. A total of 7 936 (4.5%) pregnant WRLHIV had a serum creatinine value >77.0 µmol/l (0.87 mg/dl) and 2 364 (1.3%) tested positive for TB during the current pregnancy. In total, 15 575 (8.7%) pregnant WRLHIV had evidence of ≥1 comorbidity.

Table 4.1. Provincial distribution of pregnant WRLHIV in the study cohort compared to the DHIS indicator 'total live births to HIV-positive women' between Jan 2016- Dec 2017 in South Africa.

Province	2016			2017			Total		
	Live births to HIV+ WRLHIV	Pregnant women in study	‡%	Live births to HIV+ WRLHIV	Pregnant women in study	%	Live births to HIV+ WRLHIV	Pregnant women in study	%
Eastern Cape	29 750	10 291	34.5%	31 299	8 383	26.8%	61 049	18 674	30.6%
Free State	13 005	2 203	16.9%	13 882	1 520	10.9%	26 887	3 723	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	9 007	36.7%	48 395	20 242	41.8%
Mpumalanga	24 642	6 990	28.4%	25 662	5 513	21.5%	50 304	12 503	24.9%
Northern Cape	3 912	1 242	31.7%	3 756	1 154	30.7%	7 668	2 396	31.2%
North West	14 558	3 588	24.6%	15 235	3 312	21.7%	29 793	6 900	23.2%
Western Cape	15 250	10 784	70.7%	16 673	8 356	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%**

Abbreviations: DHIS South African District Health Information System; WRLHIV women of reproductive age living with HIV. ‡% represents pregnant WRLHIV in the study cohort as a proportion of total live births to HIV-positive women reported in DHIS**.**

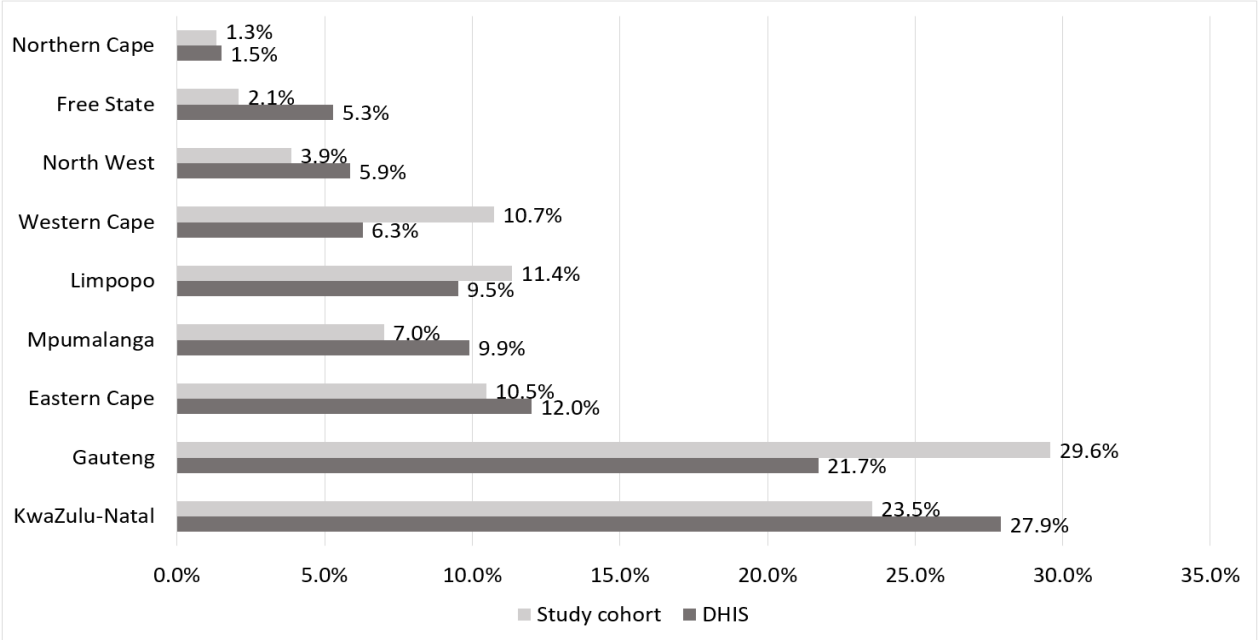

Figure 4.1. Percentage of pregnant WRLHIV by province in the study cohort compared to the South African DHIS indicator of 'total live births to HIV-positive women', demonstrating a similar distribution, with the study cohort being under-represented in some provinces (e.g. KwaZulu-Natal, Free State) and over-represented in Gauteng, Western Cape and Limpopo.

Abbreviations: WRLHIV women of reproductive age living with HIV; DHIS District Health Information System.

4.4.2 Changes in HIV VL values over time

The cohort contributed 345 174 HIV VL measurements, median= 2.2 (IQR: 2-3) HIV VLs per woman during follow up. The first HIV VL performed during pregnancy (n= 47 631/74 066) had a mean predicted VL of 3.06 $\log_{10}$ VL 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] post-partum (n= 34 881/72 673). Overall, proportions of observed viraemia (VL ≥50 copies/mL) were 39 756 (53.6%) at first HIV VL measurement during pregnancy, 14 780 (36.9%) at delivery and 24 328 (33.5%) postpartum.

Among 40 660 (47.5%) ART-experienced pregnant WRLHIV with an HIV VL at fANC visit, 17 450 (42.9%) had a VL ≥50 copies/mL and 8 451 (20.8%) had a VL ≥1000 copies/mL, with a median $\log_{10}$ VL copies/mL of 2.5 (IQR: 1.7-3.8) among women with quantifiable HIV VL at fANC visit. Among 32 325 (36.4%) pregnant WRLHIV not on ART at fANC visit with an HIV VL after the first three months of ART, 21 568 (66.7%) had a VL ≥50 copies/mL and 14 913 (46.1%) had a VL ≥1000 copies/mL (Table 4.2) after a

median of 3.9 (2.2-5.8) months. Overall, 72 702 (40.8%) women received ≥1 HIV VL during the postpartum period. Viraemia at the time of delivery and postpartum were similar in pregnant WRLHIV regardless of ART status at fANC. Figure 4.2 describes maternal HIV VL decline during follow up stratified by maternal ART status at fANC visit, overall (A) and for women with quantifiable HIV VL (B). Provincial differences in HIV VL decline during follow up were observed, Figure 4.3.

Table 4.2. Demographic and clinical characteristics of pregnant WRLHIV in South Africa, comparison of NHLS CDW dataset 2016 versus 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-<35	95 994 (53.8%)	51 849 (53.6%)	44 145 (54.2%)
35-<45	34 672 (19.4%)	18 073 (18.7%)	16 599 (20.4%)
45-49	1 000 (0.6%)	505 (0.5%)	495 (0.6%)
Province			
Eastern Cape	18 674 (10.5%)	10 291 (10.6%)	8 383 (10.3%)
Free State	3 723 (2.1%)	2 203 (2.3%)	1 520 (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%)	9 007 (11.1%)
Mpumalanga	12 503 (7.0%)	6 990 (7.2%)	5 513 (6.7%)
Northern Cape	2 396 (1.3%)	1 242 (1.3%)	1 154 (1.4%)
North West	6 900 (3.9%)	3 588 (3.7%)	3 312 (4.1%)
Western Cape	19 140 (10.7%)	10 784 (11.1%)	8 356 (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	3 897 (2.2%)	3 148 (3.3%)	749 (0.9%)
CD4 count at fANC visit among ART experienced WRLHIV 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%)	9 432 (37.0%)	9 737 (43.3%)
CD4 count at fANC visit among WRLHIV 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 VL* during pregnancy among ART experienced WRLHIV at fANC visit			
Median log_{10} VL 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-<1 000	8 999 (22.1%)	4 548 (22.6%)	4 451 (21.7%)
≥1 000	8 451 (20.8%)	4 362 (21.7%)	4 089 (19.9%)
First HIV VL* during pregnancy among WRLHIV not on ART at fANC visit			
Median log_{10} VL 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%)	4 945 (31.2%)	5 812 (35.3%)
50-<1 000	6 655 (20.6%)	3 237 (20.4%)	3 418 (20.8%)
≥1 000	14 913 (46.1%)	7 669 (48.4%)	7 244 (44.0%)
HIV VL* at delivery			
Median log_{10} VL 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-<1 000	9 047 (22.6%)	5 214 (23.9%)	3 833 (21.0%)
≥1 000	5 733 (14.3%)	3 280 (15.1%)	2 453 (13.5%)
Comorbidities during pregnancy†			
None	162 744 (91.3%)	88 355 (91.3%)	74 389 (91.3%)
Present	15 575 (8.7%)	8 446 (8.7%)	7 129 (8.8%)

*Observed HIV VLs. **Abbreviations**: fANC first antenatal care visit; IQR interquartile range; ART antiretroviral therapy; VL viral load; cps/mL copies per millilitre; †Comorbidities defined by positive test for at least one of the following conditions: syphilis, poor kidney function or tuberculosis; NHLS CDW National Health Laboratory Service's Corporate Data Warehouse, WRLHIV women of reproductive age living with HIV.

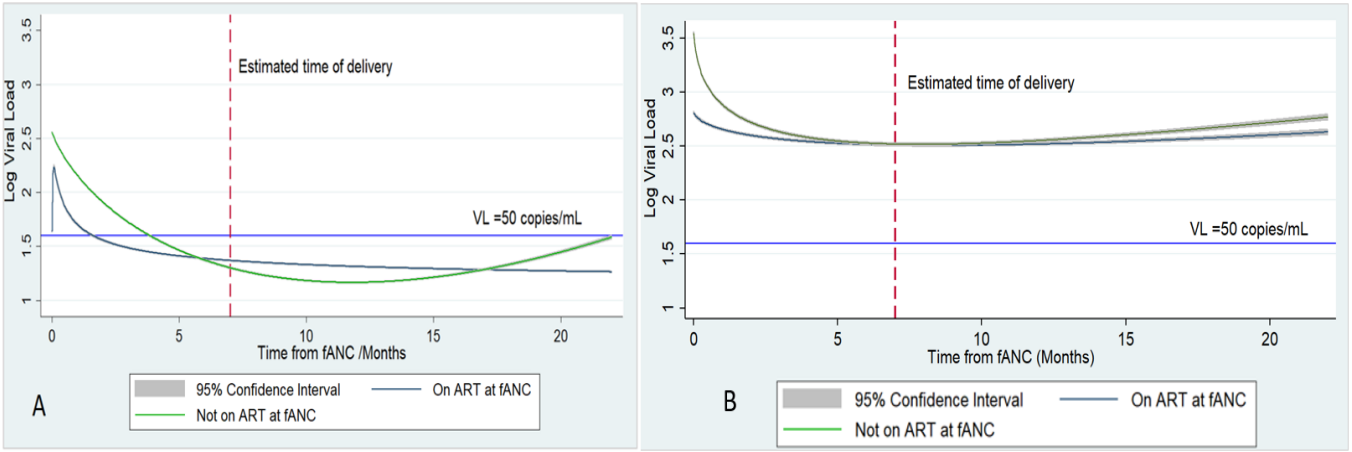

Figure 4.2 Viral load decline over time by ART status at first antenatal visit (A) Overall: HIV VL measurements n= 338 688; Observed HIV VLs that were lower than the detectable limit of the assay were assigned a value of zero (B) Among WRLHIV with quantifiable VL: HIV VL measurements n= 192 140.

Abbreviations: VL viral load; ART antiretroviral therapy; fANC first antenatal visit; CI confidence interval; WRLHIV women of reproductive age living with HIV.

4.4.3 Time to HIV VL <1000 copies/mL among pregnant women with high VLs

Among 23 904 (32.2%) pregnant WRLHIV whose first HIV VL during pregnancy was ≥1 000 copies/mL, 16 951 (70.9%) had a subsequent VL during pregnancy or postnatal period. Among those with a subsequent VL, 8 980 (53.0%) had a VL <1 000 copies/mL at the next HIV VL 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 VL <1 000 copies/mL between pregnant WRLHIV who were ART experienced, 3.7 (IQR: 2.7-5.9) months, and those not on ART at fANC visit, 3.7 (IQR: 2.5-6.1) months, respectively.

4.4.4 Factors associated with HIV VL decline during follow up

Sustained maternal HIV VL decline during follow up was predicted by having a CD4 count ≥500, VL <50 copies/mL and absence of comorbidities at baseline (Table 4.3). Older maternal age (≥25 years) was also associated with HIV VL decline, despite lack of statistical evidence for differences in virological control between the <25 years and ≥45 years age groups. The most significant decline in $\log_{10}$ VL occurred between the fourth month after fANC and the time of delivery, with increased HIV VL in the late postpartum period (Table 4.3).

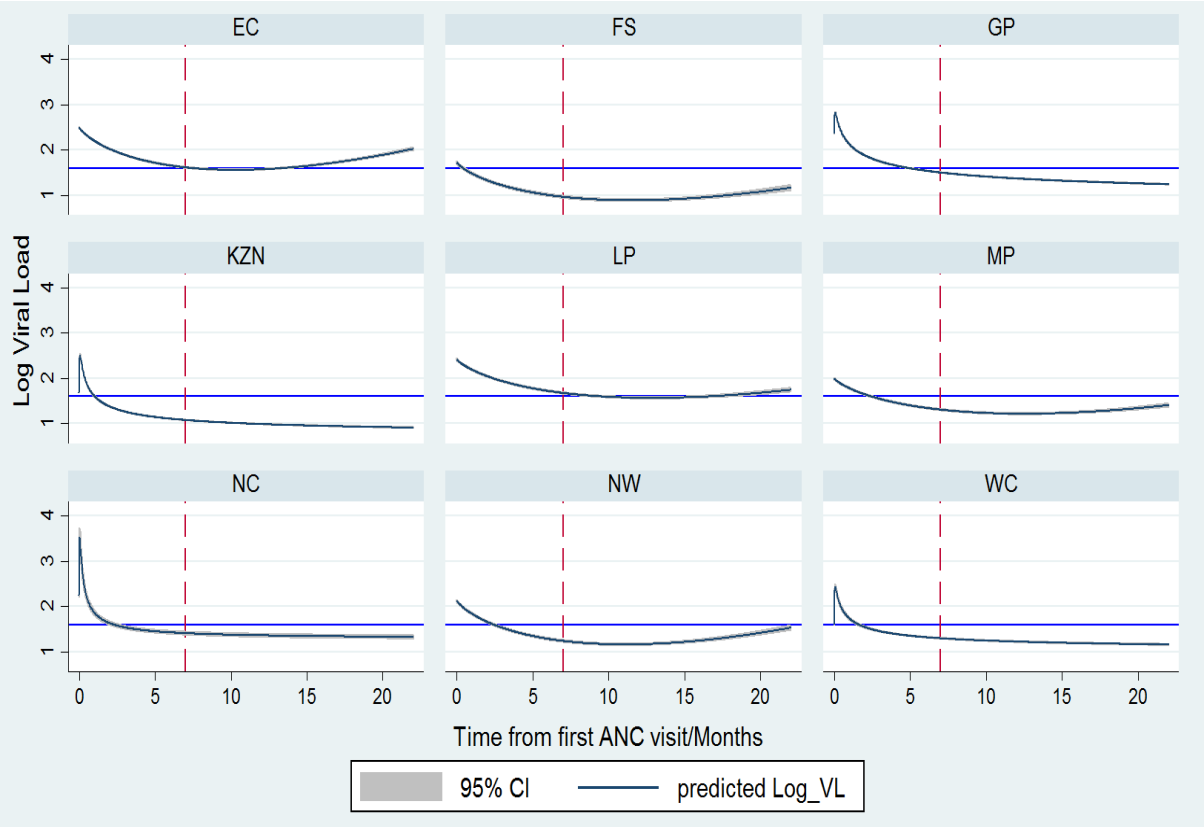

Figure 4.3. Viral load decline over time by province. Log_{10} HIV VLs of observed HIV VLs that were lower than detectable limit of assay were assigned a value of zero. Horizontal line: HIV VL <50 copies/mL; Vertical line: Estimated time of delivery (maximum 7 months from first ANC visit)**.**

Abbreviations: VL viral load; fANC first antenatal care visit; EC Eastern Cape; FS Free State; GP Gauteng province; KZN KwaZulu-Natal; LP Limpopo province; MP Mpumalanga; NC Northern Cape; NW North West; WC Western Cape. Vertical line: Estimated time of delivery (maximum 7 months from first ANC visit).

Table 4.3. Results from a piecewise linear regression model predicting log_{10} VL decline from the first ANC visit up to 15 months postpartum among pregnant WRLHIV in South Africa, Jan 2016-Dec 2018.

Predictors	Number of HIV VL measurements= 128 279[$]		
	Coefficient (log_{10} VL)	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 VL during pregnancy (cps/mL)			
<50	*1.0*	*Reference*	-
50-<1 000	1.19	1.16 to 1.20	<0.001
≥1 000	2.31	2.30 to 2.32	<0.001
CD4 count at fANC visit			
<500	*1.0*	*Reference*	-
≥500	-0.28	-0.34 to -0.22	<0.001
[†]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

[$]Missing data excluded from multivariate analysis**. Abbreviations**: CI confidence interval; fANC first antenatal care visit; VL viral load; mL millilitre; [†]Comorbidities defined by having ≥1 of the following conditions (poor kidney function, tuberculosis or syphilis); ART antiretroviral therapy WRLHIV women of reproductive age living with HIV.

4.5 Discussion

We present maternal HIV VL changes over time within the PMTCT programme at national level in SA. 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 (VL ≥50 copies/mL) from 54% at first HIV VL measurement during pregnancy to 37% at delivery and 34% during the postpartum period was observed. At fANC visit, 43% of ART-experienced pregnant WRLHIV had a VL ≥50 copies/mL while two thirds of pregnant WRLHIV not on ART at fANC visit still had VL ≥50 copies/mL after three months on ART. Provincial differences in sustaining HIV VL suppression (VLS) into the postpartum period were noted. HIV VL decline during follow up was predicted by having a CD4 count ≥500, VL <50 copies/mL, maternal age ≥25 years and absence of comorbidities at fANC visit.

These findings support previous reports from smaller, localised studies in SA.[13,14,16] A review of maternal HIV VLs from routine care settings in the Western Cape province reported a predicted mean pre-ART HIV VL of 4.0 $\log_{10}$ VL copies/mL at fANC visit, decreasing to 1.7 $\log_{10}$ VL copies/mL after approximately three months of ART use and 73% of the cohort achieving VL <50 copies/mL at delivery.[13,14]. A mean of 3.7 $\log_{10}$ VL copies/mL after three months on ART was predicted for women not on ART at fANC visit in this study. The higher VLs and lower proportion of VLS at delivery (63%) in this study were attributed 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%.[1,16] Findings suggest that despite >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 VL ≥50 and ≥1000 copies/mL thresholds respectively.

Although a decreasing trend in maternal viraemia was observed, an increase in the late postpartum period was noted. This raises concern for late postnatal transmission.[13,14,17,18] Studies from both low- and high-income countries have reported poor virologic control during the postpartum period, particularly among WRLHIV already on ART before pregnancy.[19-22] This is possibly due to social pressures (e.g. unplanned pregnancies) which facilitate poor adherence to ART and/or pregnancy-related physiological changes that predispose women to viraemia.[22,23] Alternatively, the higher proportion of viraemia among ART experienced women may be due to misclassification error introduced by the study 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. Adjusted

analyses showed quicker HIV VL decline during follow up in women not on ART at fANC visit compared to ART-experienced women. This is likely an effect of susceptibility of maternal virus to ART among women newly initiating ART during pregnancy compared to ART-experienced women. Even so, two thirds of women not on ART at fANC visit had VL ≥50 copies/mL after three months of ART use. Because 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[14,19], younger maternal age (<25 years) at baseline was associated with viraemia during follow up. A quarter of pregnant WRLHIV were aged <25 years in this study representing a significant proportion of pregnant WRLHIV who require targeted care packages to ensure VL suppression for eMTCT. Almost 70% of CD4 counts at fANC visit were <500 cells/mm^3, likely reflecting the gradual transition from CD4 count based ART eligibility criteria towards test and treat during the study period. Low CD4 counts may also be attributed to hemodilution that occurs during pregnancy.[24] Comorbid conditions were associated with high VLs during follow up. Pregnant WRLHIV co-infected with TB or syphilis are reported to have a 2-2.5 times higher risk of MTCT compared to their negative counterparts.[25,26] Thus, screening and treating all pregnant and postpartum WRLHIV co-infected with TB or syphilis is critical for eMTCT of HIV and syphilis.

4.6 Study limitations

This study 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 VLs over time within a routine programme setting as opposed to clinical trial study populations. Our data are reported nationally and sub-nationally enabling inter-provincial evaluation of maternal HIV VL 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 WRLHIV as pregnant. We anticipate that our inclusion criteria were highly specific and excluded majority of non-pregnant 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[1,13,14,16] suggesting that our cohort is representative of pregnant WRLHIV in SA. We acknowledge the uneven representation of provinces in the cohort when compared to number of live births to HIV positive women from DHIS. However, this provincial distribution may reflect the extent of VL monitoring in pregnant WRLHIV across the

provinces. Nonetheless, the data reveal a huge gap between the first and second UNAIDS 90-90-90s of >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.

4.7 Conclusion

Although SA's national PMTCT programme has reached the first and second UNAIDS 90-90-90 targets for pregnant women, the 3rd 90 remains elusive. Despite high ART coverage during pregnancy, only 63% of pregnant WRLHIV attained VL <50 copies/mL by delivery. Among pregnant WRLHIV with first HIV VL during pregnancy ≥1000 copies/mL, a third had no evidence of subsequent VL monitoring. Findings highlight the need for strengthening ART adherence, increased VL monitoring and rapid reaction to high VL. Better longitudinal data on pregnant and postpartum WRLHIV, including linkage of mother infant pairs, is required to better measure progress towards eMTCT.

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CHAPTER 5.

Characterizing viral load burden among HIV-infected women around the time of delivery: Findings from four tertiary obstetric units in Gauteng, South Africa.

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Published Faith Moyo, MSc, Ahmad Haeri Mazanderani, PhD, Tanya Murray, PhD, Karl-G. Technau, PhD, Sergio Carmona, PhD, Tendesayi Kufa, PhD, and Gayle G. Sherman, PhD. Characterizing Viral Load Burden Among HIV-Infected Women Around the Time of Delivery: Findings From Four Tertiary Obstetric Units in Gauteng, South Africa. J Acquir Immune Defic Syndr. 2020;83:390–396. (Appendix 6.1)

5.1 Introduction

Antiretroviral therapy (ART) coverage amongst antenatal clinic clients is estimated at >95% within the public health sector in South Africa.[1] The public health sector is the major health care provider, serving >80% of the South African population.[2] ART coverage amongst pregnant and postpartum women has increased steadily with the evolution of the Prevention of Mother-to-Child Transmission (PMTCT) of HIV policy in the country. The success of the PMTCT programme is well documented.[3–6] Currently, PMTCT services are available in >95% antenatal and maternal facilities in the public health sector.[6] Between 2004-2014, early infant HIV transmission rates dropped from >20% to <2% among infants aged <2 months.[7] More recently, the programme has managed to maintain the national intra-uterine (IU) transmission rate at <1.5% since 2015, in spite of high maternal HIV prevalence rates.[8,9] Notwithstanding the tremendous progress achieved to date, gaps in the programme remain. High rates of seroconversion and poor viral suppression among women initiated on ART during pregnancy and the postpartum period contribute significantly towards ongoing mother-to-child (MTCT) transmission of HIV.[9] Pregnancy has been associated with poor viral suppression.[10] Underlying factors vary from biological to social.[10,11] HIV viral load (VL) monitoring during pregnancy and the breastfeeding period is therefore critical for patient management and surveillance purposes. However, there is limited data on VL suppression (VLS) rates among women living with HIV (WLHIV) during these periods,[10] which may be related to VL monitoring only recently introduced into national PMTCT guidelines.[12-15]

MTCT of HIV occurs when women with unsuppressed VLs transmit HIV to their children in utero, during labour or during breastfeeding postpartum.[16–18] Treatment duration and maternal VL have been identified as the strongest predictors of MTCT risk.[16–18] Depending on the baseline VL, a maximum of 12-16 weeks is deemed sufficient to suppress plasma VL in pregnant women.[16–20] An 8% reduction in the odds of HIV transmission with each additional week of treatment among women initiating ART during pregnancy has been reported.[16] Zero in utero and intrapartum HIV transmission has been documented among infants born to women who conceived on ART, continued treatment during pregnancy and delivered with a plasma VL <50 copies/ml.[20] However, HIV transmission has been shown to occur among women with low-level viraemia (50-400 copies/ml) around the time of delivery.[20] Thus, ensuring WLHIV have a VL <50 copies/ml prior to conception and that VLS is maintained during pregnancy and breastfeeding is crucial if South Africa is to achieve elimination of mother-to-child transmission of HIV (eMTCT) – defined as an overall MTCT rate of <5% among breastfeeding children and a case rate of <50 HIV infections per 100 000 population.[21] Maternal VLS

may be facilitated by timely screening for HIV, early ART initiation, adequate psychosocial support, and effective VL monitoring among women of childbearing potential.[10,16]

National PMTCT guidelines since 2015 have recommended a first-line regimen of tenofovir (TDF) + lamuvidine (3TC) or emtricitabine (FTC) + efavirenz (EFV) as a fixed dose combination. Viral load monitoring in pregnant and breastfeeding women is performed at three to six monthly intervals, with VLs ≥1 000 copies/mL prompting clinical interventions to improve VLS.[22] However, this has proven difficult to implement since women present for antenatal care at different stages of their pregnancy and VLS needs to be achieved in a relatively short period of time before delivery. Although routine maternal VL testing at time of delivery was not standard practice at the time of writing, national PMTCT guidelines were reviewed and currently set the VLS threshold to <50 copies/mL during pregnancy and recommend a repeat VL at time of delivery for all WLHIV.[23]

Centralized laboratory HIV VL testing remains standard of care in South Africa. Unlike many countries in Sub-Saharan Africa, South Africa benefits from having an established national laboratory network through the National Health Laboratory Service (NHLS).[24] The NHLS has approximately 260 laboratories across the country.[23] However, only 16/260 (6.2%) of the laboratories offer HIV VL testing.[24] This often results in the laboratories operating at maximum capacity with extended result turn-around times that can lead to patients never receiving their results and being lost to care.[24] This in turn may contribute towards preventable MTCT. Point-of-care (PoC) HIV VL testing assays have been recommended as a means of improving VL monitoring among people on ART by enabling patients to receive their VL results on the day of testing prior to leaving the clinic.[25,26] This provides opportunity for rapid clinical management and reduces the number of clinic visits required. Compared to routine care, patients managed using PoC HIV VL assays have been shown to have better virologic outcomes and are more likely to be retained in care.[25] PoC HIV VL testing may be one of the game changers to fast-track eMTCT in South Africa, with maternal testing at time of delivery providing an opportunity for prompt clinical management such as enhanced adherence counselling for mothers and provision of high- versus low-risk prophylaxis for neonates. Furthermore, PoC early infant diagnosis (EID) testing at birth provides the opportunity to identify IU-infected neonates for early ART initiation.

In this paper, we describe maternal VL burden and IU transmission rates from a study implementing PoC testing among pregnant WLHIV and HIV-exposed neonates around the time of delivery at four sites in Gauteng Province, South Africa.

5.2 Materials and methods

5.2.1 Study procedures

Between June 2018 and March 2019, PoC HIV VL and EID testing was introduced at four tertiary obstetric units (TOU) in Gauteng as part of an implementation study to determine the feasibility of integrating PoC testing into routine care in busy obstetric units. Three sites were located in Johannesburg (subdistricts B, D, F) and one in Tshwane district. A routine birth testing program for all HIV-exposed neonates was already in place at all sites as per national guidelines[22] but maternal VL testing around the time of delivery for WLHIV was not routinely provided.

All WLHIV admitted to labour or postnatal wards were eligible for a PoC HIV VL test around the time of delivery using Xpert® HIV-1 VL (Cepheid, Sunnyvale, California, USA), which has a quantifiable range of 40 – 10 000 000 RNA copies/mL. Similarly, all HIV-exposed neonates were eligible for PoC EID testing at birth, defined as <72 hours after delivery, using either Xpert® HIV-1 (Cepheid, Sunnyvale, California, USA) or m-PIMA™ (Abbot, Chicago, Illinois, USA) EID assays. PoC testing was restricted to working hours (08h00-16h00) on weekdays. Mother-neonate pairs were tested where possible; however, either of the pair could be tested without the other. Samples of mothers and neonates with no reasonable chance of the PoC result being returned prior to discharge were not tested. For example, a neonate born by normal vaginal delivery on a Friday evening was likely to be discharged before a PoC test could be performed on Monday morning and was therefore not tested using PoC assay. Routine hospital staff (usually nurses or junior doctors) collected maternal and neonatal specimens while PoC operators, mostly nurses employed specifically for this purpose, tested the samples in designated PoC testing rooms at each site. In the case of errors or invalid PoC HIV VL or EID results, repeat testing was performed on leftover sample. If an error or invalid result was obtained on retest, a second sample was requested for additional testing. For each specimen tested using PoC, a corresponding sample was collected and sent to the National Health Laboratory Service (NHLS) for centralized laboratory testing.

Upon completion of PoC testing, neonates of mothers with a VL <1 000 copies/mL received low-risk prophylaxis of daily nevirapine for 6 weeks, as per standard of care.[22] Mothers of neonates with a negative EID PoC result were counselled to follow-up for a routine 10-week HIV PCR test at their local clinic. Hospital paediatric and obstetric staff were alerted via a mobile phone SMS (short messaging system) to maternal VLs ≥1 000 copies/mL and positive EID results for intervention. Mothers with a VL ≥1 000 copies/mL received adherence counselling and their neonates were prescribed high-risk prophylaxis - either daily nevirapine for 12 weeks or dual prophylaxis (nevirapine and zidovudine) for 6 weeks, according to guidelines at the time of data collection.[22] Positive EID PoC test results prompted a second sample draw to confirm an HIV positive diagnosis and referral for ART initiation.

5.2.2 Study data

Patient (name, surname and hospital number) and sample details (collection date and time, sample barcode, result, name of assay, facility and ward) were collected on a PoC test request form. These data were entered and managed in a REDCap™ database and imported into STATA™ for analysis. Analysis was restricted to participants with a valid PoC result. No additional clinical data were collected as this was beyond the scope of the PoC implementation study. Obtaining the necessary informed consent would have negatively affected the time-sensitive outcomes of the implementation study; namely testing coverage, turn-around times and result return rates.

5.2.3 Study measures

The proportion of viraemic women at time of delivery was calculated at VL thresholds of ≥50, 50-<1 000 and ≥1000 copies/mL among women with a valid VL result. The IU transmission rate was calculated as the proportion of positive EID results in relation to the total EID PoC tests with a valid result. Programmatic HIV PCR data from the NHLS' Corporate Data Warehouse (NHLS CDW) were used to determine routine IU transmission rates for each TOU site. PoC testing coverage was defined as the proportion of eligible mothers and neonates with a valid VL or EID PoC result. The country's District Health Information System (DHIS) indicator 'total live births to HIV-positive women' was used as a proxy for the total number of mothers and neonates eligible for PoC testing per TOU.

Two denominators were used for PoC testing coverage: a conservative estimate used total number of live births to HIV-positive women whilst a second estimate used only total live births to HIV-positive women during weekdays, when PoC testing was available. The conservative estimate was used as a proxy for the minimum testing coverage achieved while the second denominator measured the best-case scenario or maximum coverage (i.e. assuming PoC testing was available every day of the week).

5.2.3 Data analysis

The Pearson's Chi squared test was used to test for associations between categorical variables, otherwise Fischer's exact was used for sparse data. Logistic regression was used to assess the association between having a high VL (VL ≥1 000 copies/mL) around the time of delivery and i) quarter of the year when PoC test was performed after PoC implementation and ii) TOU in which the PoC test was performed. Variables were included in the adjusted model based on purposeful selection (p-value cut-off of 0.20 at the 5% level of significance during univariate analysis). The 'quarter of the year when PoC test was performed' was included *a priori*.

Sub analysis

Additional clinical and demographic data (maternal age at delivery and duration on ART) for women who delivered at the Johannesburg B site during the study period were extracted from a database of routinely collected clinical data from consenting patients at the site. These data were described using median (interquartile range) and proportions. Logistic regression was used to determine the association between high VL at delivery and (i) maternal age at delivery and (ii) duration on ART.

5.3 Ethics clearance

This work was approved by the Human Research Ethics Committee (HREC) of the University of the Witwatersrand (M1711115) and the Faculty of Health Sciences Research Ethics Committee of the University of Pretoria (50/2018) (Appendix 5.1). Patient identity was protected by de-identifying data prior to analysis. Maternal clinical data were available for study participants from the Johannesburg B site because of a data-sharing agreement routinely used at that facility, HREC clearance number M170778.

5.4 Results

Over the period of 10 months, the four sites had 8 147 live births to WLHIV of whom 2 769 (34.0%) had a valid VL result (Table 5.1) and 4 333 (53.2%) neonates had a valid EID result (Table 5.2). Testing coverage of maternal VL and EID varied considerably across the TOU sites with overall maximum coverage of 48.6% and 76.0%, respectively (Table 5.1 and 5.2). The median maternal VL around the time of delivery at all sites was <40 copies/mL, with an overall interquartile range of 0–398 copies/mL. Figure 5.1 shows the distribution of VLs amongst women with a detectable VL around the time of delivery by TOU.

Of 2 769 valid VL results, 1 578 (57.0%) were quantifiable with 571 (20.6%) having results of <50 copies/mL. Overall, the proportion of women with a VL ≥50, 50-<1 000 and ≥1 000 copies/mL was 36.4% (n= 1 007), 13.9% (n= 386) and 22.4% (n= 621), respectively (Table 5.1). Similar trends in proportions of viraemic women were observed for the three Johannesburg units while higher proportions were observed for the Tshwane unit at 45.1%, 16.6% and 28.5% for VL ≥50, 50-<1 000 and ≥1 000 cps/mL, respectively (Table 5.1, p=0.001). The proportion of IU-infected neonates ranged between 0.9% - 1.5% for the Johannesburg units while the Tshwane unit had an IU rate of 2.7% (p=0.005). When study data were aggregated to district level to compare IU transmission rates between the two districts, a similar trend was noted with 40/3420 (1.2%) for Johannesburg and

25/913 (2.7%) for Tshwane (p=0.002). Percentage positivity rates calculated from programmatic NHLS HIV PCR data from each site, were comparable to overall IU transmission rates suggesting generalisability (p=0.705).

Table 5.1. Description of Maternal Viral Load (VL) Around the Time of Delivery at Four Tertiary Obstetric Units in Gauteng, South Africa.

Variables	Total N= 2 769	Location of Tertiary Obstetric Unit				
		Johannesburg B n= 1 230	Johannesburg D n= 693	Johannesburg F n= 309	Tshwane n= 537	P-value
Total live births to WLHIV	8 147	2 103	3 324	1 543	1 177	
Minimum PoC VL testing coverage*	34.0%	58.5%	20.8%	20.0%	45.6%	<0.001
Maximum PoC VL testing coverage!	48.6%	90.0%	28.2%	28.6%	62.5%	<0.001
VL suppression threshold						<0.001
<50 cps/mL	1 762 (63.6%)	815 (66.3%)	445 (64.2%)	207 (67.0%)	295 (54.9%)	
≥50 cps/mL	1 007 (36.4%)	415 (33.7%)	248 (35.8%)	102 (33.0%)	242 (45.1%)	
VL suppression threshold						0.001
50-<1 000 cps/mL	386 (13.9%)	161 (13.1%)	92 (13.3%)	44 (14.2%)	89 (16.6%)	
VL suppression threshold						0.001
<1 000 cps/mL	2 148 (77.6%)	976 (79.4%)	537 (77.5%)	251 (81.2%)	384 (71.5%)	
≥1 000 cps/mL	621 (22.4%)	254 (20.7%)	156 (22.5%)	58 (18.8%)	153 (28.5%)	
Quarter of the year#						<0.001
Jul-Sep 2018	862 (34.5%)	448 (41.1%)	144 (22.9%)	96 (34.0%)	174 (34.6%)	
Oct-Dec 2018	802 (32.1%)	317 (29.1%)	199 (31.7%)	141 (50.0%)	145 (28.8%)	
Jan-Mar 2019	838 (33.5%)	324 (29.8%)	285 (45.4%)	45 (16.0%)	184 (36.6%)	

*****Denominator includes the total number of live births to WLHIV during the study period; !Denominator includes the number of live births to WLHIV occurring on weekdays only during the study period; **Abbreviations:** N, number; VL, viral load; cps/mL, copies per millilitre; WLHIV, women living with HIV; PoC, point-of-care. #June 2018, the first month of study initiation is excluded (n= 267 (9.6%) overall).

Table 5.2. Neonatal Point-of-Care Early Infant Diagnosis at Four Tertiary Obstetric Units in Gauteng, South Africa.

Variables	Total N= 4 333	Location of Tertiary Obstetric Unit				
		Johannesburg B n= 1 292	Johannesburg D n= 1 305	Johannesburg F n= 823	Tshwane n= 913	P-value
Total live births to WLHIV	8 147	2 103	3 324	1 543	1 177	
Minimum PoC EID testing coverage*	53.2%	61.4%	39.3%	53.3%	77.6%	<0.001
Maximum PoC EID testing coverage!	76.0%	94.5%	53.0%	76.2%	>99.0%	<0.001
n (%) Positivity	65 (1.5%)	19 (1.5%)	14 (1.2%)	7 (0.9%)	25 (2.7%)	0.005
IU transmission, n (%) by VL threshold in mother-neonate pairs tested†	34 (52.3%)	14 (73.7%)	8 (57.1%)	3 (42.9%)	9 (36.0%)	<0.001
<50 cps/mL	3 (0.3%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	2 (2.0%)	
50-<1 000 cps/mL	6 (3.2%)	2 (1.6%)	1 (4.0%)	1 (7.1%)	2 (8.7%)	
≥1 000 cps/mL	25 (7.9%)	11 (5.6%)	7 (14.9%)	2 (10.5%)	5 (9.6%)	
Total EID tests <3 days (Birth)	8 728 (100.0%)	2 387 (27.3%)	3 369 (38.6%)	1 713 (19.6%)	1 259 (14.4%)	
% IU transmission (Programmatic)	149 (1.7%)	39 (1.6%)	52 (1.5%)	20 (1.2%)	38 (3.0%)	<0.001

†n= 1 449; mothers of twin babies were counted twice as the mother contributed in two EID PCR events. *Denominator includes the total number of live births to WLHIV during the study period; !Denominator includes the number of live births to WLHIV during weekdays only during the study period; EID, early infant diagnosis; **Abbreviations**: N, number, WLHIV, women living with HIV; PoC, point-of-care; IU, intra-uterine; VL, viral load.

Percentage neonatal positivity was associated with high maternal VL around the time of delivery. Among 1 449 (33.4%) mother-neonate pairs with both a valid PoC VL and EID result, n (%), [95% confidence interval], 3/946 (0.3%) [0.1%-1.0%], 6/187 (3.2%) [1.4%-7.0%] and 25/316 (7.9%) [5.4%-11.5%] IU infections occurred among women with a delivery VL threshold of <50, 50-<1 000 and ≥1 000 copies/mL, respectively (Table 5.2, p<0.001). All three of the IU infections occurring in the VL <50 copies/mL threshold occurred to women with an HIV-1 RNA detectable VL result. A search for previous VL results from the NHLS' CDW showed that two of these women did not have a documented VL prior to delivery, while one woman had a VL ≥1 000 three months prior to delivery.

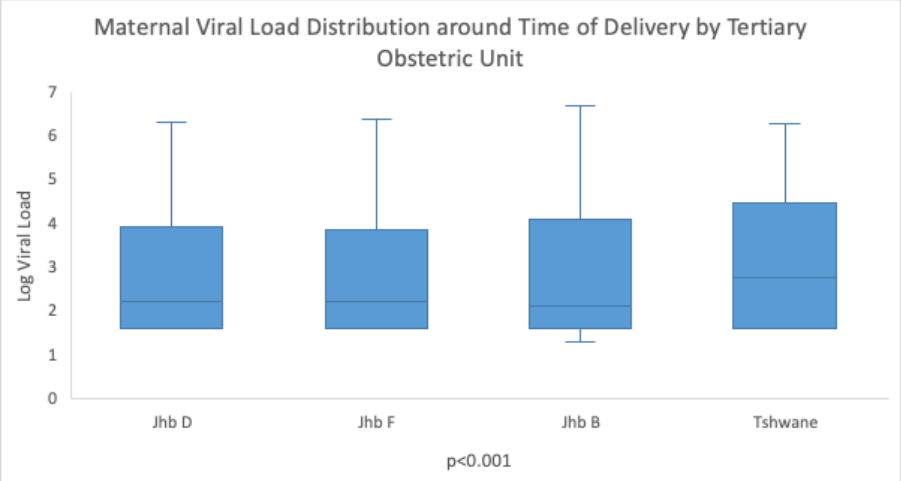

Figure 5.1. Distribution of maternal VL amongst women with detectable VL around the time of delivery by tertiary obstetric unit, n= 1 578 (57.0%) of maternal PoC VL results comprising 1 007 VL ≥50 copies/mL and 571 VL<50 copies/mL but detectable**.** VL results 'HIV less than detectable' were assigned values of 0 (n= 1 191).

Abbreviations: VL, viral load; Jhb, Johannesburg; PoC, point-of-care.

Proportions of high maternal VL remained constant during the study period suggesting similarity in participants tested throughout the implementation period despite low testing coverage (Table 5.3). While there was uniformity in the proportion of women with high VLs in the Johannesburg sites (Table 5.3), women who received their PoC HIV VL test in Tshwane were almost two times more likely to have a high VL compared to the site in Johannesburg F (AoR=1.88, 95% CI: [1.31-2.71]).

Table 5.3. Factors Associated with High Viral Load (VL ≥1 000 copies/mL) around the Time of Delivery at Four Tertiary Obstetric Units in Gauteng, South Africa.

Variable	N (%)	Univariate OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Quarter of the year[#]					
Jul-Sep 2018	197 (35.6%)	Reference	Reference	Reference	Reference
Oct-Dec 2018	183 (33.1%)	0.99 [0.79-1.25]	0.99	1.01 [0.80-1.20]	0.95
Jan-Mar 2019	173 (31.3%)	0.88 [0.70-1.11]	0.27	0.84 [0.67-1.07]	0.16
Location of TOU					
Johannesburg F	58 (9.3%)	Reference	Reference	Reference	Reference
Johannesburg D	156 (25.1%)	1.26 [0.90-1.76]	0.18	1.34 [0.93-1.97]	0.11
Tshwane	153 (24.6%)	1.72 [1.22-2.43]	**0.002**	1.88 [1.31-2.71]	**0.001**
Johannesburg B	254 (40.9%)	1.13 [0.82-1.55]	0.46	1.18 [0.84-1.65]	0.35

[#]June 2018, the first month of study initiation is excluded from this analysis (n= 267 (9.6%) overall). **Abbreviations**: OR, odds ratio; CI, confidence interval; VL, viral load; N, number; mL, millilitre; TOU, tertiary obstetric unit

Results of the sub-analysis of demographic and clinical characteristics of women who delivered at the Johannesburg B site showed that high VL at delivery was predicted by younger maternal age: (age <25 years, n= 191/1 129), (AoR= 2.17, 95% CI: [1.13-4.18]) and shorter duration on ART: (on ART for <3 months, n =61/375), (AoR= 4.11, 95% CI: [2.20-7.66].

5.5 Discussion

These findings are among the first documenting maternal VL burden around the time of delivery across multi-site, high volume obstetric units in South Africa. Approximately 20% of women delivering across the four TOUs in Gauteng had a VL ≥1 000 copies/mL with 36.4% having a VL of ≥50 copies/mL. Among mother-neonate pairs tested, higher maternal VL around the time of delivery was associated with higher IU transmission rates. While women delivering in the Johannesburg sites had similar VL profiles, higher proportions of viraemic women were seen at the Tshwane site. A similar trend was observed for the neonatal IU transmission rate, which ranged from 0.9%-1.5% in the Johannesburg sites but was 2.7% in Tshwane. Overall and site-specific IU transmission rates approximated programmatic IU transmission rates suggesting generalisability of these findings to these sites. Data to investigate the reasons for the statistically significant differences observed in both the proportion of viraemic women and percentage IU transmissions between the Johannesburg and Tshwane sites were not available. We postulate that the Tshwane site may have provided care for younger women as well as treated a

higher proportion of migrant patients who are more likely to have poorer treatment outcomes.[27-28] Our findings suggest that maternal VLS rates at the time of delivery are likely to vary between health districts, even within the same province. By monitoring maternal VL testing coverage and suppression rates at time of delivery, districts requiring targeted interventions to improve antenatal care can be identified to further reduce MTCT of HIV.

The 2017 National Antenatal Sentinel HIV survey confirmed that the PMTCT programme has reached the first and second UNAIDS 90-90-90 targets for antenatal clients in that 90% of all pregnant WLHIV know their status and 90% of these are on ART.[29] In spite of very high ART coverage during antenatal care in the public sector, our findings reveal suboptimal maternal VLS at time of delivery. Monitoring maternal VL during pregnancy and delivery instead of antenatal ART coverage, which fails to take duration of ART into account, may provide a better indicator as South Africa works towards eMTCT. In fact, since VLS prior to pregnancy is important for eMTCT, monitoring VLS of all women of childbearing potential is imperative. The proportion of viraemic (VL ≥1 000 copies/mL) women at time of delivery was much higher than has been reported for WLHIV on ART in general of ≈ 10%.[30] This likely reflects the effect of new diagnoses and recent ART initiation during pregnancy, particularly among younger women. According to the DHIS in 2018, more than one third of pregnant WLHIV were initiated on ART at their first antenatal visit and a similar proportion (34%) presented for their first antenatal clinic visit after 20 weeks of age. Thus, pregnant WLHIV often present for care after the first trimester with limited time to achieve VLS before delivery. The availability of maternal VL PoC testing during antenatal care may reduce the time to achieving VLS in pregnancy by reducing the time from sampling to result and improving the result return rate among virologically unsuppressed WLHIV.

5.6. Study limitations

Our data is limited by lack of information on ART status, ART drug regimens, time on ART, and prior VL results among study participants. These are important predictors of virologic response which we could not ascertain in the majority of our study population.[16-18] However, results of the Johannesburg B site sub-analysis confirmed what is already known. Younger maternal age and shorter duration on ART were significantly associated with high VL at delivery.[16] Regardless of patient level factors, conducting a PoC VL test at delivery within the high volume TOUs identified a third of women with detectable VLs for intervention. Given the maturity of South Africa's PMTCT programme and the need for potential game changers to achieve eMTCT, this study demonstrates the utility of PoC VL around the time of delivery within a high-burden setting.

Since the VL testing coverage was poor, the effect of targeted testing of high-risk mothers on our findings cannot be excluded. We may have disproportionately enrolled unbooked mothers, sick mothers with high VLs or mothers with ART adherence issues. However, we found that the proportion of viraemic women remained constant throughout the implementation period within each site. This suggests that despite low coverage, women included in the study were similar at each site or selection bias was uniform throughout implementation. Although most pregnant women presenting in labour wards had maternity case records with them around the time of delivery, few had documented VL results. As a result, clinical staff were less likely to be alerted to women with high VL results and unlikely to have selected women who were likely to have high VLs for PoC testing. Clinical staff also had the option to access PoC HIV VL testing on women if clinically indicated without enrolling them in the study and did not have to actively select women with high VL into the study. Lastly, there were no provisions in the current PMTCT guidelines recommending that mothers with high VLs be managed in TOUs. WLHIV routinely obtain HIV care in primary health care (PHC) facilities and are not referred for HIV management to TOUs. Therefore, it is unlikely that virologic profiles of women who participated in this study would differ from the surrounding PHC facilities.

We present findings based on a single VL measurement at delivery. We did not have historic VL measurements to understand the evolution of virologic control of these women during pregnancy. As a result, we could not ascertain the VL patterns during pregnancy that culminated in neonatal infection. Myer et al found that episodes of viraemia occurred frequently and were common in a cohort of women initiating ART during pregnancy in routine antenatal settings in the Western Cape.[31-32] This suggests that pregnant and postpartum WLHIV require close VL monitoring throughout pregnancy and during breastfeeding to minimize the risk of transmission. A follow-up study, describing the evolution of virologic control in pregnant and postpartum WLHIV at a national level would be helpful to develop evidence-based VL monitoring algorithms. At programme level, individual monitoring of every pregnant and postpartum woman may go a long way towards eMTCT using HIV VL test data stored in the NHLS DW. Results for Action reports (RfA) such as the ones currently used for linking HIV PCR positive infants to care[9] can be used by clinicians for WLHIV during pregnancy and postpartum to rapidly achieve VLS and avert transmission.

If the country is to achieve eMTCT urgent prioritization of (i) VL monitoring, (ii) ART adherence support and (iii) intervention for pregnant and breastfeeding WLHIV with unsuppressed VLs will be required.

5.7. Conclusion

Despite >95% antenatal ART coverage of pregnant WLHIV, approximately a third of WLHIV had a detectable VL around the time of delivery, thereby increasing risk of vertical transmission of HIV. Among mother-neonate pairs with valid PoC test results, 91% of IU infections occurred where maternal VL at the time of delivery was ≥50 copies/mL. Closer monitoring of VLS rates among pregnant and breastfeeding WLHIV may advance the PMTCT programme's prospects of achieving eMTCT and will be more informative than ART coverage rates. Maternal PoC VL testing during pregnancy and at delivery may facilitate VLS and reduce MTCT transmission risk. Essentially, improvement in the quality of HIV care among WLHIV is required if South Africa is to achieve eMTCT.

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CHAPTER 6.

Population-level risk factors for vertical transmission of HIV within the national prevention of mother-to-child transmission programme in South Africa: An ecological analysis.

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6.1 Background

South Africa has a well-established and mature prevention of mother-to-child transmission of HIV (PMTCT) programme in existence for close to two decades.[1] PMTCT services are available in >95% of all public health facilities in the country and HIV testing and antiretroviral therapy (ART) initiation among pregnant women were near universal by 2017.[1,2] In the same year, the proportion of first antenatal care (fANC) bookings occurring before 20 weeks gestation had increased to 67% nationally, up from 54% in 2014.[3] These data show that the national PMTCT programme had met targets for process indicators for validation for the elimination of mother-to-child transmission of HIV (eMTCT) in 2017, defined as ≥95% coverage for antenatal care, HIV testing of pregnant women and ART initiation among HIV-positive pregnant women.[4,5] Since inception of the PMTCT programme in the early 2000s, the national early MTCT transmission rate (4-6 weeks of age) has declined significantly from an infection rate of 25%-30% in 2001 to approximately 1.4% in 2016.[1] By 2017,the national intra-uterine (IU) rate (<7 days of life) had decreased to 0.9%.[6] These data demonstrate that South Africa is on a path towards eMTCT. However, the national PMTCT programme will need to overcome many challenges before it can achieve eMTCT.

The impact targets for eMTCT require reduction of MTCT rates to <50 cases per 100 000 live births at cessation of breastfeeding.[4,5] An IU transmission rate of 0.9% equates to a case rate of approximately 240 per 100 000 live births excluding intra- and postpartum transmissions in South Africa. This is attributable to a high maternal seroprevalence rate, which has plateaued at 30% since 2003.[7] Moreover, maternal seroconversion during pregnancy and the breastfeeding period is common. Further reduction of MTCT rates to levels sufficient to meet eMTCT targets will require universal early diagnosis of HIV, ART initiation and viral suppression to <50 copies/mL among pregnant women of reproductive age living with HIV (WRLHIV).[8] This strategy should also be extended to non-pregnant WRLHIV to ensure virological suppression at the time of conception. Sustained maternal viral load (VL) suppression (VL <50 copies/mL) regardless of pregnancy status will fast-track eMTCT. However, VL monitoring among pregnant and breastfeeding WRLHIV has been suboptimal.[9,10]

Maternal VL information is required for infant risk stratification and determining the nature of infant prophylaxis as well as maintaining maternal health. Calls have been made to prioritize VL monitoring among pregnant and postpartum WRLHIV in order to fast-track eMTCT in South Africa.[11,12] Currently there is limited information on rates of VL suppression among pregnant and breastfeeding WRLHIV accessing care in the national PMTCT programme. Using data from 2014 to 2017, 30%-35% of pregnant WRLHIV delivering in the public sector in South Africa have been reported as having a VL ≥50 copies/mL at time of delivery.[13,14] Women who have unplanned pregnancies, adolescent girls and

young women (AGYW) and migrant mothers have been identified as high risk groups for unsuppressed VLs as a result of factors including newly acquired infection, late booking and diagnosis and sub-optimal adherence to ART.[15-17] Geospatial differences in terms of HIV prevalence, ART coverage and viral suppression rates exist in South Africa.[18] Some provinces have higher proportions of WRLHIV and AGYW living with HIV than others.[19] However, at the time of writing (December 2020) there has been no assessment of the geospatial distribution of high maternal VL during pregnancy and the postpartum period and the potential effect this has on MTCT rates in South Africa. Identifying areas with high burden of maternal viraemia during pregnancy will guide stakeholders on where to focus attention and resources for eMTCT. Using a national laboratory dataset and other routine HIV-related data sources, we describe population-level factors associated with cases of MTCT (from birth to <24 months postpartum) at sub-district level in South Africa.

6.2 Materials and methods

6.2.1 Study design

Ecological analysis of routine laboratory HIV-related test data belonging to a cohort of pregnant and non-pregnant WRLHIV in South Africa in 2016 and 2017.

6.2.2 Creation of study cohort

Data were drawn from a study evaluating the evolution of maternal VLs during pregnancy, delivery and postpartum in the public health sector in South Africa. The data source and creation of the study cohort have been described elsewhere.[20] In brief; a cohort of WRLHIV (15-49 years) was identified from the National Health Laboratory Service's Corporate Data Warehouse (NHLS CDW) between 2016-2017 using HIV VL and CD4 count data. Because the NHLS CDW lacks a marker for pregnancy, a set of criteria based on syphilis screening and timing of HIV-related tests such as CD4 counts and VLs were applied to the routine data to differentiate pregnant WRLHIV from non-pregnant WRLHIV.[20] For pregnant WRLHIV, follow up started at cohort entry (which was the fANC visit based on syphilis test date), through delivery and up to 15 months post-delivery.[20] All VLs performed during follow up were included. Eligible VLs were categorized into 1) cohort entry VL: defined by the first VL performed during pregnancy, that is, at fANC visit for ART-experienced pregnant WRLHIV or after three months of ART use for pregnant WRLHIV not on ART at fANC visit 2) delivery VL (5-7 months after the fANC visit) and 3) cohort exit VL defined by the most recent VL measurement within the 15 month postpartum period). Analysis was restricted to the first identified pregnancy, that is, the first syphilis test date and its associated follow up VLs during the study period.

Since eMTCT requires viral suppression prior to pregnancy, we compared VLs of pregnant WRLHIV to non-pregnant WLRHIV at comparable time points. For non-pregnant WRLHIV, follow up started at cohort entry on 01 January 2016 and ended at the close of the dataset on 31 December 2018. In this group, the cohort entry VL constituted the first VL performed during the study period and the most recent VL measurement during the study period constituted the cohort exit VL. In both groups, de-duplication of test records was performed by a validated, automated patient-linking algorithm that uses probabilistic matching of patient demographics (name, surname, date of birth and geographic location) within the NHLS CDW.[21] Figure 6.1 describes follow up times stratified by pregnancy status.

Other routine indicators known to be associated with MTCT of HIV were extracted from the South African District Health Information System (DHIS) for the period 2016-2018. The DHIS has been described previously.[19] Data on relevant indicators extracted at sub-district level were 'Antenatal first visit <20 weeks rate' (ANC early booking) and 'Antenatal client start on ART rate' (ART coverage among women initiated prior to and during pregnancy). Lastly, district-level HIV prevalence rates among pregnant women were obtained from the latest National Antenatal Sentinel HIV & Syphilis Survey Report (2017).[7] Due to unavailability of disaggregated data, district-level ANC HIV prevalence estimates were used for each sub-district within that district. Table 6.1 defines population level study variables (indicators) and their sources.

Table 6.1. Population level variables, description and data sources.

Population level variable	Description	Source	Data availability
Antenatal first visit before 20 weeks rate	Proportion of pregnant women with first ANC booking before 20 weeks gestation from all first ANC visits recorded	DHIS	District and sub-district level
ANC ART coverage	Proportion of pregnant women receiving ART during pregnancy from all ANC attendees living with HIV	DHIS	District and sub-district level
ANC HIV prevalence rate	Proportion of HIV-positive pregnant women from all ANC attendees	National Antenatal Sentinel HIV & Syphilis Survey Report	District level
Maternal age <25 years	Number of WRLHIV aged <25 years at fANC visit/cohort entry stratified by pregnancy status	NHLS CDW	District and sub-district level
Viraemia of pregnant and non-pregnant WRLHIV	Number of WRLHIV with VL ≥50 copies/mL at specific time points during follow up	NHLS CDW	District and sub-district level
MTCT cases	Number of children testing HIV PCR positive at <24 months of age	NHLS CDW	District and sub-district level

Abbreviations: ANC antenatal care, ART antiretroviral therapy, MTCT mother-to-child transmission; DHIS district Health Information System, WRLHIV women of reproductive age living with HIV, NHLS CDW National Health Laboratory Service's Corporate Data Warehouse.

6.2.3 Study measures

6.2.3.1 Study outcome

The study outcome was number of MTCT cases, defined as the number of HIV PCR positive children <24 months between 2016 and 2018 in the public health sector. These test data were de-duplicated using the age at which the child first tested HIV PCR positive. De-duplication of test data was achieved by automated probabilistic matching of patient demographics supplemented by manual linkage of patient demographic information (name, surname, date of birth and geographic location).

6.2.3.2 Study exposures

The main exposure variables for this study were the numbers of WRLHIV with VL ≥50 copies/mL at specific time points of follow up, that is, at cohort entry, delivery (for pregnant WRLHIV) and cohort exit. Other exposure variables included proportions of ANC early booking among pregnant women, maternal HIV prevalence, ART coverage rate during ANC among pregnant women and number of WRLHIV aged <25 years, stratified by pregnancy status and geographic location. Patient-level data of pregnant and non-pregnant WRLHIV was aggregated and analysed at sub-district level. The geographic location of study participants was assigned to the sub-district where the entry VL was performed. Pregnant WRLHIV are a highly mobile population across healthcare facilities in South Africa.[22] Mobility of the cohort across sub-districts was minimal based on 3.3% and 4.6% of the cohort moving across sub-districts between the first and subsequent VL test during follow up for pregnant and non-pregnant WRLHIV respectively. Analysis was restricted to participants with at least two VL measurements during follow up

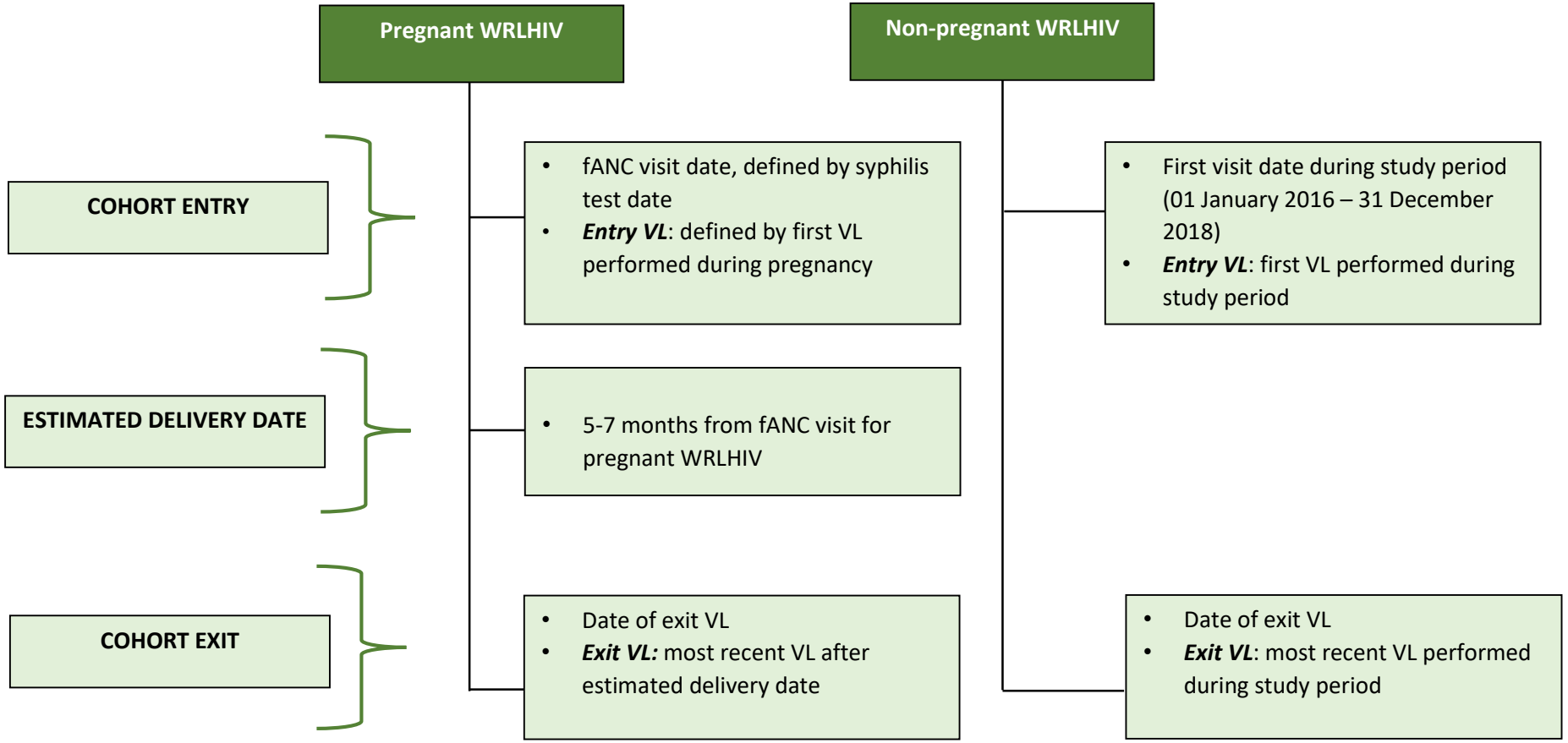

Figure 6.1 Definition of follow up time for pregnant and non-pregnant WRLHIV during the study period.

Abbreviations: WRLHIV women of reproductive age living with HIV, fANC first antenatal care visit, VL viral load.

6.2.4 Data analysis

Percentages, medians [interquartile ranges (IQR)] were used to describe the population-level variables. ArcGIS was used to describe the geospatial distribution of maternal viraemia at delivery, expressed as percentage maternal VL ≥50 or ≥1 000 copies/mL by district. A negative binomial regression model was used to determine the association between cases of MTCT and the number of WRLHIV with unsuppressed VL at specific time points that is; at cohort entry, delivery (for pregnant WRLHIV) or cohort exit controlling for sub-district-level proportions of pregnant women with early ANC booking, ART coverage during ANC, ANC HIV prevalence and number of women aged <25 years at fANC visit or cohort entry (study covariates). Variable selection was achieved by backward stepwise regression using a statistical significance level of 20%. Since younger maternal age is associated with vertical transmission of HIV[23], the number of WRLHIV aged <25 years at cohort entry were included into the model *a priori*.

Two sensitivity analyses were performed, comparing the ability of different models in predicting an eMTCT target of 50 MTCT cases adjusting for study covariates at sub-district level. The first analysis compared a negative binomial regression model using absolute numbers of maternal VL >50 copies/mL at specific time points adjusting for study covariates (Model 1) versus a model using proportions of maternal VL >50 copies/mL at specific time points adjusting for study covariates (Model 2). The second analysis compared Model 1 to a model using absolute numbers of maternal VL >50 copies/mL at specific time points as a covariate unadjusted (Model 3). Model comparison in either scenario relied on comparison of the area under the Receiver Operating Characteristic (ROC) curves at the 5% level of significance.

6.3 Ethics clearance

Ethical clearance was obtained from the Human Research Ethics Committee (HREC) of the University of the Witwatersrand (M180854). Access to data from the national Early Infant Diagnosis programme was covered by ethical clearance issued to the National Institute for Communicable Diseases (M160667).

6.4 Results

6.4.1 Description of pregnant and non-pregnant WRLHIV included in the study

A total of 3 386 507 WRLHIV from 262 sub-districts were identified from test records archived in the NHLS CDW of whom 178 319 (5.3%) met criteria for pregnancy and 3 208 188 (94.7%) did not. Median age at fANC visit was 29.4 (24.6-33.7) years for pregnant WRLHIV and 34.0 (33.0-35.0) years at cohort entry for non-pregnant WRLHIV respectively, p value <0.001 (Table 6.2). During the study period, the median proportion of women with early first booking during ANC (<20 weeks gestation) was 68.2% (62.9%-72.8%) at sub-district level. At the same time, the median ANC HIV prevalence rate per district was 31.5% (23.4%-35.7%). Antiretroviral therapy coverage during ANC was almost universal with a median coverage rate of 94.8% (89.7%-97.8%).

6.4.2 Unsuppressed VL among pregnant and non-pregnant WRLHIV

Overall, the median sub-district level proportion of WRLHIV with VL ≥50 copies/mL at cohort entry was 41.7% (27.8%-57.8%). When stratified by pregnancy status, the median sub-district level proportion of pregnant WRLHIV with VL ≥50 copies/mL at cohort entry was 42.9% (38.3%-59.3%) versus 35.0% (25.9%-49.0%) for non-pregnant WRLHIV at cohort entry (p value <0.001). By time of delivery, the proportion of pregnant WRLHIV with elevated VL had decreased, resulting in a median sub-district level proportion of pregnant WRLHIV with VL ≥50 copies/mL of 38.2% (27.3%-52.1%). However, maternal VL ≥50 copies/mL at cohort exit remained higher when compared to non-pregnant WRLHIV with a median of 36.3% (25.0%-48.4%) versus 29.6% (21.0%-42.6%), respectively (p value <0.001) (Table 6.2). A total of 4 535 children <24 months tested HIV PCR positive representing a median total case rate of 1 372 (914-2 077) per 100 000 live births at sub-district level during the study period.

Table 6.2. Description of population-level estimates related to mother-to-child transmission risk amongst women of reproductive age living with HIV in South Africa, 2016-2018 (N= 262 sub districts).

Variable	Sub-district level estimates: Median (IQR)			
	Overall	**Pregnant WRLHIV**	**Non-pregnant WRLHIV**	**P value**
Age at cohort entry	33.4 (27.8-39.6)	29.4 (24.6-33.7)	34.0 (33.0-35.0)	**<0.001**
fANC visit <20 weeks gestation rate (%)	-	68.2 (62.9-72.8)	-	-
ANC HIV prevalence (%)	-	31.5 (23.4-35.7)	-	-
ANC ART coverage (%)	-	94.8% (89.7-97.8)	-	-
MTCT case rate /100 000 live births	-	1 372 (914-2 077)	-	-
HIV VL ≥50 copies/mL (%):				
At cohort entry	41.7 (27.8-57.8)	42.9 (38.3-59.3)	35.0 (25.9-49.0)	**<0.001**
At delivery	-	38. 2 (27.3-52.1)	-	-
At cohort exit	34.6 (21.6-44.1)	36.3 (25.0-48.4)	29.6 (21.0-42.6)	**<0.001**

HIV VL ≥1000 copies/mL (%):				
At cohort entry	19.8 (14.6-26.4)	35.8 (28.7-42.1)	18.3 (14.4-24.7)	**<0.001**
At delivery	-	15.6 (12.5-21.6)	-	-
At cohort exit	13.3(10.1-17.5)	15.4 (11.3-20.0)	13.8 (10.1-19.2)	**<0.001**

Abbreviations: WRLHIV women of reproductive age living with HIV, fANC first antenatal care visit, IQR interquartile range, ART antiretroviral therapy, MTCT mother-to-child transmission, mL millilitre. *Among WRLHIV who were ART experienced at fANC visit, †among pregnant WRLHIV regardless of HIV status at fANC visit

6.4.3 Geospatial distribution of maternal viraemia at delivery by district

At delivery, 36.9% and 14.3% pregnant WRLHIV were viraemic at VL ≥50 and ≥1000 copies/mL, respectively at national level. At district level, proportions of pregnant WRLHIV with VL ≥50 copies/mL at delivery varied greatly, ranging from 18%-61%. Proportions of maternal viraemia at delivery were highest in Limpopo province, with at least 50% of WRLHIV having VL ≥50 copies/mL at delivery in all five districts (Figure 6.2). A similar trend was observed in 3/5 districts in Gauteng province (Ekurhuleni, Sedibeng and West Rand), 1/4 districts in the Free State province (Fezile Dabi) and 2/8 districts in the Eastern Cape province (Sarah Baartman and Nelson Mandela). Namakwa district in the Northern Cape province also had a high proportion of maternal VL ≥50 copies/mL at delivery probably due to very low numbers of pregnant WRLHIV. District-level proportions of maternal VL ≥1 000 copies/mL at delivery followed a similar distribution. Districts with the highest proportions of women with VL <50 copies/mL at delivery were mostly located in KwaZulu-Natal province (Figure 6.2).

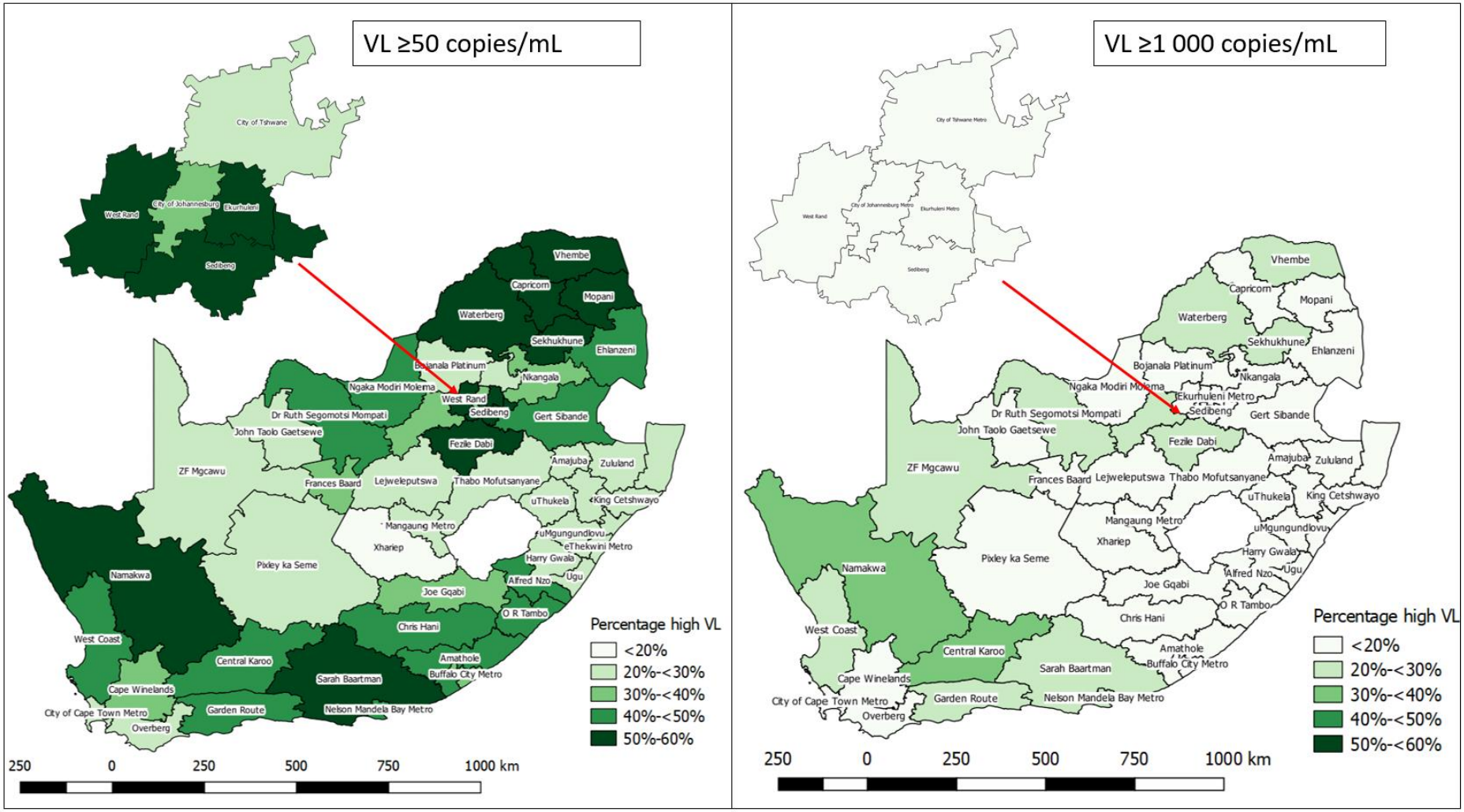

Figure 6.2. Maternal viraemia at delivery by district, 2016-2017 in South Africa.

Abbreviations: VL viral load, mL millilitre.

Table 6.3. Variable selection for multivariable model for sub-district level factors associated with vertical transmission of HIV from birth to <24 months of age in South Africa, 2016-2018.

Variable	Full Model (Backward elimination) Selection cut-off: p value <0.20	
	p value	Selection
ANC HIV prevalence rate	**0.067**	Included
Number of pregnant WRLHIV aged <25 years at cohort entry	0.320	Included *a priori*
Number of pregnant WRLHIV with VL ≥50 cps/mL at cohort entry	0.372	Excluded
Number of pregnant WRLHIV with VL ≥50 cps/mL at delivery	0.677	Excluded
Number of pregnant WRLHIV with VL ≥50 cps/mL at cohort exit	**<0.001**	Included
Number of non-pregnant WRLHIV aged <25 years at cohort entry	**0.090**	Included
Number of non-pregnant WRLHIV with VL ≥50 cps/mL at cohort entry	0.969	Excluded
Number of non-pregnant WRLHIV with VL ≥50 cps/mL at cohort exit	**<0.001**	Included
ART coverage among ANC clients rate	**0.187**	Included
ANC first booking <20 weeks gestation rate	**0.003**	Included

Abbreviations: WRLHIV women of reproductive age living with HIV, fANC first antenatal care visit, VL viral load, cps/mL copies per millilitre, ART antiretroviral therapy

6.4.4 Population-level factors associated with vertical transmission of HIV

Viraemia during the postpartum period (for both pregnant WRLHIV and non-pregnant WRLHIV), ANC HIV prevalence rate and ANC first booking <20 weeks gestation rate were associated with number of MTCT cases in the univariate analysis (Table 6.3). In the adjusted analyses, for every 100 WRLHIV with VL ≥50 copies/mL postpartum, the number of MTCT cases increased by three at sub-district level (Figure 6.3). Maternal HIV prevalence also positively correlated with number of children testing HIV PCR positive. That is, a 100% increase in sub-district level maternal HIV prevalence increased the number of children testing HIV PCR positive by 2 (Figure 6.3). An inverse association between proportion of women with first ANC booking <20 weeks gestation and the number of cases of MTCT was observed. A 100% increase in proportion of WRLHIV booking at gestation age <20 weeks decreased the number of children testing HIV PCR positive by 2 at sub-district level (Figure 6.3). An increase in ART coverage was also associated with increase in cases of MTCT, suggesting increasing ART coverage among women presenting late in pregnancy and or cases of incident maternal HIV during pregnancy. A separate model adjusting for maternal VL threshold ≥1 000 copies/ml at the same time points during follow up yielded similar results.

Results from the sensitivity analyses demonstrated that there was no difference in the accuracy of predicting the eMTCT target of 50 cases using the model including absolute numbers of maternal

viraemia versus the model using % maternal viraemia at specific time points as a covariate in the adjusted analyses (ROC p value =0.789), Figure 6.4a. The model using absolute numbers of maternal VL at specific time points adjusting for study covariates was superior to the model using maternal VL at specific time points unadjusted. However, the difference was not statistically significant (ROC p value =0.166), Figure 6.4b.

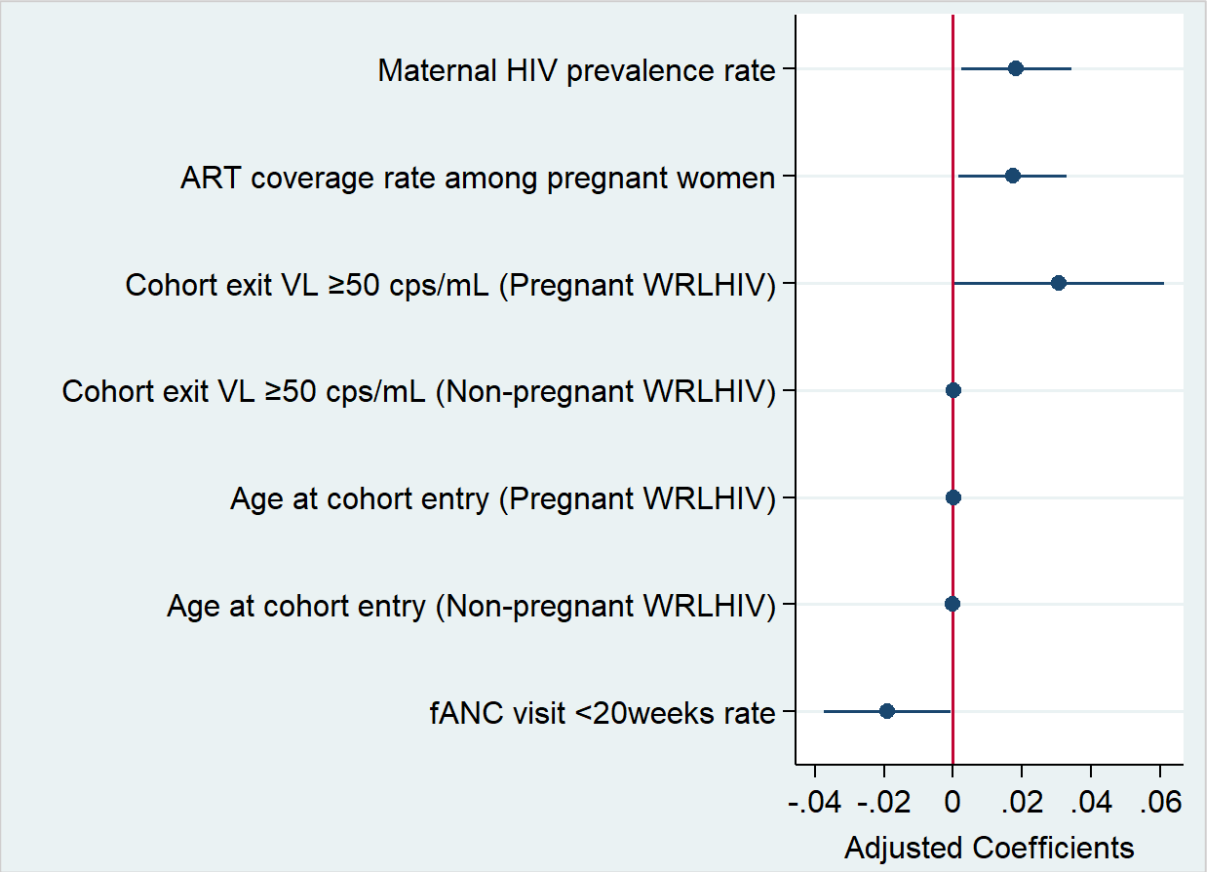

Figure 6.3. Negative binomial regression model showing sub-district level factors associated with vertical transmission of HIV from birth to <24 months of age in South Africa, 2016-2018 (n =204‡ sub districts).

Abbreviations: WRLHIV women of reproductive age living with HIV, fANC first antenatal care visit, VL viral load, cps/mL copies per millilitre, ART antiretroviral therapy, ‡sub districts with missing data excluded (Listwise deletion)

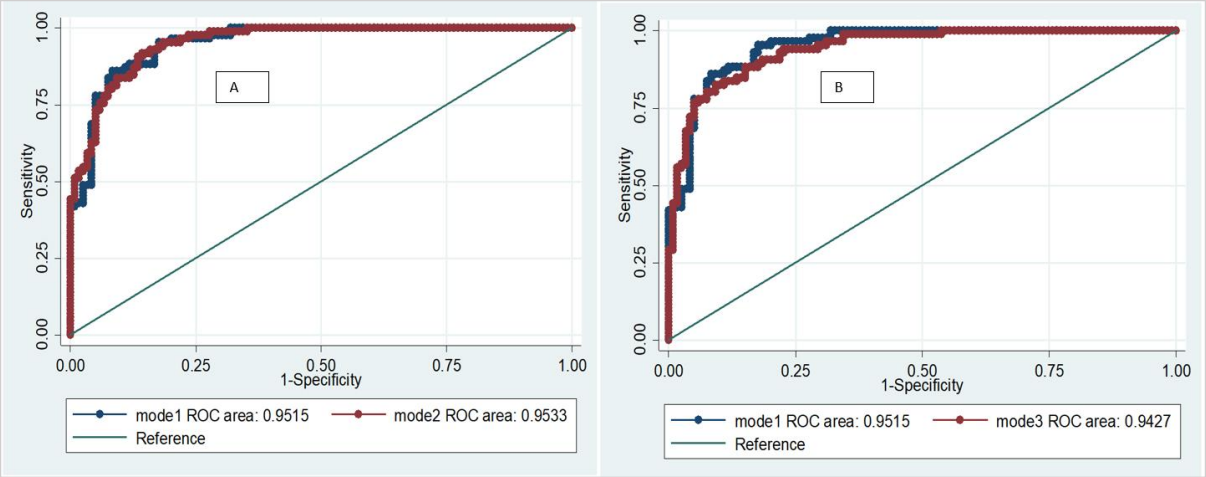

Figure 6.4 Sensitivity analyses: ROC curves comparing: A) Model 1 (using absolute number of maternal VL ≥50 copies/mL) versus Model 2 (% maternal VL ≥50 copies/mL) at specific time points as a covariate adjusted for other study covariates B) Model 1 versus model using absolute number of maternal VL at specific time points unadjusted (Model 3).

Abbreviations: ROC receiver operating characteristic curves, VL viral load.

6.5 Discussion

We present findings from an analysis evaluating sub-district level determinants of MTCT in South Africa, at a time when the national PMTCT programme is working towards achieving eMTCT. Understanding factors driving MTCT across the country will assist in developing targeted interventions to facilitate eMTCT. The study found that proportions of unsuppressed VLs were higher among pregnant WRLHIV compared to non-pregnant WRLHIV throughout follow up. For example, median proportions of women with viraemia (VL ≥50 copies/mL) were 43% versus 35% at cohort entry (p value <0.001) and 36% versus 30% at most recent VL measurements (p value <0.001) for pregnant and non-pregnant WRLHIV respectively. Maternal viraemia during the postpartum period correlated positively with cases of vertical transmission, with every 100 viraemic postpartum WRLHIV increasing the number of MTCT by three cases. Furthermore, higher rates of HIV prevalence among ANC clients was associated with a higher number of MTCT cases, whereby a 100% increase in maternal HIV prevalence resulted in an increase of MTCT cases by 2 at sub-district level. The same trend was observed for ART coverage during ANC among pregnant women. A higher proportion of women booking early for ANC was associated with a decline in number of HIV PCR positive children. District-level differences in

proportions of maternal viraemia (VL ≥50 or ≥1 000 copies/mL) at delivery were noted across the country.

These findings are among few examining population-level determinants of vertical transmission of HIV within the national PMTCT programme in the era of near universal rates of maternal ART coverage. Previous studies and surveys using data ranging from 2010-2013, reported a positive association between early MTCT rates and suboptimal PMTCT service coverage (provincial maternal ART coverage rate <80% and insufficient health-care personnel in facilities)[24] and recommended early treatment of maternal HIV as a way of reducing vertical transmission.[24] Almost a decade later, our data show that PMTCT coverage (ART coverage amongst ANC clients) was near universal at 95% and the proportion of ANC clients booking early for care was almost 70% during the study period nationally. These programmatic changes may have contributed to the further decline in early (4-8 weeks postpartum) MTCT rates from 3.5%[1,25] to 1.5% (7days-<10 weeks postpartum) between 2010 and 2017. Early ART initiation during pregnancy is known to be protective against MTCT of HIV.[26,27] However in this study, results of the adjusted regression model showed increased vertical transmission with increasing ART coverage among pregnant women. This finding is suggestive of increased ART coverage among women newly diagnosed during pregnancy due to seroconversion. Approximately 1 in 2 pregnant WRLHIV included in the study were ART naïve at the fANC visit[20] and these figures were similar to reports from the DHIS during the study period. As a result, even though ART coverage during pregnancy was high, women initiating ART (particularly late in pregnancy) or seroconverting during pregnancy would not have had sufficient time to suppress their VL, hence transmitting HIV to their children. Moreover, high levels of viraemia have been documented from ART-experienced women at the fANC visit from a separate analysis using the same data as this study.[20] Hence, ART coverage does not equate to reduced MTCT as it does not take into account VL suppression. Achieving eMTCT will require early diagnosis of HIV and early ART initiation for all pregnant WRLHIV to ensure sustained maternal VL suppression. This can be facilitated by early booking for ANC. Findings continue to show that early booking for ART, and by extension, early treatment for maternal HIV is still relevant within the programme and is associated with lower number of MTCT cases. This suggests that the programme needs to continue to raise awareness on the importance of early attendance for ANC and the need for repeat HIV testing among HIV negative women throughout pregnancy and postpartum to facilitate early ART initiation to prevent MTCT.[26-28]

Findings showed that maternal viraemia during the postpartum period was associated with MTCT of HIV and was the main driver of vertical transmission at sub-district level. This finding concurs with reports from other studies which show higher rates of MTCT during the postnatal period within routine settings.[23,29,30] This emphasizes the need for continued engagement in PMTCT care and VL

monitoring among postpartum WRLHIV to prevent MTCT. Disengagement from care among postpartum WRLHIV is common in South Africa and other high HIV burden countries and this may lead to women becoming viraemic due to non-adherence to ART.[31-33] In South Africa, this has important programmatic implications given the extended breastfeeding period of up to 24 months among WRLHIV on ART.[34] In order to achieve eMTCT the programme requires better systems for tracking WRLHIV throughout pregnancy and postpartum period to enable retention in care and efficient VL monitoring to guide clinical management in this population. Study data did not show the effect of maternal viraemia at cohort entry and at delivery on cases of MTCT. This can be attributed to fewer VL measurements, median number of VLs was 2.2 (interquartile range: 2-3) per woman during follow up therefore potentially insufficient data points to establish the longitudinal effect of viraemia on vertical transmission at sub-district level and requires further study.

Ensuring all WRLHIV are virally suppressed is probably one of the most practical ways of fast-tracking eMTCT in South Africa given 1) the magnitude of the programme 2) inadequacies of other methods for fast-tracking eMTCT in these settings (cannot avoid breastfeeding and universal caesarean births not feasible).[34,35] Study data showed that community VLs were higher in pregnant WRLHIV than non-pregnant WRLHIV throughout follow up suggesting that pregnancy was associated with lower rates of viral suppression. While there are no physiological reasons why pregnancy should correlate with lack of viral suppression[36], psycho-social factors related to pregnancy are known to impact maternal adherence to ART and subsequently lead to lack of VL suppression.[36] Thus, a patient centred approach towards managing pregnant WRLHIV is recommended to improve viral suppression rates and prevent vertical transmission. This can be achieved by scaling up mentor-mother and community health care programmes to assist women adhering to treatment from within their communities.

Lastly, varying proportions of maternal VL ≥50 copies/mL at delivery amongst districts were observed. High burden areas for maternal viraemia at delivery were observed in Limpopo, Gauteng and some parts of the Eastern Cape and Mpumalanga. Pregnant WRLHIV accessing care in districts in KwaZulu-Natal and Western Cape provinces had better rates of VL suppression compared to the rest of the country. These district-level differences in maternal viraemia highlight high burden areas for maternal viraemia in the country and the need for targeted responses. As for KwaZulu-Natal, despite having optimal maternal VL suppression rates overall, the province still had higher cases of MTCT on account of a high maternal seroprevalence rate. These data concur with results of the adjusted regression model whereby higher maternal seroprevalence rates correlated positively with number of MTCT cases. This further emphasizes the need for targeted responses in order to achieve eMTCT. It is also worth noting that maternal VL suppression rates at time of delivery may have improved subsequent to the study period. The guidelines of 2019 now recommend a VL test at delivery for all pregnant

WRLHIV in an attempt to prompt appropriate clinical management for mother-child pairs during the postpartum period, since the postnatal period is the new frontier of MTCT.[37,23] In addition the introduction of Dolutegravir into standard first line therapy may improve maternal VL suppression rates during pregnancy and the postpartum period.[37]

6.6 Study limitations

Interpretation of these findings requires acknowledgement of a number of limitations. Results for pregnant WRLHIV are based on a synthetic cohort that was created by applying a set of criteria to routine HIV test data due to lack of a marker for pregnancy in the NHLS CDW. Thus, the generalizability of study data rely on the accuracy of algorithms used. It is anticipated that the study algorithm used to identify pregnant WRLHIV from the NHLS CDW was highly specific, resulting in a small number of women identified as pregnant during the study period. As a result, some pregnant WRLHIV were misclassified as being non-pregnant. However, results emanating from this study cohort are similar to results from other studies which enrolled known pregnant WRLHIV from routine settings.[13,38]

The lack of a unique patient identifier in the NHLS CDW may have resulted in poor linkage of VL test data, thus leading to under-estimation of VL suppression for both pregnant and non-pregnant WRLHIV. In addition, VL monitoring within the PMTCT programme was not widely implemented during the study period, therefore VL testing coverage was low. As a result testing may have been biased towards women with unsuppressed VLs. However, the large sample size of the individual-level data potentially minimized this bias. As for MTCT cases, the reported national case rate may be over-estimated due to decreased linkage in the NHLS CDW. On the other hand, the case rate may be an under-estimate because children diagnosed with HIV <24 months of age were tested using HIV PCR. The national PMTCT guidelines required HIV PCR testing in <18 month year olds and rapid HIV tests ≥18 months of age during the study period. However, results of rapid HIV tests are not recorded in the NHLS CDW, therefore the study likely missed MTCT cases between the 18-24 months age group.

On a population-level, the analysis was based on 262 data points representing sub-districts in the country. A facility-level analysis would have provided a larger dataset, with greater geographical variability in the exposures and outcomes. However, some of the indicators analysed were not available at facility level, restricting analysis to sub district level. Furthermore, the ecological design of this study makes the study liable to ecological fallacy. That is, findings from a population level analysis may not apply to a patient level analysis. For example, sub-district level data did not show the effect of younger maternal age on MTCT, when patient level analyses have shown that younger maternal age is a significant predictor of vertical transmission of HIV in these settings.[23,27] Nonetheless, the data

provide useful insight on population-level parameters that require addressing in order to fast-track eMTCT in South Africa.

6.7 Conclusion

Despite near universal coverage of PMTCT services in South Africa, MTCT case rates at the end of the breastfeeding period are still in excess of eMTCT targets. Results from this ecological analysis suggests that maternal viraemia during the postpartum period, geographic areas with higher maternal sero-prevalence rates, women initiating ART late in pregnancy and/or incident maternal HIV during pregnancy are significant population level predictors of vertical transmission within the national PMTCT programme. Scale up of HIV prevention like family planning services is required to lower maternal HIV prevalence while expanded access to HIV testing will fast-track ART initiation among WRLHIV. Retention in care and increased VL monitoring, with prompt clinical action for abnormal results, among pregnant and postpartum WRLHIV is critical to improve VL suppression rates and maternal health throughout the continuum of PMTCT care for eMTCT.

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CHAPTER 7.

Maternal HIV viral load testing during pregnancy and postpartum care in Gauteng Province, South Africa.

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7.1 Introduction

Maternal viral load (VL) is closely associated with the risk of mother-to-child transmission of HIV (MTCT).[1-3] Thus, frequent and timely VL testing among pregnant and breastfeeding women living with HIV (WLHIV) is critical to prevent MTCT. This is because there is limited time for identifying women with high VL and instituting interventions, such as switching regimens and/or intensifying adherence support, to ensure VL suppression. The South African Prevention of Mother-to-Child Transmission of HIV (PMTCT) programme has evolved to enable universal HIV testing and antiretroviral therapy (ART) coverage in the public sector. For monitoring treatment response, the PMTCT guidelines since 2015 have recommended a VL test at the first antenatal care (ANC) visit for WLHIV already on ART, irrespective of when the last VL was done.[4] For WLHIV newly diagnosed with HIV during pregnancy, a VL is recommended after three months of ART use. In both groups, six monthly VL monitoring follows throughout pregnancy and the breastfeeding period. In November 2019, the guidelines were revised to include a VL at delivery for all WLHIV, and the VL threshold was lowered from ≥1 000 to ≥50 copies/mL for instituting intensified adherence support and/or regimen changes.[5]

Despite the existence of a robust PMTCT policy framework, minimal attention has been placed on maternal VL monitoring during pregnancy and the postpartum period in South Africa.[2] Previous reports have found VL testing coverage as low as 30% during pregnancy or the breastfeeding period[6], with frequent disengagement from care during the postpartum period particularly among WLHIV newly initiating ART during pregnancy.[7,8] Furthermore, approximately 20% of maternal VLs were ≥1 000 copies/mL during antenatal and postpartum care[9], while up to 37% of pregnant WLHIV have VL ≥50 copies/mL at delivery in the public health sector.[10-12] This has important implications for vertical transmission, as elimination of mother-to-child transmission of HIV (eMTCT) requires sustained suppression of maternal VL at <50 copies/ml throughout pregnancy, delivery and the breastfeeding period. The foregoing suggests that the programme is far from achieving UNAIDS 90-90-90 and eMTCT targets.[13,14]

South Africa's public health sector provides routine HIV VL testing via a well-established, centralized laboratory network which is accessible to 4 300 ANC facilities nationally.[15] However, delays exist from specimen collection to testing and ultimately the return of results to patients.[2] Point-of-care (PoC) HIV VL testing has been proposed as a game changer for fast-tracking eMTCT in South Africa. Point-of-care VL testing can reduce gaps along the VL monitoring cascade by accelerating return of results to patients and facilitating prompt clinical management in cases with elevated maternal VL.[16-18] Previous reports suggest that PoC HIV VL technologies have a place within routine settings in South Africa.

However, scale up needs to complement existing laboratory-based systems and address site-level health system factors.[15]

This article reviews compliance of VL testing with national guidelines and suppression rates during the antenatal period and up to nine months postpartum among WLHIV who received a PoC HIV VL at delivery at four tertiary hospitals in Gauteng Province, South Africa.

7.2 Methods

Between June 2018 and February 2020, PoC HIV VL testing was piloted at four tertiary obstetric units in Gauteng Province- three in the City of Johannesburg and one in Tshwane District. All pregnant WLHIV presenting at labour or postnatal wards were eligible for PoC HIV VL testing using Xpert® HIV-1 VL (Cepheid, Sunnyvale, California, USA). Specimen collection was performed by nurses and doctors as part of routine care, while testing was performed by trained PoC operators onsite. Testing was performed on weekdays between 08h00-16h00. No clinical details, such as time of first HIV diagnosis, PMTCT regimen, ANC attendance, were recorded. All women who received a PoC HIV VL test at delivery were included in the study. For each PoC HIV VL performed, a corresponding sample was sent for routine testing to the National Health Laboratory Service (NHLS), with the two samples sharing the same laboratory barcode. Prior and subsequent HIV VL tests associated with the same patient, as per the NHLS' Corporate Data Warehouse (CDW) generated unique patient identifier, were extracted from the NHLS CDW. HIV VL test data extracted included VLs performed up to nine months prior to and post the delivery HIV VL. Viral loads performed up to nine months prior to delivery were used as a proxy for VL monitoring during the antenatal period. Record linkage within the NHLS CDW relied on a validated probabilistic patient-linking algorithm which uses patient demographics (name, surname, date of birth, etc) for linking test records to unique individuals.[19]

7.2.1 Study outcomes and analysis

The analysis evaluated proportions of women who received a VL test during the antenatal period, at delivery and within nine months postpartum, expressed as percentages. Eligible VLs analyzed included any VL performed within nine months pre- and post-delivery. Proportions of pregnant WLHIV with a documented VL and proportions of VL suppression during the antenatal period, at delivery and postpartum were calculated. Analyses were stratified by i) receipt of PoC HIV VL result prior to discharge from hospital or not, to determine the impact of PoC HIV VL testing on rate of retention postpartum and ii) maternal VL ≥50 copies/mL versus VL <50 copies/mL at time of delivery. The

Pearson's Chi squared test was used to test for associations between categorical variables, and Fischer's exact in the case of sparse data.

7.3 Ethics approval

Ethics approval for the study was obtained from the Wits Human Research Ethics Committee (HREC) (M1711115) and from the Faculty of Health Sciences Research Ethics Committee of the University of Pretoria (50/2018).

7.4 Results

A total of 4 989 pregnant WLHIV received PoC HIV VL testing at time of delivery from the four tertiary obstetric units between June 2018 and February 2020. Among these, 3 671 (73.6%) women received their PoC HIV VL result prior to discharge from the hospital and 1 318 (26.4%) did not. Median maternal age was 31.1 years (interquartile range: 26.6-35.6) (Table 7.1). A total of 917 (18.4%) women had a documented VL during the antenatal period of which, 335 (36.5%) had a VL ≥50 copies/mL and 165 (18.0%) had a VL ≥1 000 copies/mL (Figure. 7.1). At delivery, 1 911 (38.3%) women had a VL ≥50 copies/mL and 1 028 (20.6%) had a VL ≥1 000 copies/mL. A total of 627 (12.6%) women had a documented VL within nine months postpartum, of which 234 (37.3%) had a VL ≥50 copies/mL and 93 (14.8%) had a VL ≥1 000 copies/mL (Table 7.1). Women with a documented VL during the antenatal period versus those without, were more likely to i) have VL <50 copies/mL at delivery, 652 (71.1%) versus 2 426 (59.6%); p value <0.001 and ii) have a documented VL postpartum, 216 (23.6%) versus 411 (10.1%); p value <0.001, respectively. However, VL suppression postpartum was not associated with having a VL performed during the antenatal period (p value = 0.478). Overall, 216 (4.3%) of 4 989 women received VL monitoring during the antenatal period, at delivery and within nine months postpartum.

Receipt of a PoC VL result before discharge from the hospital was associated with having a VL test performed within nine months postpartum. However, the association did not reach statistical significance (p value = 0.055, Table 7.1). A significant proportion of younger women (age <25 years) had a VL ≥50 copies/mL at time of delivery (Table 7.1). When compared to women with VL <50 copies/mL, women with VL ≥50 copies/mL at time of delivery had fewer VLs during the antenatal period (265/1 911 (13.8%) versus 652/ 3 078 (21.2%); p value = 0.001) and tended to have unsuppressed VLs if they had a VL during the antenatal period (VL ≥50 copies/mL for 220/265 (83.0%) versus 115/652 (17.6%) women, p value <0.001) (Figure. 7.1). Rates of postpartum VL monitoring were similar between the two groups at 251 (13.1%) for women with a VL ≥50 copies/mL and 376 (12.2%)

for women with a VL <50 copies/mL at time of delivery (p value = 0.341). However, women with VL ≥50 copies/mL at time of delivery were more likely to remain unsuppressed at postpartum follow-up compared to women with VL <50 copies/mL at time of delivery (Figure. 7.1).

Table 7.1: Demographic and clinical characteristics of WLHIV who received a PoC HIV VL test at delivery from four tertiary obstetric units in Gauteng Province, June 2018-February 2020.

Variables	Total N= 4 989	PoC Result receipt at delivery			PoC HIV VL category at delivery (*copies/mL*)		
		Not received n= 1 318	*Received n= 3 671*	P-value	*VL <50 n= 3 078*	*VL ≥50 n= 1 911*	P-value
Maternal age at delivery				0.416			**<0.001**
Median (years)	*31.1 (26.6-35.6)*	*31.0 (26.2-35.4)*	*31.1 (26.5-35.5)*	*0.402*	*32.2 (27.6-36.1)*	*29.8 (25.1-34.6)*	**<0.001**
<25	616 (12.3%)	139 (10.5%)	477 (13.0%)		296 (9.6%)	320 (16.7%)	
25-34	1 855 (37.2%)	377 (28.6%)	1 478 (40.3%)		1 148 (37.3%)	707 (37.0%)	
35-44	990 (19.8%)	200 (15.2%)	790 (21.5%)		692 (22.5%)	298 (15.6%)	
≥45	16 (0.3%)	2 (0.2%)	14 (0.4%)		11 (0.4%)	5 (0.3%)	
missing[†]	1 512 (30.3%)	600 (45.5%)	912 (24.8%)		931 (30.2%)	581 (30.4%)	
VL test during ANC							
VL done	917 (18.4%)	186 (14.1%)	731 (19.9%)	**<0.001**	652 (21.2%)	265 (13.9%)	**<0.001**
VL not done	4 072 (81.6%)	1 132 (85.9%)	2 940 (80.1%)		2 426 (78.8%)	1 646 (86.1%)	
VL at ANC (copies/mL)				0.663			**<0.001**
Median[*] (IQR)	*20 (0-222)*	*20 (0-423)*	*20 (0-182)*	*0.158*	*20 (0-28)*	*718 (0-14 059)*	**<0.001**
<50	582 (63.5%)	113 (60.8%)	469 (64.2%)		537 (82.4%)	45 (17.0%)	
50-<1 000	170 (18.5%)	36 (19.4%)	134 (18.3%)		75 (11.5%)	95 (35.9%)	
≥1 000	165 (18.0%)	37 (19.9%)	128 (17.5%)		40 (6.1%)	125 (47.2%)	
VL test ≤9 months postpartum				**<0.007**			0.341
VL done	627 (12.6%)	138 (10.5%)	489 (13.3%)		376 (12.2%)	251 (13.1%)	
VL not done	4 362 (87.4%)	1 180 (89.5%)	3 182 (86.7%)		2 702 (87.8%)	1 660 (86.9%)	
VL ≤9 months postpartum				0.055			**<0.001**
Median (IQR)	0 (0-66)	0 (0-70)	20 (0-66)	0.092	0 (0-20)	107 (20-4 697)	**<0.001**
<50	393 (62.7%)	83 (60.1%)	310 (63.4%)		322 (85.6%)	71 (28.3%)	
50-<1 000	141 (22.5%)	26 (18.8%)	115 (23.5%)		46 (12.2%)	95 (37.9%)	
≥1 000	93 (14.8%)	29 (21.0%)	64 (13.1%)		8 (2.1%)	85 (33.9%)	

[*]Zero values were assigned for VL values were target was not detected; the value of the lower limit of quantification was assigned where HIV RNA was detected but below the lower limit of quantification of the VL assay. [†]Missing age category excluded from bivariate analyses. **Abbreviation (s)** WLHIV women living with HIV; PoC point of care; VL viral load, IQR interquartile range, ANC antenatal care, mL millilitre.

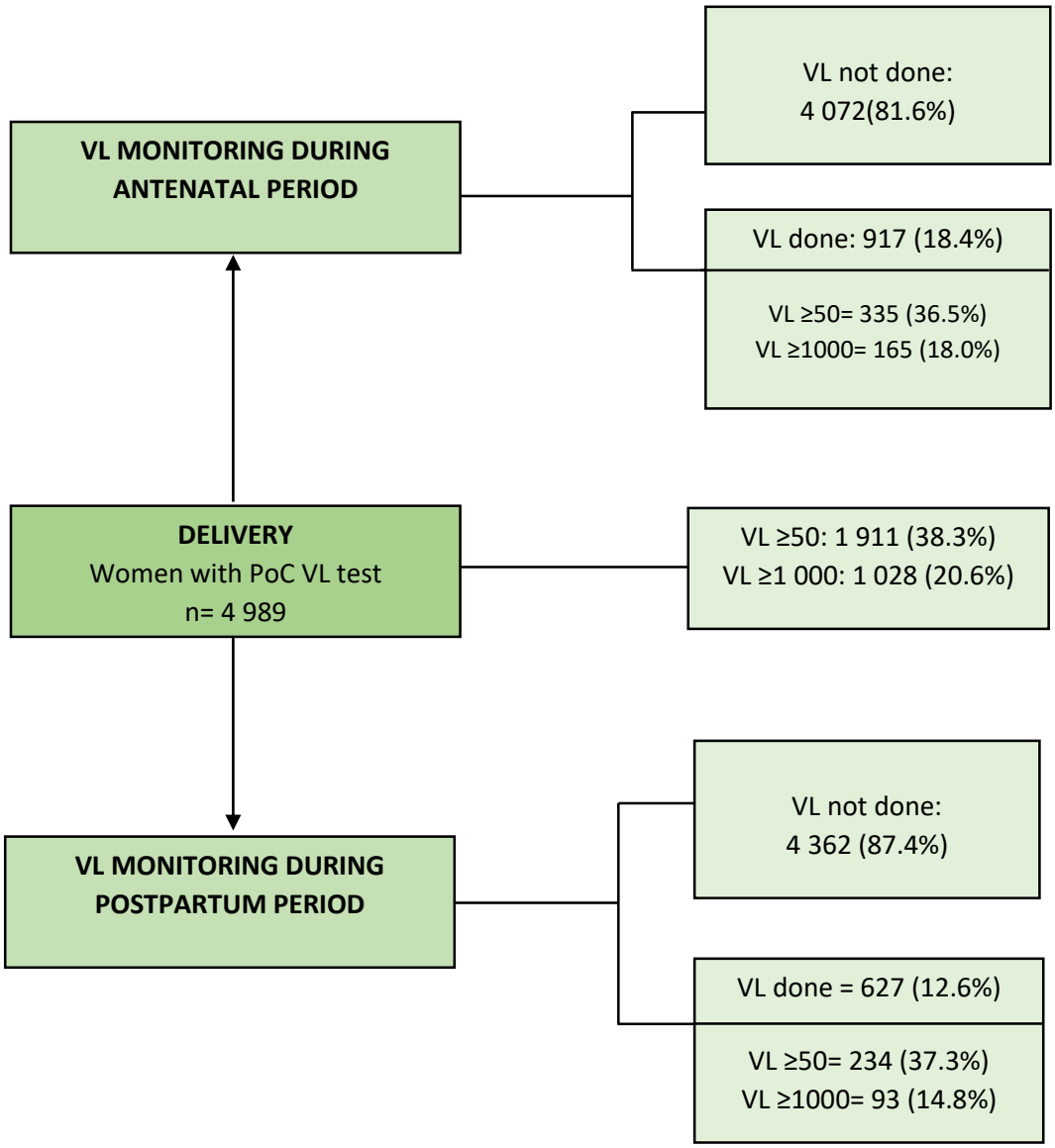

Figure 7.1. Compliance of VL testing and rates of suppression amongst pregnant and postpartum women living with HIV amongst the cohort.

Abbreviations: PoC point-of-care, VL viral load in copies/mL

7.5 Discussion

We present findings from a review of compliance to national VL testing guidelines and suppression rates during the antenatal and postpartum periods in Gauteng Province. Less than 20% of pregnant WLHIV had evidence of VL monitoring during the antenatal period, with 37% of these women having VL ≥50 copies/mL prior to delivery. At delivery, 38% and 21% of the women had VL ≥50 and VL ≥1 000 copies/mL, respectively. Overall, the rate of VL monitoring within nine months postpartum was 13%

and 37% of women with a VL test within nine months postpartum had VL ≥50 copies/mL. Women with evidence of VL monitoring during the antenatal period were more likely to be virally suppressed at delivery and receive VL monitoring during the postpartum period. We observed that a significant proportion of women aged <25 years had VLs ≥50 copies/mL at delivery and that women with VL ≥50 copies/mL at delivery were less likely to be virally suppressed at postpartum follow-up compared to women with VL <50 copies/mL at delivery. Since similar proportions of VL ≥50 copies/mL were observed during the antenatal period (37%), delivery (38%) and within nine months postpartum (37%), findings show that a similar proportion of women are transitioning the care continuum with unsuppressed VLs. In which case, the programme is failing to identify distinct groups of women with specific needs that require targeted packages of care for maternal VL suppression. However, VL data was too few to determine the proportion of women consistently unsuppressed at all three time points.

Elimination of MTCT requires sustained maternal VL suppression from conception through pregnancy to the end of the breastfeeding period. Over 80% of women in our cohort had no evidence of VL monitoring during the antenatal period. Given the small window of opportunity for intervention between detecting high maternal VL during the antenatal period and time of delivery, it is not surprising that 40% of these women had VL ≥50 copies/mL at delivery. Findings speak to the need for improved implementation of frequent maternal VL monitoring and rapid reaction to elevated maternal VL during pregnancy and postpartum period. South Africa already has a robust policy framework that provides for optimal monitoring of maternal VL during pregnancy. What is required are systems for improving clinical management of pregnant and postpartum WLHIV within the PMTCT programme including PoC VL testing.[15] Point-of-care VL utilization varied across our study sites as previously reported 15 and these data show that approximately one in three women who received a PoC VL test at delivery did not receive their result prior to discharge from the hospital, suggesting suboptimal utilization. Nonetheless, higher proportions of VL monitoring in the postpartum period were seen in women who received their delivery PoC HIV VL result prior to discharge from the hospital than those who did not. Although the difference was not clinically relevant (11% versus 13%), the finding demonstrated the potential of PoC VL testing in improving maternal VL testing and subsequent retention in care postpartum within routine settings. This is particularly important in the current context of very low maternal VL testing coverage within the national PMTCT programme, such that any intervention that improves VL testing coverage is welcome. However further research is required to explore this association as findings may be biased by underlying health system and patient level factors which were beyond the scope of this study.

Evidence from different studies show that approximately 30%-37% of women delivering in the public sector have VL ≥50 copies/mL at time of delivery.[9-11] We present similar findings for maternal viraemia

at delivery and within nine months postpartum. These proportions are unacceptably high if the programme is in pursuit of eMTCT, especially considering recommendations for extended breastfeeding for two years postpartum. We found that women who had unsuppressed VLs at time of delivery, continued to be unsuppressed during the postpartum period. Even more concerning was the observed high rate of absent VL monitoring within nine months postpartum amongst the cohort. This places HIV-exposed infants at a higher risk of MTCT during breastfeeding.[20-22] Poor monitoring of maternal VL during the postpartum period undermines the benefits of high ART coverage prior to delivery by compounding the risk of MTCT in the postnatal period. These findings emphasize the need for on-going patient support and improved systems for monitoring patient care during pregnancy and postpartum period in order to achieve eMTCT. Until clinical databases can assume this role, routine near real-time surveillance of maternal VL during pregnancy, delivery and postpartum periods using the NHLS laboratory database can fast-track attainment of eMTCT and the third 90 in this population. The revised PMTCT guidelines of 2019 make provision for accurate, national surveillance of maternal VL during pregnancy, at delivery and the postpartum period by introducing the electronic gate keeping (EGK) codes C#PMTCT and C#DELIVERY to distinguish maternal VL testing at these three time points.[5] The EGK codes are meant to be captured on standard laboratory requisition forms for specimens submitted to and processed by the NHLS. As with other policy recommendations, the success of this initiative depends on uptake and implementation by stakeholders.

At patient level, investing in patient support services may sensitize mothers on the importance of VL monitoring and empower them to take charge of their own health and health care, for example young mothers and women who are struggling with adherence to treatment. The success of the PMTCT programme to date is largely attributable to implementation of broad-based and programme-level interventions. These interventions were necessary and are still relevant. However, achieving eMTCT requires a further shift towards focusing on case management during pregnancy and postpartum period. This may explain the constant figure of approximately 37% of women that remain unsuppressed throughout the continuum of care in this study. These are probably women with specific needs that are not addressed by programme-level interventions and require extra services. While this approach may be time- and resource-intensive, the PMTCT programme can leverage on services provided by 'MomConnect' and the community health care worker programme to address such needs.[23] MomConnect is a mobile phone based health initiative of the South African National Department of Health that sends targeted health promotion messages to pregnant women (regardless of HIV status) accessing antenatal care in the public health sector. The targeted health messages aim at improving both maternal and infant health.[23] Subscription to the service is on a voluntary basis and is free of charge.

7.6 Study limitations

Interpretation of our findings requires consideration of certain limitations. We relied on the national laboratory database for VL testing patterns throughout the continuum of PMTCT care for the study cohort. However, the laboratory database is not a clinical longitudinal cohort management system. The VL testing cascade generated from laboratory data is based on availability of VL testing according to HIV monitoring guidelines. Therefore, some women may be in care but not receiving appropriate HIV testing. In addition, the laboratory database may be inaccurate for longitudinal cohort monitoring as, in the absence of a unique identifier, record linkage relies on probabilistic matching of patient demographic information. Therefore, some VL results may not have been linked to study participants due to inconsistent documentation of demographics (for example due to data capturing error and or surname changes due to marriage) which would cause the patient linking algorithm to fail to link VL results belonging to the same patient. This is particularly worth noting considering pregnant women often attend multiple facilities during the antenatal period, delivery and postpartum[24] and each facility may capture their personal identifiers differently. However, a manual search for longitudinal VL test results for 200 randomly selected participants was performed from the Laboratory Information System (LIS). The manual search did not yield additional VL data to results obtained from the patient linking algorithm. This suggests reasonable performance of the linking algorithm in finding most of the HIV VLs performed on each patient, thereby validating the study findings. However, the use of markers specific for maternal VL monitoring during pregnancy and breastfeeding period, such as the recommended EGK codes, is anticipated to provide accurate surveillance data from the laboratory database in the near future.

Another limitation includes the lack of clinical information for study participants. Data on maternal ART status during the antenatal period was not available to the study to determine timing of first VL and or the impact of ART duration on maternal viraemia during the antenatal and postpartum periods. In addition, the study lacked information of when pregnant or breastfeeding women last received ART, whether they were on first- or second-line therapy, and whether any changes to therapy were made in response to the VL results. Lastly, considering the low maternal VL testing coverage during both the antenatal and postpartum periods, testing may have been biased towards unsuppressed women. This may explain why women with unsuppressed VLs during pregnancy tended to be unsuppressed during the postpartum period. Furthermore, the few VL data in this study limited a longitudinal analysis of maternal VL evolution.

7.7 Conclusion

Less than 5% of WLHIV enrolled in this study received VL monitoring during antenatal and postpartum periods according to national guidelines. Approximately one fifth of women had evidence of VL monitoring during the antenatal period. Women living with HIV who did not have VL monitoring during the antenatal period were more likely to be virally unsuppressed at delivery and receive no postpartum VL monitoring. Women with high VL at delivery were more likely to remain virally unsuppressed postpartum. These results emphasize the need for closer monitoring of and urgency in responding to elevated maternal VL during pregnancy, at delivery and postpartum for the attainment of eMTCT in South Africa.

7.6 References

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SECTION 3: GENERAL DISCUSSION

CHAPTER 8.

General Discussion and Conclusions

8.1 Introduction

This chapter summarizes the main findings of the PhD research project and places the findings in the broader context of eMTCT in South Africa, sub-Saharan Africa and globally. The chapter also discusses the implications of the findings on eMTCT policy, programme implementation and operational research. This research project was based on a framework which places a direct link between maternal viraemia and mother-to-child transmission of HIV (MTCT) as presented in Chapter 1, Figure 1.2. This association is widely known.[1-3] The framework relates maternal viral load (VL) suppression during pregnancy and the postpartum period to a number of factors such as socio-economic, policy environment and clinical factors. Thus, this research project sought to describe maternal viraemia as a key driver of vertical transmission of HIV to establish a baseline from which to improve virological control among South African pregnant and postpartum women of reproductive age living with HIV (WRLHIV) in order to fast-track eMTCT. The project focused on 1) clinical factors (timing of HIV diagnosis, duration of antiretroviral therapy (ART), comorbidities) 2) policy environment (compliance to ART and VL testing coverage during pregnancy and postpartum and 3) geospatial differences in HIV response and their impact on maternal VL suppression to direct interventions for the achievement of eMTCT in the country.

8.1.1 Summary of key findings

The demographic profile of target populations for eMTCT (WRLHIV and adolescent girls and young women (AGYW) living with HIV) was greatest in six of the nine provinces in 2018, (Chapter 3, Publication 1). While prevention of mother-to-child transmission of HIV (PMTCT) service coverage was near universal in the public sector during the study period, this research project found that rates of maternal VL suppression were suboptimal when using VL thresholds required for elimination of mother-to-child transmission of HIV (eMTCT) (VL <50 copies/mL), (Chapter 4, Publication 2). Data from a national level, synthetic cohort of pregnant WRLHIV showed that maternal VL was ≥50 copies/mL for 54% of WRLHIV at first VL measurement during pregnancy, 37% at delivery and 34% during the postpartum period. Similar rates of maternal VL suppression at delivery were observed from a cohort of known, pregnant women living with HIV (WLHIV) delivering in the public health sector in Gauteng province, (Chapter 5, Publication 3). Importantly, the study found that approximately 45% of ART-experienced WRLHIV at the first antenatal care (fANC) visit had a VL ≥50 copies/mL at fANC visit nationally (Chapter 4, Publication 2). Moreover, proportions of maternal viraemia were higher in WRLHIV who were ART-naïve at fANC visit, with two thirds having VL ≥50 copies/mL after 12 weeks of ART use. However, differences in maternal viraemia were not apparent between the two groups at

delivery and postpartum. A slight increase in viraemia was observed late postpartum (12-15 months after delivery) for ART-naïve WRLHIV at the fANC visit in comparison to their ART-experienced counterparts. Sustained decline in maternal viraemia during follow up was predicted by a CD4 count ≥500, maternal age ≥25 years, VL <50 copies/mL and absence of comorbidities at baseline. Provincial differences in rates of maternal VL suppression during pregnancy, delivery and postpartum periods were noted, with greater variation observed at district level. Higher rates of maternal VL suppression were observed in KwaZulu-Natal and Western Cape provinces while the poorer performing programmes were Limpopo, Gauteng and the Eastern Cape provinces during the study period.

Results from a sub-district level ecological analysis (Chapter 6) demonstrated that maternal viraemia during the postnatal period, high maternal seroprevalence and women initiating ART late in pregnancy and/or incident maternal HIV during pregnancy were significant drivers of vertical transmission within the national PMTCT programme. Booking early (<20 weeks gestation) for ANC was associated with reduction in of number MTCT cases in the programme.

Viral load monitoring according to national guidelines among pregnant and postpartum WLHIV was poorly implemented (Chapter 7, Publication 4), albeit at a time when VL monitoring had relatively recently been introduced into the national PMTCT program. A review of compliance to national VL testing guidelines for pregnant and postpartum WLHIV in Gauteng province showed that <5% of WLHIV with a VL at delivery received VL monitoring during antenatal and postpartum periods according to national guidelines. More than 80% of WLHIV delivering had no evidence of VL monitoring during the antenatal period and these women were more likely to be virally unsuppressed at delivery and receive no VL monitoring postpartum.

8.2 Discussion points

The discussion points for this thesis are based on factors that impact rates of maternal VL suppression as guided by the framework of the research project (Figure 1.2).

8.2.1 Maternal VL suppression rates were suboptimal during pregnancy and postpartum

Despite near universal PMTCT service coverage in the public health sector in South Africa[4,5], rates of maternal VL suppression were poor during the study period. Over a third of WRLHIV had VL ≥50 copies/mL at delivery and postpartum, thereby increasing risk of transmission. Study data showed an increase in MTCT risk with increase in maternal VL, where percentage neonatal positivity was 0.3%, 3.2% and 7.9% for maternal VL <50, 50-<1 000 and ≥1 000 copies/mL around the time of delivery. These findings confirmed reports from a smaller, cohort from the Western Cape province as well as

from a French cohort of WLHIV.[1,3] Given >95% ART coverage among antenatal clients, the high proportions of viraemia observed in this study reflect gaps in maternal HIV diagnosis and subsequent late ART initiation or viraemia as a result of incident maternal infections.[6,7] This may explain the observed positive association between increase in ART coverage and number of MTCT cases in the population level analyses, suggesting provision of ART late in pregnancy or in women seroconverting during pregnancy. Hence, some women did not have sufficient time on ART to suppress their VL and transmitted HIV to their children. Alternatively, suboptimal maternal VL suppression during pregnancy and postpartum could be attributed to poor quality of care at these times since more than 50% of pregnant WRLHIV in this study were already on ART at the fANC visit. Poor case management may also explain the suboptimal VL suppression observed in women newly diagnosed and starting ART during pregnancy, whereby two thirds of these women had VL ≥50 copies/ml after three months of ART use. These findings emphasize that pregnant and postpartum WLHIV require close monitoring throughout the continuum of PMTCT care. Close monitoring needs to adopt a holistic approach, starting with ascertainment of maternal HIV and ART status at every contact with the health system, continuous assessment of adherence and frequent, timely VL monitoring for women on ART. This approach is labour intensive given high maternal HIV burden and shortage of human resources in the public health sector, which provides >80% of HIV care in the country.[8,9]

The community health worker programme, which is already operational in South Africa can supplement PMTCT services to alleviate work load on mainstream health care providers.[10] Furthermore, engagement of community health care workers has potential to improve retention in care and VL suppression rates among pregnant and postpartum WLHIV by providing individualized, on-going patient support from within communities. Pregnant and postpartum WLHIV can also benefit from peer-mentor mother programmes such as Mothers2Mothers.[11] In this model, the mentors are individuals who have been through the PMTCT programme themselves and provide support to other mothers living with HIV. This programme has been shown to improve maternal and child outcomes in the Western Cape province in South Africa as well as in Uganda.[12,13] A patient-centred approach has potential to foster accountability and build relationships between health care workers, patients and the community to fast-track eMTCT. Regarding VL suppression, the guidelines of 2019 now recommend a triple regimen containing Dolutegravir (DTG) for first line therapy for all people on ART, including WRLHIV.[14] Dolutegravir achieves VL suppression rapidly, has a high genetic barrier to resistance and is well tolerated.[15,16] A randomized controlled trial comparing maternal VL suppression in women using DTG versus Efavirenz (EFV) reported that time to VL suppression reduced by half in DTG users compared to EFV.[17] These attributes can improve maternal VL suppression within the programme towards achievement of eMTCT. Furthermore, the near universal access of DTG has

potential to achieve optimal population level viral suppression, facilitating VL suppression at conception among WRLHIV.

Alternative models of care for preventing MTCT include elective caesarean deliveries among WLHIV. This approach is widely implemented in developed countries, where resources allow universal access to caesarean deliveries for all WLHIV. This model of care may have contributed to the achievement of eMTCT among countries that have achieved this milestone. This approach may not be feasible in our setting due to high maternal seroprevalence and high costs involved with the procedure. However, this model can be adopted in cases of high maternal VL at time of delivery. A study from Cameroon demonstrated caesarean delivery to be effective at reducing MTCT among women presenting with high VL at time of delivery in resource limited settings.[18] As of December 2020, there is guideline ambiguity around the mode of delivery for women presenting with high VL at time of delivery in South Africa, hence this model of care is proposed for 'high risk' mothers at time of delivery.

8.2.2 Poor VL monitoring among pregnant and postpartum WRLHIV during the study period

Maternal VL monitoring during pregnancy, delivery and postpartum was poor during the study period. Elimination of MTCT requires maternal VL <50 copies/mL prior to pregnancy, during pregnancy and the postpartum period and this can only be ascertained by frequent and timely VL monitoring.[19,20] Although it was suspected that VL monitoring was suboptimal, the very low proportions of ante- and postpartum women receiving VL monitoring were unexpected and are very concerning. In Gauteng province, <5% of pregnant WLHIV received VL monitoring according to national VL testing guidelines and majority (>80%) of the cohort had no evidence of VL monitoring during ANC. These findings emphasize the need for prioritizing VL monitoring for pregnant and postpartum WLHIV to prevent MTCT as well as to achieve the third 90 of UNAIDS 90-90-90 targets for this population.[21] South Africa has a well-established PMTCT policy framework that provides for adequate VL monitoring among pregnant and postpartum WLHIV.[14] However, recommendations of guidelines did not translate into practice in the field as shown by findings of this study. The PMTCT programme will benefit from regular training and supervision of health care workers to ensure compliance to national guidelines and improvement in quality of care provided to users. The programme also needs to educate WLHIV on the importance of VL monitoring and VL suppression to create demand for VL testing and to empower women to take charge of their health. These initiatives can be augmented by the mentor mother and community health worker programmes mentioned previously. Within the health system, a new model of care for pregnant and postpartum WLHIV can utilize mid-wives or obstetric services to continue providing care for WLHIV until cessation of breastfeeding before they transition back to routine HIV care. A randomized controlled trial from the Western Cape province demonstrated improved

retention and higher rates of maternal VL suppression in women enrolled in the intervention arm of integrated postnatal service for the mother-infant pair versus standard of care which refers mothers for routine HIV care separately from infant services.[22] Results from the population level analyses of this study showed that maternal viraemia in the postnatal period is a significant predictor of vertical transmission in the national PMTCT programme thereby confirming results from other studies that the postnatal period is the new frontier for MTCT in the country.[23] This may be attributable to the disconnect between ante- and postnatal HIV care, which facilitates maternal attrition postpartum.[24,25] Thus, the approach of using mid-wives and obstetric services to continue providing HIV care to postpartum WLHIV will contribute positively towards eMTCT.

Viral load monitoring and clinical management during pregnancy and postpartum can also be improved by scale up of point-of-care (PoC) testing modalities within routine settings. Although widely accessible in the country, centralized laboratory testing is under strain from large testing volumes as a result of a high HIV burden. The short duration from pregnancy to the time of delivery means there is limited window for intervention, necessitating quick turn-around-times from VL testing to receipt of results among pregnant WLHIV. The PMTCT programme can leverage PoC VL testing to lower result turn-around-times among pregnant and postpartum WLHIV and facilitate urgency in responding to elevated maternal VLs. This can be implemented in the form of targeted testing of high risk mothers as opposed to offering PoC for all WLHIV, which may not be feasible in large hospitals. In addition, availability of VL results before mothers leave the healthcare facility, has potential to improve retention in care.[26] Findings from the Gauteng cohort showed that women who received their PoC VL test result prior to discharge from the hospital, were likely to have a VL test six months postpartum compared to those who did not. As of December 2020, PoC VL and EID modalities had not been scaled up within routine settings despite the availability of a large footprint of PoC instruments used for tuberculosis diagnosis in the country. This initiative has potential to improve maternal VL monitoring and retention in care during pregnancy and the postpartum period.[27,28] However, benefits from PoC technologies are conditional on addressing health system level factors.[28]

8.2.3 Community VL higher in pregnant WLHIV than non-pregnant WLHIV

There are few studies that have compared VL suppression between pregnant and non-pregnant WLHIV in the context of eMTCT. Women living with HIV alternate between being pregnant and not and eMTCT requires VL suppression prior to pregnancy, maintained through pregnancy until breastfeeding cessation. Programmatically, this means that all WRLHIV need to be virally suppressed at all times to ensure they are in the best possible health prior to conception. Scale up of pre-

conception services for women and couples living with HIV is needed. South Africa has a high rate of unintended pregnancies, regardless of HIV status.[29-31] Different levels of VL suppression (VL <1 000 copies/mL) have been reported for WLHIV in South Africa, ranging from 79% (all females), 90% (15-64 years), 67% (15-49 years) and 48% for AGYW in HIV care.[32,33] None of these studies reported on pregnant WLHIV, hence this study attempted to fill this gap, using VL thresholds required for eMTCT.

Findings from this study demonstrated higher proportions of maternal VL ≥50 copies/mL in pregnant versus non-pregnant WLHIV at comparable time points during follow up, proving the study hypothesis. This difference was apparent at the fANC visit, where proportions of maternal VL ≥50 copies/mL were 43% for ART-experienced, pregnant WRLHIV versus 35% for non-pregnant WRLHIV at cohort entry (p<0.001). Albeit using a different threshold, a Zimbabwean study reported similar findings of VL ≥1 000 copies/mL at fANC visit in 22% versus 16% of pregnant WLHIV and non-pregnant WLHIV respectively.[34] These data demonstrate that the period of pregnancy is a critical point in the lives of WRLHIV, which is prone to suboptimal viral control. Consequently, in order to achieve eMTCT, PMTCT programmes need to strength adherence support, monitor maternal VL timeously to improve maternal VL suppression and maternal health. In some instances, suboptimal VL suppression could be due to drug resistance.[35,36] However, the introduction of DTG into national ART guidelines is anticipated to alleviate this problem due to it having a higher genetic barrier compared to EFV[15], although concerns of weight gain associated with DTG use might discourage adherence.

In this study, comorbid conditions were associated with high maternal VL during follow up. Approximately 10% of the national cohort of pregnant WRLHIV had evidence of ≥1 comorbid condition (syphilis, TB and kidney disease) during pregnancy with syphilis seropositivity documented in 3% of the cohort. These findings concur with other reports on syphilis positivity among pregnant WLHIV from South Africa.[37] It is known that pregnant WLHIV co-infected with TB or syphilis have a 2-2,5 times higher risk of MTCT compared to their negative counterparts.[37,38] Thus, screening and treating all pregnant and postpartum WRHIV co-infected with TB or syphilis is critical for achieving eMTCT of both HIV and syphilis.

8.2.4 Young mothers and vertical transmission in the era of eMTCT

Youth pregnancies (15-24 years) are common in South Africa, with one in three 15-19 year old women reporting ever being pregnant.[39-41] This same age group has the highest lifetime risk for HIV acquisition among females.[42] In this study, patient-level analyses showed that maternal viral control during follow up was poor in younger mothers (<25 years at fANC visit) compared to older women. Younger mothers were 1) less likely to have documented evidence for VL monitoring during the ANC period ii) less likely

to be virally suppressed at delivery and iii) less likely to be retained in care postpartum. These findings are not new.[39-41] Adolescent and younger mothers are more likely to be unaware of their HIV status at programme entry, leading to a shorter duration of ART during pregnancy and therefore, have a higher risk of transmitting HIV to their children. Prior to the universal test and treat (UTT) strategy, antenatal testing was the main entry point for HIV diagnosis for many women[43,44] and this is likely the case for most AGYW. Poor viral control in younger mothers is also attributed to slower uptake of PMTCT services due to social and behavioural issues, such as stigma and relational barriers with health care providers.[45] However, population-level analyses in this study did not show any association between younger maternal age and vertical transmission. This may be attributable to less variability in proportions of pregnant women < 25 years of age at sub district level.

Younger mothers constituted a quarter of WRLHIV accessing care within the national PMTCT programme in this study. These women represented a significant proportion of mothers that require attention, given they have the highest risk of MTCT. The mentor-mother programme has a place in facilitating adherence and social support for these women.[12,13] For non-pregnant HIV-positive AGYW, the PMTCT programme needs to intensify family planning services to prevent unplanned pregnancies. Research shows that unplanned pregnancies are associated with MTCT.[39-41] For HIV negative AGYW, scaling up sexual and reproductive health represents low hanging fruit for eMTCT. The DREAMS project and School Health Programme are necessary to empower AGYW and promote sexual reproductive health education in schools respectively.[46,47] Pre-exposure prophylaxis (PreP) needs to be widely accessible to youth and to all other pregnant and breastfeeding HIV-uninfected women.[48,] According to modelling data from the Thembisa model, provision of PreP to HIV-uninfected pregnant and breastfeeding mothers would reduce cases of incident paediatric HIV infections by between 2.5% and 7.2% between 2020-2030 in South Africa.[48] In 2020, provision of PreP to pregnant and breastfeeding HIV-uninfected mothers was not policy, nevertheless this approach would be recommended to assist in achieving eMTCT. Overall, HIV prevention services among HIV-uninfected women of reproductive age require prioritization to reduce maternal seroprevalence and rates of seroconversion during pregnancy and postpartum periods to fast-track eMTCT.

8.2.5 Existence of geospatial differences in maternal viraemia during pregnancy and postpartum

Geospatial differences in maternal viraemia during follow up were observed during the study period. Although provincial differences were noted, greater variation was observed at district level. Rates of maternal VL suppression at specific time points were higher in KwaZulu-Natal, Western Cape and Free State provinces, while higher proportions of virally unsuppressed WRLHIV were noted from Limpopo,

Gauteng and Eastern Cape provinces. Geospatial differences in maternal viraemia could be a result of challenges that are unique to PMTCT programmes at sub-national level, suggesting contextualized interventions for eMTCT. For example, migration may have contributed to the lower rates of maternal VL suppression in Limpopo, Gauteng and Mpumalanga provinces. Limpopo and Mpumalanga provinces share borders with Zimbabwe and Mozambique respectively. Migrant pregnant WLHIV from these and other countries often seek care from the South African health system.[49,50] Migrant mothers are more likely to be virally unsuppressed due to barriers to optimal care[51,52] hence they may have contributed to maternal viraemia in these provinces. However, there is no published data quantifying the extent of HIV care provided to migrant mothers and their impact on the performance of provinces and/or districts in South Africa. Gauteng province on the other hand, has high rates of migration-inter-provincially and internationally. High mobility of pregnant WRLHIV may disrupt continuity of care and contribute to poor maternal VL suppression.[53]

At population-level, findings demonstrated increase in cases of MTCT with increase in maternal HIV seroprevalence rate at sub-district level. These results highlight the need for intensifying HIV prevention services to reduce maternal HIV prevalence. In the interim, sub-districts with maternal HIV prevalence above the national average should be prioritized for eMTCT resources.

8.2.6 Routine monitoring of maternal VL suppression rates for eMTCT and UNAIDS 90-90-90 targets

In order to fast-track eMTCT, there is need for improved systems for tracking VL monitoring and suppression rates among pregnant and postpartum WLHIV. Current systems for following up pregnant and postpartum women in HIV care are weak.[23,25] Inconsistent documentation of demographic details (such as names and surnames) when switching between clinics for ante- or postnatal care or errors in data capture may result in failure to accurately monitor longitudinal care among pregnant and postpartum WLHIV.[24] In some instances, women change their demographic information when accessing care in multiple clinics and this is often associated with lack of HIV disclosure.[54] Regardless of reasons for changes in demographic details, a disconnect between ante- and postpartum HIV care compromises longitudinal monitoring of care. Thus, the PMTCT programme will benefit from better systems for tracking of pregnant and postpartum WLHIV throughout the continuum of care, such as use of unique patient identifiers.[55,56] At programme level, the use of electronic gate keeping (EGK) codes associated with maternal VLs performed during pregnancy, delivery and the postpartum period enable accurate, routine surveillance from the NHLS.[26] However, the success of this endeavor is dependent on uptake from stakeholders.

8.3 Study Strengths and limitations

Findings of this study are based on a large, nationally representative cohort of pregnant and postpartum WRLHIV accessing PMTCT care within routine settings. These findings reflect real-life performance of the national PMTCT programme. The large sample size of the study maximizes representativeness and generalizability of findings to pregnant and postpartum WRLHIV in the country, as opposed to clinical trial populations.[57] The study data were available at provincial and district level, allowing evaluation of study outcomes sub-nationally. However, the study was limited by several factors.

The main study cohort is a synthetic cohort of pregnant WRLHIV, created by applying a set of criteria to routine HIV-test data from the NHLS CDW. This is because there was no marker for pregnancy within the NHLS CDW during the study period. Therefore syphilis screening, based on universal testing coverage at the fANC visit, in association with ward type and/or post-pregnancy cervical screening and/or birth HIV test and/or positive β-hCG was used as a proxy for pregnancy (inclusion criteria).[57] It is anticipated that the inclusion criteria were highly specific and excluded non-pregnant and some pregnant WRLHIV. This potentially explains the lower numbers of pregnant WRLHIV in the study cohort when compared to reported figures from the DHIS.[57] However, the provincial distribution of pregnant WRLHIV in the study cohort was similar to DHIS.[57] In addition, the ratio of ART-experienced versus ART-naïve WRLHIV at the fANC visit was 1:1 in the synthetic cohort, whilst it was reported at 3.2 by the end of 2017 according to DHIS. This difference may be attributable to the fact that the synthetic cohort was enrolled earlier in time (start of UTT) and focused on specificity for pregnancy. However, findings from the study cohort concurred with reports from similar studies, which enrolled known pregnant or postpartum WRLHIV.[58] This suggested representativity of pregnant WRLHIV in South Africa by the study cohort.

Longitudinal record linkage within the NHLS CDW relies on probabilistic matching of patient demographics due to lack of a unique identifier. This may compromise record linkage, especially where there is inconsistent documentation of patient demographics. Pregnant WRLHIV in South Africa are a mobile population and the fragmentation of ante- and postpartum HIV care forces women to access care at different facilities, sometimes in different provinces.[59] In cases where demographics are not captured consistently, historical records of care cannot be linked. Thus, maternal VL suppression rates may have been under-estimated in this study due to suboptimal record linkage within the NHLS CDW. A previous validation of the performance of the NHLS CDW patient-linking algorithm against a gold standard dataset of adult ART patients yielded good results.[32,60] However, the algorithm has not been validated for pregnant WRLHIV. Furthermore, the NHLS CDW is not a clinical database. This meant

that clinical data that were relevant to the study were not available. For example, information on maternal ART start dates and antiretroviral (ARV) regimens were not available to the study to evaluate impact of ART duration on maternal VL suppression. However, >95% ART coverage in the public health sector implies that the majority of women would have received ART at fANC visit.

Maternal VL testing coverage was low during the study period. As a result, testing may have been biased to women with high VL during follow up. This may also explain why women with unsuppressed VL during pregnancy tended to have unsuppressed VL at delivery or during the postpartum period. In the case of this bias being substantial, these findings may have under-estimated rates of VL suppression. However, the fact that study findings concur with reports from other studies on similar work, suggests that study data were representative of VL outcomes of pregnant and postpartum WRLHIV.

8.4 Implications for policy and next steps

This study has succeeded in providing a baseline for maternal VL suppression rates during pregnancy, delivery and the postpartum period, nationally and sub-nationally. Overall, rates of maternal VL suppression were low during the study period in spite of high ART coverage. Findings suggest that the programme needs to focus efforts on achieving maternal VL suppression to achieve eMTCT. The study identified sub-national programmes with high maternal viraemia and those achieving VL suppression. Next steps need to investigate reasons for suboptimal performance in Limpopo, Gauteng and Mpumalanga provinces, whilst acknowledging that rates of VL suppression may have changed subsequent to 2017.

The synthetic cohort utilized in this study is amongst the first cohorts to provide a longitudinal description of maternal viraemia during pregnancy, delivery and postpartum nationally. Currently there is no national cohort of pregnant WLHIV to monitor and measure impact of PMTCT policy in South Africa, when the country has the largest PMTCT programme globally. Historically, surveys and more localized studies have been utilized to serve this purpose. However, surveys are costly and time consuming while localized studies limit generalizability of their findings to other populations.[61] With this study, algorithms and methodology utilized in the creation of the synthetic cohort, can be further refined to guide creation of a national cohort from routine laboratory data for on-going review of the programme as well as linking mother infant pairs for longitudinal surveillance. In addition, the use of a unique patient identifier would allow the laboratory database access to the PMTCT module in Tier.net for maternal clinical data such as ART start dates, ART regimens, comorbidities and information on drug resistance. Tier.net is an electronic patient management system for people living

with HIV, accessing care in the public health sector.[62] Tier.net belongs to the South African National Department of Health and does not yet provide national coverage. The system relies on data being captured at health care facility level during patient visits.

The PMTCT guidelines of 2019 have made provision for routine, national surveillance of maternal VL during pregnancy, delivery and postpartum by introducing EGK codes to identify maternal VL testing at these time points within the NHLS.[14] Health care providers are required to capture two codes, C#PMTCT or C#DELIVERY on standard laboratory requisition forms for specimens belonging to pregnant WLHIV, submitted for processing by the NHLS. The C#DELIVERY code indicates VL testing at time of delivery. The C#PMTCT identifies VL testing during the antenatal or postnatal period. A pregnant WLHIV without a previous C#PMTCT code during her current pregnancy is assumed to be receiving an ANC VL test, while patient records with subsequent C#PMTCT codes following a C#DELIVERY code represent VL testing postnatally. Currently, the study methodology is being applied to the development of routine surveillance reports for near real-time monitoring of maternal VL suppression rates amongst pregnant, delivering and postpartum WLHIV within the NHLS CDW. The reports use maternal HIV VL EGK codes and ward type (labour, delivery or postnatal) to demonstrate VL suppression by geographic location (Appendix 8.1). Overall, this study highlights the utility of the NHLS CDW as a cost-effective and robust surveillance system for near real-time monitoring of maternal viraemia towards eMTCT. This surveillance system provides coverage at all sub-national levels, without any surveillance fieldwork except for writing the EGK codes on the laboratory requisition forms.

8.5 Summary of key recommendations

1. **Improve VL monitoring among pregnant and postpartum WRLHIV**

- Educate and train health care providers on provisions and implementation of PMTCT guidelines specifically the correct use of maternal VL EGK codes and HIV VL Results for Action reports to identify pregnant women with high VL requiring clinical action
- Improve systems for tracking pregnant and postpartum WLHIV for effective longitudinal monitoring by utilizing unique patient identifiers
- Integrate targeted PoC VL testing in routine settings
- Create demand for VL testing during pregnancy and postpartum by educating women in communities on the importance and implications of VL testing such as educational programmes offered by the Treatment Action Campaign[63]

- Investigate whether all factors during pregnancy that cause suboptimal VL suppression in our local setting have been identified and intervene where possible

2. **Improve case management of pregnant and postpartum WRLHIV to improve VL suppression rates**

- Maternal HIV testing to be provided at every contact with the health system to facilitate early ART initiation
- Consider elective caesarean deliveries in WLHIV with high VL at time of delivery
- Engage community health care workers to allow for individualized care
- Provide on-going support throughout pregnancy and postpartum periods (peer-mentor mothers), particularly for younger mothers

3. **Prioritize HIV prevention among all women of reproductive age to lower maternal seroprevalence**

- Scale up family planning services, particularly in geographic areas with high a burden of women of reproductive age
- Scale up PreP for all youth and other women of reproductive age
- Invest in school based sexual reproductive health programmes to lower maternal seroprevalence in future which is critical for eMTCT

8.6 Conclusion

Despite near-universal PMTCT service coverage, maternal VL suppression rates during pregnancy, delivery and postpartum were suboptimal during the study period in South Africa. Closer VL monitoring and improved case management throughout pregnancy, delivery and postpartum are required to improve maternal VL suppression. Training on and implementation of the 2019 national guidelines with respect to maternal VL monitoring requires attention. Further investigation on how to improve VL suppression during pregnancy and the postpartum period in comparison to VL suppression in non-pregnant WRLHIV is warranted.

Maternal viraemia during the postnatal period, geographic areas with high maternal seroprevalence, women initiating ART late in pregnancy and/or incident maternal HIV during pregnancy require extra attention to prevent vertical transmission. School sexual and reproductive health programs are vital to reduce maternal seroprevalence and unintended pregnancies in the long term. Community awareness to create a demand for maternal VL monitoring and early antenatal clinic booking needs to be created. The PMTCT programme can leverage the community health care worker and mentor-mother programmes for closer management of all pregnant and postpartum WRLHIV to achieve VL suppression to levels required for eMTCT. Findings from this research have informed the development

of routine surveillance reports for near real-time monitoring of VL suppression rates among pregnant WLHIV from the NHLS CDW for measuring progress to eMTCT and the UNAIDS 90-90-90 targets.

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APPENDICES

Appendix 2.1: Approval to access National Health Laboratory Service (NHLS) data

NATIONAL HEALTH LABORATORY SERVICE

Academic Affairs and Research
Modderfontein Road, Sandringham, 2031
Tel: +27 (0)11 386 6142
Fax: +27 (0)11 386 6296
Email: babatyi.kgokong@nhls.ac.za
Web: www.nhls.ac.za

09 October 2019

Applicant: Faith Moyo
Institution: National Institute for Communicable Diseases
Department: CHIVSTI
Email: faithmo@nicd.ac.za
Tel: 011 555 0467 **Cell:** 084 596 3622

CC: Gayle Sherman – Pathologist
National Institute for Communicable Diseases

Re: Approval to access National Health Laboratory Service (NHLS) Data

Your application to undertake the research project titled **"A national-level evaluation of viral load outcomes of HIV-infected pregnant women: closing the gaps towards eliminating mother-to-child transmission of HIV in South Africa"** using data from the NHLS database has been reviewed. This letter serves to advise that the application has been approved and the required data will be prepared and made available to you by the NHLS Corporate Data Warehouse.

Please note that approval is granted on condition that you conduct the research in accordance with the NHLS conditions of service and additional conditions listed below:

- Processes are discussed with the relevant NHLS departments (i.e. Information Management Unit and Operations Office) and are agreed upon.
- Confidentiality is maintained at participant and institutional level and there is no disclosure of personal information or confidential information as described by the NHLS policy.
- NHLS Data cannot be used to track patients as no pre-approval/consent is obtained from Patients.
- CDW form is to be completed for the request with clear indications of the data required.
- All data requested should be in accordance with the research protocol submitted and approved by the relevant Ethics Committee.
- The NHLS must be acknowledged as a source of data in the research protocol approved by Ethics and any outputs emanating from research.
- A final report of the research study and any published manuscript(s) resulting from this study are submitted and addressed to the NHLS Academic Affairs and Research office and the NHLS has been acknowledged appropriately.
- Prof. Gayle Sherman is noted as NHLS collaborator for this research.

Please note that this letter constitutes approval by the NHLS Academic Affairs and Research Office. Any data related queries may be directed to NHLS Corporate Data Warehouse, contact number: 011 386 6074 email: zarina.sabat@nhls.ac.za

pp

Dr Babatyi Malope-Kgokong
National Manager: Academic Affairs and Research

Appendix 2.2: Wits HREC Ethics clearance certificate 1

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Miss Faith Moyo

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180854

NAME: (Principal Investigator)	Miss Faith Moyo
DEPARTMENT:	Public Health National Institute for Communicable Diseases
PROJECT TITLE:	A national-level evaluation of viral load outcomes of HIV-infected pregnant women: Closing the gaps towards eliminating mother-to-child transmission of HIV in South Africa
DATE CONSIDERED:	31/08/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof G Sherman and Dr T Kufa-Chakezha
APPROVED BY:	Doctor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	19/11/2018

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

DECLARATION OF INVESTIGATORS

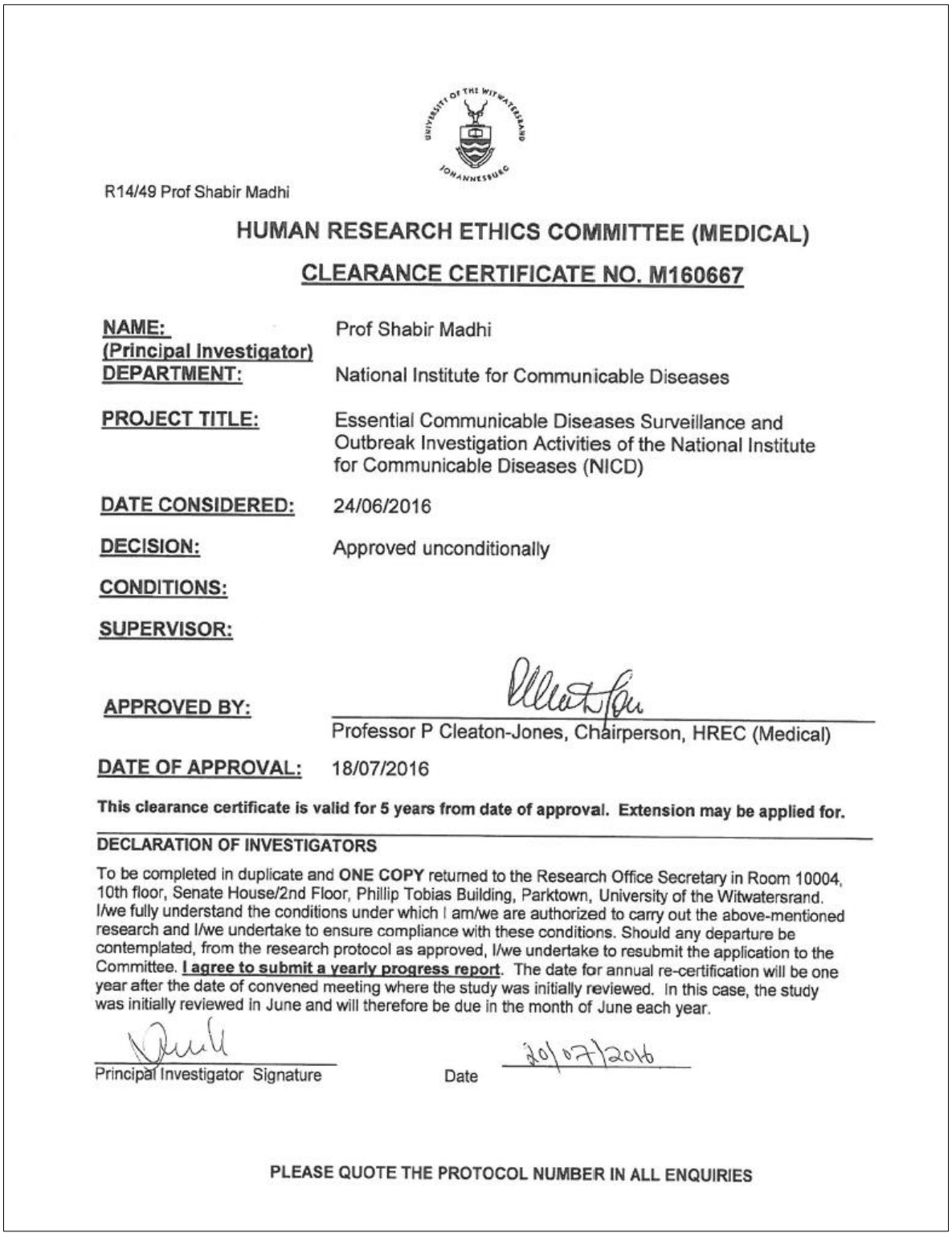
To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are 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**. 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 in **August** and will therefore be due in the month of **August** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

16/11/2018
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 3.1: Wits HREC Ethics clearance certificate 2*



R14/49 Prof Shabir Madhi

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160667

NAME: (Principal Investigator)	Prof Shabir Madhi
DEPARTMENT:	National Institute for Communicable Diseases
PROJECT TITLE:	Essential Communicable Diseases Surveillance and Outbreak Investigation Activities of the National Institute for Communicable Diseases (NICD)
DATE CONSIDERED:	24/06/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	18/07/2016

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004, 10th floor, Senate House/2nd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. 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**. 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 in June and will therefore be due in the month of June each year.

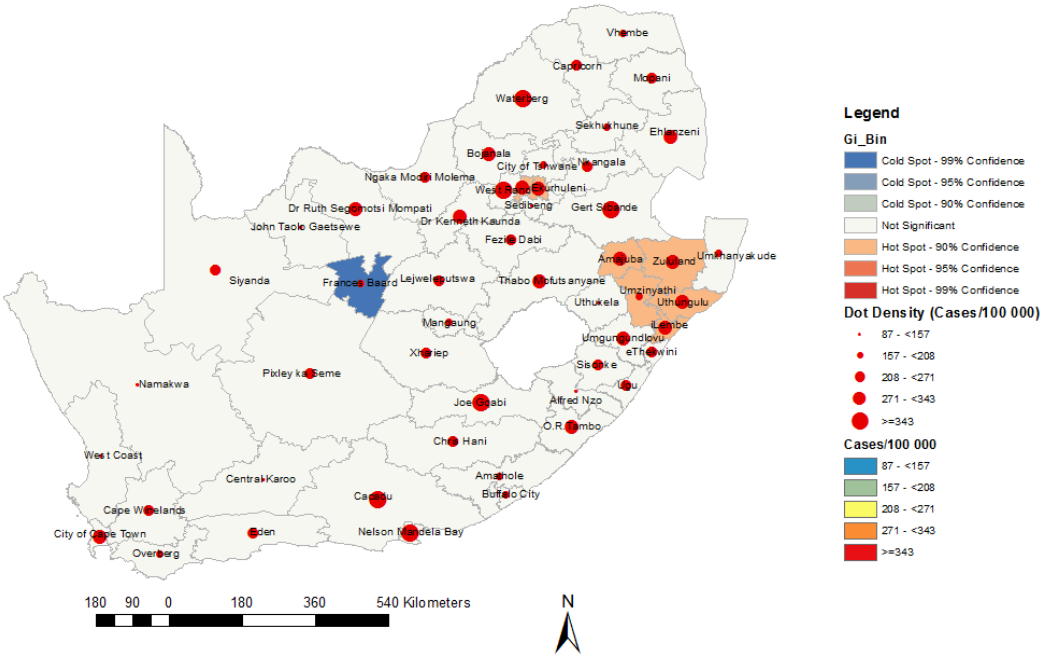
Principal Investigator Signature

Date 20/07/2016

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

*Ethical clearance issued to the NICD which waives the requirement for patient consent for studies which audit routine programmatic data from the national HIV surveillance programme, that is, access to routinely collected HIV PCR data utilized in Chapter 3.

Appendix 3.2: Showing Optimized hot spot analysis of intra-uterine case rate per 100 000 by district in South Africa, 2018.



Appendix 3.3: 95% Confidence Intervals by indicator: Thembisa Model

Province	Total Population		Number of live births		Number of live births to HIV-positive women		HIV prevalence in females 15-49 years		HIV prevalence in females 15-24 years		HIV prevalence in pregnant females	
	LL	UL	LL	UL	LL	UL	LL	UL	LL	UL	LL	UL
EC	6 480 370	6 712 180	124 781	127 933	25 712	29 088	23,8%	27,1%	9,3%	12,0%	20,6%	23,8%
FS	2 838 470	2 922 610	57 221	582 44	12 702	14 289	26,0%	29,2%	9,9%	12,6%	22,2%	25,2%
GP	14 754 600	15 161 000	278 769	282 459	50 225	59 785	21,8%	24,8%	8,1%	11,2%	17,9%	21,5%
KZN	11 088 400	11 401 000	229 482	233 967	66 499	73 702	33,2%	36,7%	13,5%	17,0%	28,9%	32,4%
LP	5 717 500	5 880 160	138 928	141 966	17 473	22 264	16,3%	20,3%	4,6%	7,3%	12,6%	16,4%
MP	4 598 630	4 720 100	94 039	95 800	22 862	26 608	27,8%	31,4%	11,3%	15,2%	24,4%	28,6%
NC	1 147 180	1 164 990	25 331	25 565	2 733	3 292	13,1%	15,3%	4,4%	6,1%	10,9%	13,2%
NW	3 864 190	3 978 380	76 049	77 400	16 080	18 139	24,6%	27,5%	10,6%	13,2%	21,1%	24,1%
WC	6 742 130	6 867 980	121 150	122 736	11 184	17 313	10,4%	16,0%	3,6%	6,9%	9,2%	14,4%
RSA	**57 546 600**	**58 766 100**	**1 158 300**	**1 173 860**	**239 664**	**262 159**	**23,8%**	**25,7%**	**9,9%**	**12,1%**	**20,7%**	**22,8%**

Abbreviations: EC Eastern Cape; FS Free State; GP Gauteng Province; KZN KwaZulu-Natal; LP Limpopo Province; MP Mpumalanga Province; NC Northern Cape; NW North West; WC Western Cape; RSA South Africa; LL lower limit; UP Upper limit.

Appendix 4.1: The geographic distribution of priority population groups for the elimination of mother-to-child transmission of HIV in South Africa

PLOS ONE

RESEARCH ARTICLE

The geographic distribution of priority population groups for the elimination of mother-to-child transmission of HIV in South Africa

Faith Moyo[1,2,3]*, **Ahmad Haeri Mazanderani**[1,4], **Tendesayi Kufa**[1,2], **Gayle G. Sherman**[1,3,5]

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OPEN ACCESS

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Competing interests: Authors declare no competing interests. Paediatric HIV Diagnostics is not a commercial company; it is a division of Wits Health Consortium(WHC), which is wholly-owned by the University of the Witwatersrand where authors FM and GGS are employed. Authors did not receive any additional funding from any commercial company other than funds received from the ELMA Foundation which have been declared already in the initial submission.

Abstract

Background

Women of reproductive age living with HIV (WRLHIV), HIV-positive pregnant women, adolescent girls and young women (AGYW) are key populations for eliminating mother-to-child of HIV (eMTCT) in South Africa. We describe the geographical distribution of WRLHIV, their pregnant counterparts and AGYW for risk-adjusted allocation of eMTCT interventions.

Methods

For the year 2018, we triangulated data from the Thembisa Model with five routine HIV-related and demographic data sources to determine the distribution of WRLHIV (15–49 years) and AGYW (15–24 years) nationally and by province. Data analysed included total population estimates, number of live-births, live-births to HIV-positive women, age-specific HIV prevalence rates, intrauterine (IU)-transmission rates and IU-case rates/100 000 live-births. IU-transmission rates and IU-case rates were calculated from de-duplicated routine HIV test-data for neonates (aged <7days). Data de-duplication was achieved by a patient-linking algorithm that uses probabilistic matching of demographics (name, surname, date of birth), supplemented by manual matching to account for spelling errors.

Results

There were 58 million people in South Africa in 2018. Females (all ages) constituted 51% of the population. Women of reproductive age constituted 27% and AGYW constituted 8% of the total population. WRLHIV, AGYW living with HIV and HIV-positive pregnant women accounted for 7%, 0.8% and 0.4% of the total population respectively. Gauteng was the most populous province followed by KwaZulu-Natal, with Western Cape and Eastern Cape in third and fourth positions. The distribution of WRLHIV and AGYW followed a similar trend. However, Mpumalanga and Limpopo provinces had higher proportions of WRLHIV and AGYW living with HIV ahead of Western Cape. KwaZulu-Natal had the highest number of live-births to HIV-positive women. The national IU-transmission rate of <1% translated into 241 cases/100 000. While provincial IU-case rates were fairly similar at 179–325, districts IU-case rates varied, ranging from 87–415 cases/100 000 live-births.

Conclusion

Findings suggest that the need for eMTCT interventions is greatest in Gauteng, KwaZulu-Natal, Western Cape and Eastern Cape. Limpopo and Mpumalanga provinces may require more HIV prevention and family planning services because of high fertility rates, high number of WRLHIV and AGYW living with HIV. eMTCT will require robust viral load monitoring among WRLHIV, pregnant and breastfeeding women. The national laboratory database can provide this service near-real time.

Introduction

Women constitute the highest proportion of people living with HIV globally [1]. In South Africa, the HIV epidemic also disproportionately affects women. In 2017, approximately two thirds of people living with HIV, aged 15–49 years and on antiretroviral therapy (ART), were female [2]. In the same year, disparities in HIV prevalence by sex were most pronounced among young adults. HIV prevalence among 20–24 year olds was three times higher in females (15.6%) compared to males (4.8%) [2]. Potential reasons for gender disparities in the profile of the HIV epidemic are both economic and sociocultural [3]. Extensive geospatial heterogeneity in the distribution of the HIV epidemic has been reported previously [4]. In 2018, provincial HIV prevalence estimates among people living with HIV aged 15–49 years ranged from 6.7% in the Western Cape to 18.4% in KwaZulu-Natal [4]. While poorly understood, variations in provincial HIV prevalence rates have been linked to differences in the uptake of HIV prevention interventions and societal norms between provinces [4]. Thus, provincial variations in the profile of the HIV epidemic necessitate optimized allocation of resources and targeted interventions for HIV/AIDS programmes. This is particularly pertinent for the prevention of mother-to-child transmission of HIV (PMTCT) programme, which has prioritized the elimination of mother-to-child transmission of HIV (eMTCT). The national MTCT rate of 1.0% at birth in 2017 equalled just under 250 cases per 100 000 live births [5]. However, this figure was five times higher than the World Health Organization (WHO) eMTCT target, defined as ≤50 cases per 100 000 live births at completion of breastfeeding and an overall mother-to-child transmission (MTCT) rate of <5% in breastfeeding populations [5]. Sub-national level variations in MTCT rates also exist, with some districts reporting almost double the national MTCT rate at birth [6]. This suggests the need for contextualized and tailored responses to maternal and paediatric HIV in South Africa.

We describe the distribution of women of reproductive age (15–49 years) living with HIV (WLHIV) as well as those without HIV by province in South Africa, in order to identify areas that may require additional eMTCT interventions. These may include interventions aimed at reducing the risk of HIV acquisition by women of reproductive age and unplanned pregnancies among WRLHIV (pillars 1–2 of the South African PMTCT strategy) [7]. Women of

reproductive age living with HIV and sub-groups (adolescent girls and young women (AGYW) aged 15–24 years) are priority populations for achieving eMTCT. These women can potentially fall pregnant and transmit HIV to their infants. While the risk of vertical transmission of HIV is low in planned pregnancies, where WRLHIV fully access and utilize preconception and post conception PMTCT services, the contrary is true for unplanned pregnancies [8]. Pregnancies are more likely to be unplanned in AGYW compared to older women [9]. In addition, AGYW represent a sub-population that will remain in the reproductive age group for the longest time; are associated with high incident infections and where HIV positive, AGYW have poorer PMTCT outcomes compared to older WRLHIV [9]. Therefore, the risk of MTCT is higher in this population. However, an increase in number of women conceiving on ART is anticipated with the scale up of the universal test and treat strategy [10]. Consequently, understanding where WRLHIV, including AGYW (regardless of their HIV status) and those who are pregnant, are located in South Africa is key for eMTCT. Scaling up family planning services and ART/PMTCT services (for example, stock planning of Efavirenz based regimens and Dolutegravir rollout in relation to new ART guidelines) in geographic areas with a high burden of these groups may be beneficial for maternal HIV care and eMTCT.

Obtaining accurate estimates of vertical transmission is challenging in South Africa because of the lack of a unique patient identifier in the health system. Monitoring of early infant MTCT rates and coverage of early infant diagnosis currently relies on routine data from the District Health Information System (DHIS) and the National Health Laboratory Service (NHLS) [11]. There are no accurate, national data sources for postnatal transmission rates, breastfeeding practices, maternal virological control during pregnancy and the postpartum period. An analysis of current data sources used for tracking eMTCT, their strengths and weakness, are described elsewhere by Sherman et al [11]. Using six different data sources, we describe the distribution of WRLHIV in South Africa during 2018 in relation to where the intra-uterine transmissions occur.

Materials and methods

Data for these analyses were extracted from six independent data sources for HIV-related and demographic indicators from the public health sector in South Africa. These were the Thembisa Model, DHIS, Statistics South Africa (Stats SA), the South African National HIV Prevalence, Incidence, Behaviour and Communication Survey (SABSSM), the National Antenatal Sentinel HIV & Syphilis Survey Report, (herein referred to as the ANC sero-prevalence survey) and the National Institute for Communicable Diseases' Surveillance Data Warehouse (NICD SDW), a division of the NHLS. The Thembisa Model was used as the primary data source because it had most of the indicators required for the analyses. The other sources were used for triangulation purposes where applicable. The reporting period was the year 2018. Where data for 2018 was not available, available data from the most recent year were used. A brief description of each data source and indicators that were used for the analyses follows (Table 1).

1. Description of data sources

a) Thembisa Model. The Thembisa Model is an integrated epidemiological and demographic mathematical model developed to describe the South African HIV epidemic and to evaluate the impact of HIV prevention and treatment strategies [12]. The model also provides demographic statistics and is used to evaluate the demographic impact of HIV in South Africa [12]. The model provides data at national and provincial level. Data were obtained from Thembisa 4.1, published in 2018.

Table 1. Indicators used in the analyses by data sources.

Indicators	Data Sources					
	Thembisa Model	Stats SA	DHIS	ANC sero-prevalence survey	SABSSM	NICD SDW
Total Population estimates (males and females, all ages)	✓	✓				
Total Population for females (All ages)	✓	✓				
Total Population for females 15–49 years	✓	✓				
Total Population for females 15–24 years	✓	✓				
Number of live births	✓	✓	✓			
Total births to HIV-positive women	✓		✓			
HIV prevalence in females 15–49 years	✓					
HIV prevalence in females 15–24 years	✓					
HIV prevalence in pregnant females 15–49 years				✓		
HIV prevalence in pregnant females	✓					
HIV prevalence in adults 15–49 years	✓	✓			✓	
HIV PCR tests at age <7 days (Birth HIV PCR)						✓
Total fertility rate	✓	✓				
Reporting Unit	National Province	National Province	National Province District Sub-district Facility	National Province District	National*	National Province District Sub-district Facility
Year for which data was available	2018	2018	2018	2017	2017	2018

Abbreviations: Stats SA Statistics South Africa; DHIS Demographic Health Information System; PCR polymerase chain reaction; ANC antenatal care; NICD National Institute for Communicable Diseases SDW Surveillance Data Warehouse; SABSSM South African National HIV Prevalence, Incidence, Behaviour and Communication Survey.

*Data available at national level only at time of publication. Blocked out areas indicate absence of data for a specific indicator per data source.

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b) DHIS. The DHIS collects aggregated data on health services provided by all health facilities in the public sector in South Africa since 2001. The data are collected from paper-based registers at facility level then entered electronically onto the DHIS software for collation at sub-district, district, provincial and national level on a monthly basis [13]. In some facilities, the data is collected from Tier.net, a national electronic HIV register for aggregation onto DHIS.

c) STATS SA statistical release P0302 and P0305. The P0302 document provides data on mid-year population estimates for South Africa and the nine provinces on an annual basis. The projections are based on the cohort component method for population estimation which has been described elsewhere [14]. The population estimates approximate the actual population as at 1 July of a given year. The P0305 document provides data on recorded live births in the public sector in South Africa. The data are based on births registered in the national birth registry system, which is collated and maintained by the Department of Home Affairs in South Africa. The latest P0302 and P0305 documents were released in 2018 [14–15] at the time of writing.

d) National antenatal sentinel HIV & syphilis survey report (ANC sero-prevalence survey). South Africa has been conducting the ANC sero-prevalence survey annually to monitor

HIV & syphilis prevalence among pregnant women aged 15–49 years, attending antenatal clinics since the 1990s [16]. The survey is cross sectional by design and is conducted across the 52 health districts in South Africa. Sentinel sites are randomly selected from public sector facilities across the country using probability proportional to size sampling methods [10]. The most recent report for the 2017 survey was published in 2019 [10].

e) SABSSM survey. The SABSSM is a population based, cross sectional survey of all households in South Africa that evaluates trends in HIV prevalence and other health indicators related to HIV across the country. The surveys are conducted every five years. At the time of writing, only an executive summary of findings from the latest 2017 survey was available [2].

f) National Institute for Communicable Diseases (NICD) Surveillance Data Warehouse (SDW). All pathology tests performed in the public sector are processed by the National Health Laboratory Service through a network of about 260 laboratories across South Africa [17]. A single Laboratory Information System (LIS) used by all laboratories stores data pertaining to test specimens (viz. patient identifiers, clinical and geographic information). These data are archived in near real-time in a central data repository called the Surveillance Data Warehouse (SDW) of the NICD within the NHLS.

2. Data management and analysis

The distribution of WRLHIV and AGYW for the year 2018 was described with respect to the following:

a) Total population estimation. Total population estimates were extracted from the Thembisa Model and Stats SA to describe: i) overall population ii) total population of women of all ages and ii) total population of WRLHIV (15–49 years) and iii) total population of AGYW (15–24 years) and iv) total population of AGYW living with HIV nationally and by province.

b) Number of live births. The number of births (Thembisa Model), number of live births at a facility (DHIS) and number of registered live births from Stats SA were extracted nationally and by province and used to describe child-birth patterns by geographic location.

c) Number of WRLHIV. In order to estimate the number of WRLHIV in South Africa, the total population estimates for women aged 15–49 years were multiplied by the mean HIV prevalence rate amongst women aged 15–49 years. To estimate number of pregnant WRLHIV, total births to HIV-positive women were extracted from the Thembisa Model. For comparison, number of live births from Stats SA were multiplied by the HIV prevalence rate amongst pregnant women aged 15–49 years obtained from the ANC sero-prevalence survey.

d) Number of HIV-positive AGYW. The number of AGYW living with HIV were calculated by multiplying the total population of AGYW by the prevalence of HIV in females aged 15–24 years obtained from the Thembisa Model.

e) Number of live births to women living with HIV. The indicators used to provide these data were obtained from the Thembisa Model and compared to i) number of live births to women living with HIV (DHIS), number of HIV-exposed infants (obtained by multiplying the number of registered live births from Stats SA by the HIV prevalence estimates from the ANC sero-prevalence survey) and iii) number of HIV PCR tests performed among neonates aged <7 days from the NICD SDW, considering that birth testing coverage for HIV-exposed neonates is >95%. These data were also used as a proxy for number of HIV-positive, pregnant women as explained in 2c.

f) Intra-uterine transmission rates. These were calculated as the number of de-duplicated HIV PCR positive tests performed at birth (<7 days of life) divided by total HIV PCR tests performed at birth expressed as a percentage from the NICD SDW. The number of intra-uterine infections per 100 000 live births was also reported (intra-uterine case rates). Test data for HIV PCR positive neonates were de-duplicated by a patient-linking algorithm that uses probabilistic matching of demographics (for example name, surname, date of birth) supplemented by manual matching to account for spelling errors. Because of availability of data, intra-uterine transmission rates were also calculated to district level. Intra-partum and postnatal case rates could not be accurately calculated from the SDW because of the lack of a unique identifier to allow for longitudinal monitoring.

Ethics clearance

Part of this work utilized routinely collected surveillance data for HIV programs under ethical clearance issued to the NICD (M160 667) by the Human Research Ethics Committee (HREC) of the University of the Witwatersrand. This clearance waives the requirement for patient consent for studies conducted by the NICD, which audit routine programmatic data from the national HIV surveillance programme. Patient identity was protected by anonymizing the data prior to analysis.

Results

There were approximately 58 million people in South Africa in 2018 with half of the population (51%) being female (Fig 1). Women of reproductive age constituted 27% of the total population, while WRLHIV (3.8 million) accounted for approximately 7% of the total population. There was a total of 4.7 million (8.1%) AGYW of which 477 798 (10.1%) were living with HIV in South Africa. Gauteng province had the highest number of females (all ages) followed by KwaZulu-Natal (KZN), the Eastern Cape and the Western Cape (Fig 2). The Northern Cape had the lowest number of females during the analysis period. A similar trend was observed for women of reproductive age (Fig 3A) and AGYW (Fig 3B), where 69.5% and 67.9% occurred in the four most populous provinces, respectively. However, the analysis of the geographic distribution of WRLHIV (Fig 3C) and HIV-infected AGYW (Fig 3D) showed that 74.4% and 86.7% respectively, of these women were located in four provinces. The latter comprised three of the four most populous provinces but included Mpumalanga instead of the Western Cape. KwaZulu-Natal and Gauteng provinces recorded the highest numbers of WRLHIV at approximately 1 million each, contributing 53.7% of the total population of WRLHIV in the country followed by the Eastern Cape, Mpumalanga and Limpopo provinces.

Overall, out of approximately 1 million live births in the country; between 250 000–286 000 births occurred to women living with HIV in 2018 (Table 2). Limpopo province had the third highest number of live births in 2018 ahead of the Eastern Cape and Western Cape provinces (Table 2). This was in keeping with Limpopo province having the highest fertility rate throughout the country at (3.1%) (Table 2). KwaZulu-Natal province recorded the highest number of live births to women living with

HIV, followed by Gauteng and the Eastern Cape respectively (Table 2). Similarly, KZN had the highest HIV prevalence rate among pregnant women (S1 Table) followed by Mpumalanga province (S1 Table). The intra-uterine transmission rate for South Africa was 0.8%, translating into 241 cases of HIV-infected neonates per 100 000 live births (Table 2). Provincial intra-uterine transmission rates ranged from 0.6% in KZN to 1.1% in Limpopo province. Districts intra-uterine transmission rates ranged from 0.4% to 1.7% with KZN districts recording intra-uterine transmission rates lower than the national average of 0.8% (Table 3). Provincial intra-uterine case rates were fairly similar and ranged from 179–325 cases per 100 000 live births in the Northen Cape and Mpumalanga respectively. District level intra-uterine case rates had a greater spread, ranging from 87–415 cases per 100 00 live births (Table 3). Overall, the four

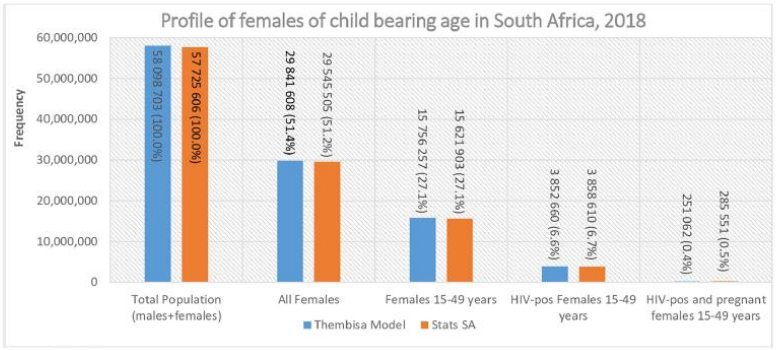

Fig 1. Profile of females of reproductive age in South Africa in 2018. Abbreviation: Stats SA Statistics South Africa.

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provinces with the most WRLHIV yielded 1 417 (65.5%) of all intra-uterine infections in 2018. In addition, Limpopo's intra-uterine infections contributed a further 264 (12.2%). Therefore focussing eMTCT efforts in five provinces has the potential to reduce 1 681 (77.8%) of all intra-uterine infections per annum, nationally.

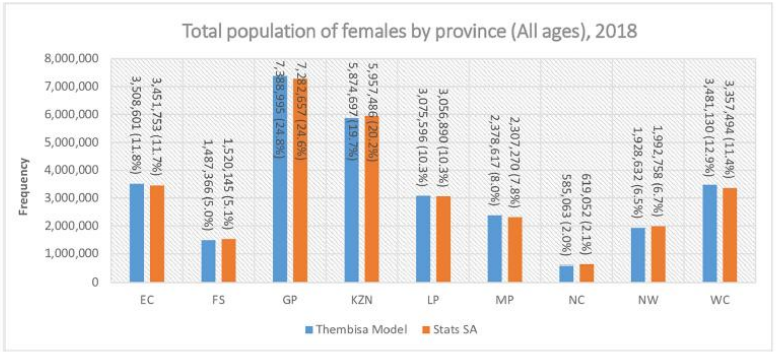

Fig 2. Population density of females by province in South Africa, 2018. Abbreviations: EC Eastern Cape, FS Free State, GP Gauteng Province, KZN KwaZulu-Natal, LP Limpopo Province, NC Northern Cape, NW North West, WC Western Cape, Stats SA Statistics South Africa.

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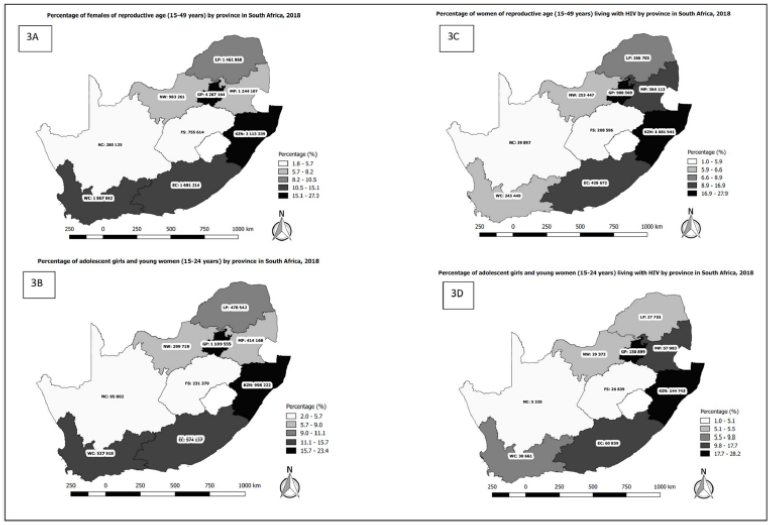

Fig 3. Provincial distribution of percentages of: 3A) females of reproductive age 3B) adolescent girls and young women 3C) women of reproductive age living with HIV 3D) adolescent girls and young women living with HIV in South Africa, 2018. **Source**: Thembisa Model 4.1. **Abbreviations**: EC Eastern Cape, FS Free State, GP Gauteng Province, KZN KwaZulu-Natal, LP Limpopo Province, NC Northern Cape, NW North West, WC Western Cape.

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Discussion

In 2018, South Africa's population of 58 million people was evenly distributed between males and females. Gauteng province had the highest number of females, accommodating a quarter of the total population of females (all ages). The majority of all women, 20 253 423 (68%), and women of reproductive age, 10 958 758 (70%), were located in the densely populated provinces; that is Gauteng, KwaZulu-Natal, Western Cape and Eastern Cape provinces ("the big four"). Although the distribution of WRLHIV followed a similar trend, Mpumalanga and Limpopo had the fourth [364 113 (10%)] and fifth, [266 705 (7%)] highest number of WRLHIV ahead of the Western Cape. Adolescents and young women were also mostly located in the big four provinces, 3 219 832 (68%). Ten percent (477 798) of all AGYW were living with HIV in South Africa in 2018. Gauteng, KwaZulu-Natal, Eastern Cape and Mpumalanga, had the highest percentage of AGYW living with HIV at 32%, 30%, 13% and 12% respectively. Although the national intra-uterine transmission rate was <1.0%, 241 per 100 000 neonates acquired HIV from their mothers in 2018 at birth. Mpumalanga, North West and KwaZulu-Natal had intra-uterine case rates that were above the national average at 325, 283 and 254 cases per 100 000 live births. Districts intra-uterine case rates varied greatly and ranged from as low as 87–

Table 2. Number of live births (total), number of live births to women living with HIV and intra-uterine transmission rates by province in South Africa, 2018.

Province	Total Population	Number of Live births (Total)			Live births to women living with HIV				Fertility rates		HIV PCR positive (<7 days)	IU transmission rate	IU Case rate/ 100 000
	Thembisa Model	Thembisa Model	Stats SA	DHIS	Thembisa Model	Stats SA	DHIS	NICD SDW	(Stats SA)	Thembisa Model	NICD SDW		
EC	6 593 566 (11.3%)	126 530 (10.8%)	105 796 (11.4%)	104 016 (11.0%)	27 448 (10.9%)	31 950 (11.9%)	32 164 (11.2%)	31 316 (11.7%)	2,8%	2,5%	248	0,8%	238
FS	2 875 955 (5.0%)	57 744 (5.0%)	47 306 (5.1%)	47 062 (5.0%)	13 553 (5.4%)	14 097 (5.3%)	14 386 (4.9%)	14 963 (5.6%)	2,6%	2,5%	106	0,7%	225
GP	14 931 713 (25.7%)	280 597 (24.1%)	205 612 (22.2%)	219 958 (23.2%)	54 976 (21.9%)	62 095 (20.6%)	55 497 (21.7%)	56 340 (21.0%)	1,9%	2,0%	471	0,8%	235
KZN	11 214 103 (19.3%)	231 742 (19.9%)	190 923 (20.6%)	195 292 (20.6%)	70 126 27.9%)	84 770 (29.2%)	78 662 (29,7%)	75 195 (28.1%)	2,6%	2,3%	453	0,6%	254
LP	5 794 578 (10.0%)	140 604 (12.1%)	123 414 (13.3%)	122 932 (13.0%)	19 885 (7.9%)	26 781 (9.4%)	25 265 (9.4%)	24 978 (9.3%)	3,1%	3,1%	264	1,1%	227
MP	4 650 305 (8.0%)	94 957 (8.1%)	77 353 (8.3%)	79 669 (8.4%)	24 708 (9.8%)	26 996 (9.8%)	26 558 (9.5%)	26 350 (9.8%)	2,7%	2,4%	245	0,9%	325
NW	3 914 669 (6.7%)	76 700 (6.6%)	55 094 (5.9%)	58 097 (6.1%)	17 119 (6.8%)	16 087 (5.8%)	15 746 (5.6%)	16 353 (6.1%)	2,7%	2,9%	157	1,0%	283
NC	1 154 340 (2.0%)	25 451 (2.2%)	24 195 (2.6%)	21 549 (2.3%)	3 024 (1.2%)	4 597 (1.5%)	3 970 (1.6%)	4 192 (1.6%)	2,6%	2,5%	42	1,0%	179
WC	6 809 913 (11.7%)	122 076 (10.5%)	97 298 (10.5%)	98 535 (10.4%)	14 389 (5.7%)	18 389 (6.5%)	17 395 (6.4%)	18 198 (6.8%)	2,0%	2,1%	176	1,0%	183
RSA	**58 098 703**	**1 166 440**	**927 113**	**947 110**	**251 062**	**285 551**	**269 643**	**267 887**	**2,4%**	**2,4%**	**2 162**	**0,8%**	**241**

Abbreviations: EC Eastern Cape; FS Free State; GP Gauteng Province; KZN KwaZulu-Natal; LP Limpopo Province; MP Mpumalanga Province; NC Northern Cape; NW North West; WC Western Cape; RSA South Africa; Stats SA Statistics South Africa; DHIS District Health Information System; NICD National Institute for Communicable Diseases' Surveillance Data Warehouse

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415 cases per 100 000 live births. However, even districts with the lowest intra-uterine transmission rate at birth, still had case rates higher than the eMTCT target without taking infections after birth into account.

Based on the demographic profiles of provinces, findings of these analyses suggest disparities in the need for eMTCT interventions. In this last mile to eMTCT, it may be worthwhile strengthening interventions in provinces that have the largest numbers of WRLHIV (north eastern parts of the country) as well as those regions with the highest intra-uterine transmission rates and intra-uterine case rates while maintaining current levels of support elsewhere. Although early transmission rates are below the eMTCT target of <5%, South Africa is not positioned to achieve eMTCT case rate targets because of the extremely high maternal HIV seroprevalence [18]. However, the country has a well-established PMTCT programme in place. Closing PMTCT gaps [5] and scaling up sexual and reproductive health for preventing vertical transmission of HIV could represent low hanging fruit. Sexual and reproductive health services should include intensifying family planning and contraception services amongst all women of reproductive age regardless of HIV status and providing pre-exposure prophylaxis to AGYW. As expected, most women & AGYW were situated in the 'big four' provinces. However, we found that the burden of HIV in women and AGYW was also pronounced in Limpopo and Mpumalanga provinces. Limpopo province has the highest fertility rate in the country and a high proportion of AGYW without HIV who may benefit from family planning and pre-exposure prophylaxis initiatives. Mpumalanga also has a significant amount of WRLHIV who may be in need of family planning services. Cross border mobility of pregnant

Table 3. Intra uterine transmission rates and intra uterine case rates per 100 000 live births by geographic location in South Africa, 2018.

Geographic Area	District	ANC prevalence among pregnant women*(ANC seroprevalence survey)	Registered live births per year (Stats SA)	Total PCR <7 days	PCR Positive (<7 days)	IU transmission rate	IU Case rate/100 000
South Africa		**30,8%**	**897750**	**267 887**	**2 162**	**0,8%**	**241**
Eastern Cape	**Total**	**30,2%**	**104325**	**31 316**	**248**	**0,8%**	**238**
Eastern Cape	Alfred Nzo	26,6%	18230	4 171	28	0,7%	154
	Amathole	28,3%	11070	3 092	23	0,7%	208
	Buffalo City Metro	31,2%	17468	4 156	30	0,7%	172
	Chris Hani	31,9%	11178	3 839	22	0,6%	197
	Joe Gqabi	28,3%	2475	1 476	9	0,6%	364
	Nelson Mandela Bay Metro	29,9%	16717	3 717	54	1,5%	323
	O R Tambo	33,3%	21847	9 068	63	0,7%	288
	Sarah Baartman	25,4%	5340	1 797	19	1,1%	356
Free State	**Total**	**29,8%**	**47047**	**14 963**	**106**	**0,7%**	**225**
	Fezile Dabi	26,5%	7353	2 570	15	0,6%	204
	Lejweleputswa	27,3%	9832	3 260	21	0,6%	214
	Mangaung Metro	31,7%	15559	4 475	29	0,6%	186
	Thabo Mofutsanyana	31,0%	12942	4 328	38	0,9%	294
	Xhariep	35,1%	1361	330	3	0,9%	220
Gauteng	**Total**	**30,2%**	**200726**	**56 340**	**471**	**0,8%**	**235**
	City of Johannesburg Metro	29,6%	57855	17 317	165	1,0%	285
	City of Tshwane Metro	25,3%	62923	12 524	109	0,9%	173
	Ekurhuleni Metro	31,6%	57406	17 761	152	0,9%	265
	Sedibeng	34,0%	14835	4 039	17	0,4%	115
	West Rand	35,5%	7707	4 699	28	0,6%	363
KwaZulu-Natal	**Total**	**44,4%**	**178456**	**75 195**	**453**	**0,6%**	**254**
	Amajuba	39,7%	8199	3 303	22	0,7%	268
	eThekwini Metro	46,2%	55992	23 409	139	0,6%	248
	Harry Gwala	39,5%	8371	3 050	18	0,6%	215
	iLembe	44,3%	9170	4 616	27	0,6%	294
	Ugu	45,9%	12595	5 659	31	0,5%	246
	uMgungundlovu	46,2%	14523	7 173	47	0,7%	324
	uMkhanyakude	46,3%	13232	6 067	26	0,4%	196
	Umzinyathi	36,7%	11867	3 640	21	0,6%	177
	uThukela	36,3%	11441	4 577	17	0,4%	149
	uThungulu	45,9%	16894	7 403	55	0,7%	326
	Zululand	48,4%	16172	6 298	50	0,8%	309
Limpopo	**Total**	**21,7%**	**116276**	**24 979**	**264**	**1,1%**	**227**
	Capricorn	21,6%	26133	5 847	61	1,0%	233
	Greater Sekhukhune	22,6%	25747	5 098	50	1,0%	194
	Mopani	24,5%	22170	5 335	53	1,0%	239
	Vhembe	16,8%	30009	4 560	54	1,2%	180
	Waterberg	25,8%	12217	4 139	46	1,1%	377

(*Continued*)

Table 3. (Continued)

Geographic Area	District	ANC prevalence among pregnant women*(ANC seroprevalence survey)	Registered live births per year (Stats SA)	Total PCR <7 days	PCR Positive (<7 days)	IU transmission rate	IU Case rate/100 000
Mpumalanga	**Total**	**34,9%**	**75369**	**26 350**	**245**	**0,9%**	**325**
	Ehlanzeni	38,5%	39407	13 524	128	0,9%	325
	Gert Sibande	38,6%	15886	7 195	66	0,9%	415
	Nkangala	25,1%	20076	5 631	51	0,9%	254
North West	**Total**	**29,2%**	**55392**	**16 353**	**157**	**1,0%**	**283**
	Bojanala Platinum	33,8%	18421	6 299	54	0,9%	293
	Dr Kenneth Kaunda	30,9%	12291	3 618	37	1,0%	301
	Dr Ruth Segomotsi Mompati	22,1%	9182	2 314	24	1,0%	261
	Ngaka Modiri Molema	23,9%	15498	4 122	42	1,0%	271
Northern Cape	**Total**	**19,0%**	**23402**	**4 192**	**42**	**1,0%**	**179**
	Frances Baard	24,3%	8957	1 733	15	0,9%	167
	John Taolo Gaetsewe	21,9%	5162	1 171	7	0,6%	136
	Namakwa	2,9%	1550	113	2	1,8%	129
	Pixley Ka Seme	15,8%	2843	540	7	1,3%	246
	ZF Mgcawu	14,5%	4890	635	11	1,7%	225
Western Cape	**Total**	**18,9%**	**95997**	**18 199**	**176**	**1,0%**	**183**
	Cape Winelands	15,2%	13354	2 127	25	1,2%	187
	Central Karoo	11,8%	1156	109	1	0,9%	87
	City of Cape Town Metro	21,6%	63800	13 288	121	0,9%	190
	Eden	15,7%	9062	1 415	18	1,3%	199
	Overberg	19,8%	3855	723	6	0,8%	156
	West Coast	13,8%	4770	537	5	0,9%	105

Abbreviations: Stats SA Statistics South Africa; PCR polymerase chain reaction; ANC antenatal care; IU intra-uterine.

*ANC sero-prevalence survey was used because the Thembisa Model does not provide district level estimates.

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women seeking healthcare from neighbouring countries may be a contributing factor to high WRLHIV and fertility rates in these two provinces.

The findings from our analysis of intra-uterine transmission rates did not necessarily follow the underlying population densities. We observed lower transmission rates in KwaZulu-Natal which has the highest number of WRLHIV and live births to women living with HIV. We attribute the low intra-uterine rates in this province and its districts to the larger denominator (total live births, Table 2) and/or a more effective PMTCT programme. The converse probably explains the high intra-uterine transmission rate in the Northern Cape and its districts, where smaller denominators result in higher intra-uterine rates. Poor de-duplication of HIV PCR positive test data may also result in some provinces like the Western Cape having intra-uterine transmission rates that are above the national average. These results suggest that case rates per 100 000 may be a better indicator for monitoring programme performance at the various geographic levels [18] as it is directly linked to the performance of the PMTCT programme, for example coverage of services and attainment of viral suppression in pregnancy. Since most provincial level intra-uterine case rates were fairly similar, it is necessary to tackle the intra-uterine case rates at district level where there is considerable variation. Districts with high intra-uterine case rates deserve special attention with respect to improving PMTCT services.

Despite the distinct geographical differences in WRLHIV and AGYW, attainment of eMTCT will require more than understanding the geographic distribution of all WRLHIV. In order to fast-track eMTCT, it is critical to target PMTCT pillars of prevention of HIV infection [7] and family planning particularly in AGYW. The proposed School Health Programme which caters for sexual and reproductive health education and HIV testing in schools among children aged ≥12 years, has the potential to reduce maternal HIV prevalence in future and enable eMTCT. Among AGYW with HIV and other WRLHIV, the focus needs to shift towards virologic control, with specific attention to pregnant women, especially considering maternal viral load is the strongest predictor of MTCT risk [19]. Therefore, improving viral load monitoring during pregnancy, delivery and breastfeeding, and improving quality of patient management among WRLHIV and all HIV positive pregnant women may translate into improved viral load suppression rates. Achieving this in the big four provinces may fast-track eMTCT. There is urgent need to effectively track and monitor viral loads of all HIV positive pregnant women. A marker of pregnancy, delivery and the postpartum period within the NICD SDW as recommended in the 2019 National PMTCT guidelines, should allow for monitoring of viral load suppression rates at facility level in near real time to advance UNAIDS 90-90-90 [20] targets in women of reproductive age, particularly in high-risk areas. Such monitoring will provide information on the true picture of viral load burden during pregnancy and prompt rapid intervention. Currently this information is lacking.

In our analyses, the Thembisa Model was used as our primary data source because the model was specifically designed and is used for estimating HIV populations in SA. As a result it contained data for 10/12 indicators reviewed for these analyses. However, estimates may be inaccurate if underlying assumptions are incorrect. We therefore used other data sources to validate the data. Although there were differences in absolute numbers; we found that data from the other sources was generally within the upper and lower limits of the Thembisa model estimates (S2 Table). This may be because the Thembisa Model uses some of the data we triangulated with it, for example Statistics South Africa. Where there were significant differences, we attribute these to differences in (i) methodology or (ii) in reporting intervals or (iii) data quality issues for some of the data sources used for triangulation purposes. For example, the latest data for the ANC seroprevalence survey is 2017, while the reporting period for these analyses was 2018 (S1 Table). The laboratory based data lacks unique patient identifiers therefore de-duplication may be incomplete, resulting in over-estimation of transmission rates. Intra-partum transmission rates would be anticipated to be similar to intra-uterine transmission rates however; postnatal transmissions would depend on breastfeeding practices (e.g. duration of breastfeeding), postnatal virologic control and incident maternal infections which we were not able to measure.

Conclusions

We have attempted to quantify the need for eMTCT interventions based on the demographic profile of provinces in South Africa. Our results confirm what is mostly known. The need for HIV/eMTCT resources is greatest in Gauteng, KwaZulu-Natal and Eastern Cape. Limpopo and Mpumalanga provinces also warrant attention. While advocating for allocation of interventions for eMTCT on a needs-basis; it is important not to neglect those provinces with the least need. Routine monitoring and surveillance needs to continue until the country reaches eMTCT. Ending paediatric HIV will require robust viral load monitoring & intervention among WRLHIV in general, as well as pregnant and breastfeeding women. The NHLS laboratory data have the potential to provide viral load monitoring service near-real time until clinical databases can assume this role.

Supporting information

S1 Table. HIV prevalence rates by province in South Africa, 2018.
(DOCX)

S2 Table. 95% Confidence Intervals by indicator: Thembisa Model.
(DOCX)

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Writing – review & editing: Ahmad Haeri Mazanderani, Tendesayi Kufa, Gayle G. Sherman.

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Appendix 5.1: Wits HREC Ethics clearance certificate 3

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)

TO: Dr S Carmona et al
School of Pathology
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FROM: Iain Burns
Human Research Ethics Committee (Medical)
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DATE: 16/05/2017

REF: *R14/49*

PROTOCOL NO: **M1711115** *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

PROJECT TITLE: *Evaluating implementation of HIV virological point-of-care testing with remote quality assurance monitoring, in high-prevalance clinical settings*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to the Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

Appendix 5.2: Achieving maternal viral load suppression for elimination of mother-to-child transmission of HIV in South Africa

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

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

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.

AIDS 2021, **35**:307–316

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

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Information System (DHIS). The DHIS collates routine health data from all public health facilities in the country.

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.

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. 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).

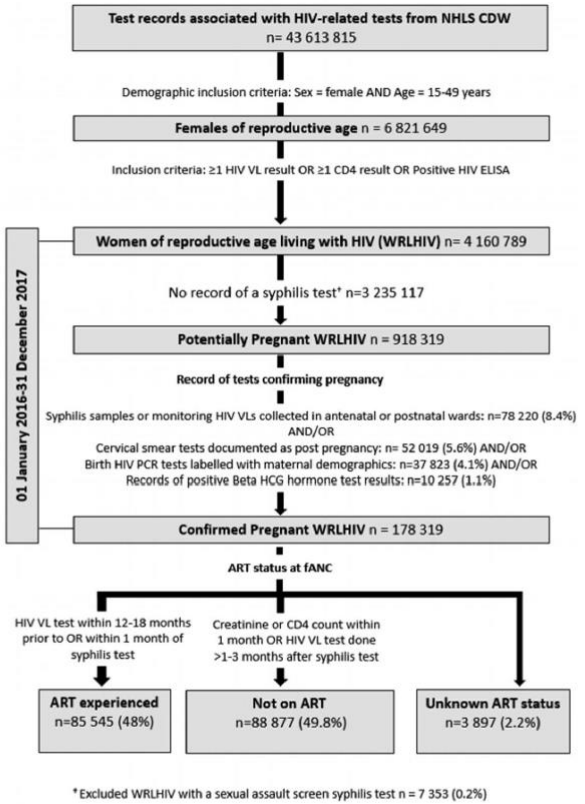

Fig. 1. Criteria for identifying HIV viral load tests performed on pregnant women living with HIV, in the National Health Laboratory Service's Corporate Data Warehouse between 1 January 2016 and 31 December 2017. ART, antiretroviral therapy; fANC, first antenatal care visit; HCG, human chorionic gonadotropin; NHLS CDW, National Health Laboratory Service's Corporate Data Warehouse; VL, viral load.

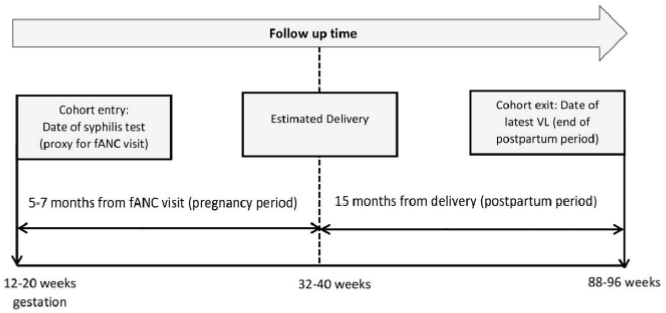

Fig. 2. Definition of study follow-up times among pregnant and postpartum women living with HIV identified from the National Health Laboratory Service's Corporate Data Warehouse. fANC, first antenatal care visit.

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, http://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

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.

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%)
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	162 744 (91.3%)	88 355 (91.3%)	74 389 (91.3%)
Present	15 575 (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.

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.

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,

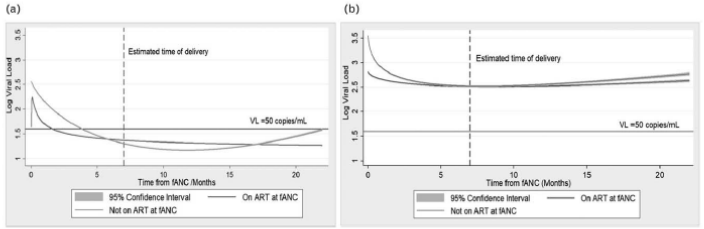

Fig. 3. Viral load decline over time by antiretroviral therapy status at first antenatal visit (a) overall: HIV viral load measurements, $n = 338\,688$; observed HIV viral loads that were lower than the detectable limit of the assay were assigned a value of zero (b) among WLHIV with quantifiable viral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

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, http://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).

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.

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.

Predictors	Number of HIV viral load measurements = 128 279[a]		
	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).

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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Appendix 6.1: Characterizing viral load burden among HIV-Infected women around the time of delivery: Findings from four tertiary obstetric units in Gauteng, South Africa

Characterizing Viral Load Burden Among HIV-Infected Women Around the Time of Delivery: Findings From Four Tertiary Obstetric Units in Gauteng, South Africa

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Background: Elimination of mother-to-child transmission of HIV requires sustained viral load suppression during pregnancy and breastfeeding among women living with HIV (WLHIV). Antenatal antiretroviral therapy coverage is reported at >95% in South Africa, but viral load suppression rates are unknown. We describe maternal VL burden around time of delivery at 4 tertiary obstetric units (TOUs) in Gauteng Province.

Methods: Between June 2018 and March 2019, routine point-of-care (PoC) maternal HIV VL and early infant diagnosis (EID) testing were implemented at 3 TOUs in Johannesburg and 1 in Tshwane district. WLHIV and HIV-exposed neonates were eligible for HIV VL (Xpert HIV-1 VL) and EID (Xpert HIV-1 EID or m-PIMA HIV1/2 detection) testing around time of delivery, respectively. Proportions of viremic women and intrauterine (IU)-infected neonates were calculated among valid PoC results.

Results: Among 8147 live births to WLHIV, 2769 (34.0%) women and 4333 (53.2%) neonates had valid PoC results. Median VL at delivery was <40 copies/mL (interquartile range: 0–398). The proportion of women with a VL < 50, 50 to <1000, and ≥1000 copies/mL was 63.6%, 13.9% and 22.4%, respectively. There were 65/4333 (1.5%) IU-infected neonates. Among 1449 mother–neonate pairs with both VL and EID results, IU transmission by VL threshold was 3/946 (0.3%), 6/187 (3.2%), and 25/316 (7.9%) for VL < 50, 50 to <1000, and ≥1000 copies/mL, respectively ($P < 0.001$).

Conclusions: Despite high antiretroviral therapy coverage, >1/3 of WLHIV had a VL ≥50 copies/mL at delivery. Among mother–neonate pairs, maternal VL ≥50 copies/mL accounted for 31/34 (91%) IU infections. Improvement in the quality of HIV care among WLHIV is essential if South Africa is to achieve elimination of mother-to-child transmission.

Key Words: mother-to-child transmission, HIV, viral load suppression, intrauterine transmission, point-of-care, pregnancy

(*J Acquir Immune Defic Syndr* 2020;83:390–396)

INTRODUCTION

Antiretroviral therapy (ART) coverage among antenatal clinic clients is estimated at >95% within the public health sector in South Africa.[1] The public health sector is the major health care provider, serving >80% of the South African population.[2] ART coverage among pregnant and postpartum women has increased steadily with the evolution of the prevention of mother-to-child transmission (PMTCT) of HIV policy in the country. The success of the PMTCT program is well documented.[3–6] Currently, PMTCT services are available in >95% antenatal and maternal facilities in the public health sector.[6] Between 2004 and 2014, early infant HIV transmission rates dropped from >20% to <2% among infants aged <2 months.[7] More recently, the program has managed to maintain the national intrauterine (IU) transmission rate at <1.5% since 2015, in spite of high maternal HIV prevalence rates.[8,9] Notwithstanding the tremendous progress achieved to date, gaps in the program remain. High rates of seroconversion and poor viral suppression among women initiated on ART during pregnancy and the postpartum period contribute significantly toward ongoing mother-to-child (MTCT) transmission of HIV.[9] Pregnancy has been associated with poor viral suppression.[10] Underlying factors vary from biological to social.[10,11] HIV viral load (VL) monitoring during pregnancy and the breastfeeding period is therefore critical for patient management and surveillance purposes. However, there are limited data on VL suppression (VLS) rates among women living with HIV (WLHIV) during these periods,[10] which may be related to VL monitoring only recently introduced into national PMTCT guidelines.[12–15]

MTCT of HIV occurs when women with unsuppressed VLs transmit HIV to their children in utero, during labor, or during breastfeeding postpartum.[16–18] Treatment duration and maternal VL have been identified as the strongest predictors of MTCT risk.[16–18] Depending on the baseline VL, a maximum of 12–16 weeks is deemed sufficient to suppress plasma VL in pregnant women.[16–20] An 8% reduction in the odds of HIV transmission with each additional week of treatment among women initiating ART during pregnancy has been reported.[16] Zero in utero and intrapartum HIV transmission has been documented among infants born to women who conceived on ART, continued treatment during pregnancy, and delivered with a plasma VL <50 copies/mL.[20] However, HIV transmission has been shown to occur among women with low-level viremia (50–400 copies/mL) around the time of delivery.[20] Thus, ensuring WLHIV have a VL <50 copies/mL before conception and that VLS is maintained during pregnancy and breastfeeding is crucial if South Africa is to achieve elimination of MTCT of HIV (eMTCT)–defined as an overall MTCT rate of <5% among breastfeeding children and a case rate of <50 HIV infections per 100,000 population.[21] Maternal VLS may be facilitated by timely screening for HIV, early ART initiation, adequate psychosocial support, and effective VL monitoring among women of childbearing potential.[10,16]

National PMTCT guidelines since 2015 have recommended a first-line regimen of tenofovir (TDF) + lamuvidine (3 TC) or emtricitabine (FTC) + efavirenz (EFV) as a fixed dose combination. Viral load monitoring in pregnant and breastfeeding women is performed at 3–6 monthly intervals, with VLs ≥1000 copies/mL prompting clinical interventions to improve VLS.[22] However, this has proven difficult to implement because women present for antenatal care at different stages of their pregnancy and VLS need to be achieved in a relatively short period of time before delivery. Although routine maternal VL testing at time of delivery was not a standard practice at the time of writing, national PMTCT guidelines were reviewed and currently set the VLS threshold to <50 copies/mL during pregnancy and recommend a repeat VL at time of delivery for all WLHIV.[23]

Centralized laboratory HIV VL testing remains standard of care in South Africa. Unlike many countries in sub-Saharan Africa, South Africa benefits from having an established national laboratory network through the National Health Laboratory Service (NHLS).[24] The NHLS has approximately 260 laboratories across the country.[23] However, only 16/260 (6.2%) of the laboratories offer HIV VL testing.[24] This often results in the laboratories operating at maximum capacity with extended result turn-around times that can lead to patients never receiving their results and being lost to care.[24] This in turn may contribute toward preventable MTCT. Point-of-care (PoC) HIV VL testing assays have been recommended as a means of improving VL monitoring among people on ART by enabling patients to receive their VL results on the day of testing before leaving the clinic.[25,26] This provides opportunity for rapid clinical management and reduces the number of clinic visits required. Compared with routine care, patients managed using PoC HIV VL assays have been shown to have better virologic outcomes and are more likely to be retained in care.[25] PoC HIV VL testing may be one of the game changers to fast-track eMTCT in South Africa, with maternal testing at time of delivery providing an opportunity for prompt clinical management such as enhanced adherence counseling for mothers and provision of high- versus low-risk prophylaxis for neonates. Furthermore, PoC early infant diagnosis (EID) testing at birth provides the opportunity to identify IU-infected neonates for early ART initiation.

In this article, we describe maternal VL burden and IU transmission rates from a study implementing PoC testing among pregnant WLHIV and HIV-exposed neonates around the time of delivery at 4 sites in Gauteng, South Africa.

METHODS

Study Procedures

Between June 2018 and March 2019, PoC HIV VL and EID testing was introduced at 4 tertiary obstetric units (TOUs) in Gauteng as part of an implementation study to determine the feasibility of integrating PoC testing into routine care in busy obstetric units. Three sites were located in Johannesburg (subdistricts B, D, F) and 1 in Tshwane district. A routine birth testing program for all HIV-exposed neonates was already in place at all sites as per national guidelines,[22] but maternal VL testing around the time of delivery for WLHIV was not routinely provided.

All WLHIV admitted to labor or postnatal wards were eligible for a PoC HIV VL test around the time of delivery using Xpert HIV-1 VL (Cepheid, Sunnyvale, CA), which has a quantifiable range of 40–10,000 000 RNA copies/mL. Similarly, all HIV-exposed neonates were eligible for PoC EID testing at birth, defined as <72 hours after delivery, using either Xpert HIV-1 (Cepheid, Sunnyvale, CA) or m-PIMA (Abbot, Chicago, IL) EID assays. PoC testing was restricted to working hours (08:00–16:00) on weekdays. Mother–neonate pairs were tested where possible; however, either of the pair could be tested without the other. Samples of mothers and neonates with no reasonable chance of the PoC result being returned before discharge were not tested. For example, a neonate born by normal vaginal delivery on a Friday evening was likely to be discharged before a PoC test could be performed on Monday morning and was therefore not tested using the PoC assay. Routine hospital staff (usually nurses or junior doctors) collected maternal and neonatal specimens, whereas PoC operators, mostly nurses employed specifically for this purpose, tested the samples in designated PoC testing rooms at each site. In the case of errors or invalid PoC HIV VL or EID results, repeat testing was performed on the leftover sample. If an error or invalid result was obtained on retest, a second sample was requested for additional testing. For each specimen tested using PoC, a corresponding sample was collected and sent to the National Health Laboratory Service (NHLS) for centralized laboratory testing.

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G.G.S., S.C., and A.H.M. conceived the study design and selected indicators for analysis. G.G.S., A.H.M., T.M., and K-G.T. acquired the data. F.M., A.H.M., T.K., and G.G.S. analyzed/interpreted the data. F.M., A.H.M., T.K., T.M., and G.G.S. wrote the article. K-G.T., S.C., T.K., A.H.M., and G.G.S. provided critical revision and final approval.

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Upon completion of PoC testing, neonates of mothers with a VL <1000 copies/mL were received low-risk prophylaxis of daily nevirapine for 6 weeks, as per standard of care.[22] Mothers of neonates with a negative EID PoC result were counseled to follow-up for a routine 10-week HIV PCR test at their local clinic. Hospital pediatric and obstetric staff were alerted through a mobile phone SMS (short messaging system) to maternal VLs ≥1000 copies/mL and positive EID results for intervention. Mothers with a VL ≥1000 copies/mL received adherence counseling, and their neonates were prescribed high-risk prophylaxis—either daily nevirapine for 12 weeks or dual prophylaxis (nevirapine and zidovudine) for 6 weeks, according to guidelines at the time of data collection.[22] Positive EID PoC test results prompted a second sample draw to confirm an HIV positive diagnosis and referral for ART initiation.

Study Data

Patient (name, surname, and hospital number) and sample details (collection date and time, sample barcode, result, name of assay, facility, and ward) were collected on a PoC test request form. These data were entered and managed in a REDCap database and imported into STATA for analysis. Analysis was restricted to participants with a valid PoC result. No additional clinical data were collected because this was beyond the scope of the PoC implementation study. Obtaining the necessary informed consent would have negatively affected the time-sensitive outcomes of the implementation study, namely testing coverage, turn-around times, and result return rates.

Study Outcomes

The proportion of viremic women at time of delivery was calculated at VL thresholds of ≥50, 50 to <1000, and ≥1000 copies/mL among women with a valid VL result. The IU transmission rate was calculated as the proportion of positive EID results in relation to the total EID PoC tests with a valid result. Programmatic HIV PCR data from the NHLS' Data Warehouse (NHLS DW) were used to determine routine IU transmission rates for each TOU site. PoC testing coverage was defined as the proportion of eligible mothers and neonates with a valid VL or EID PoC result. The country's district health information system (DHIS) indicator "total live births to HIV-positive women" was used as a proxy for the total number of mothers and neonates eligible for PoC testing per TOU.

Two denominators were used for PoC testing coverage: a conservative estimate used total number of live births to HIV-positive women, whereas a second estimate used only total live births to HIV-positive women during weekdays, when PoC testing was available. The conservative estimate was used as a proxy for the minimum testing coverage achieved, whereas the second denominator measured the best-case scenario or maximum coverage (ie, assuming PoC testing was available every day of the week).

Data Analysis

The Pearson's χ^2 test was used to test for associations between categorical variables; otherwise, the Fischer exact test was used for sparse data. Logistic regression was used to assess the association between having a high VL (VL ≥1000 copies/mL) around the time of delivery and (1) quarter of the year when the PoC test was performed after PoC implementation and (2) TOU in which the PoC test was performed. Variables were included in the adjusted model based on purposeful selection (P value cut-off of 0.20 for statistical significance during univariate analysis and 0.05 during multivariate analysis). The "quarter of the year when the PoC test was performed" was included a priori.

Subanalysis

Additional clinical and demographic data (maternal age at delivery and duration on ART) for women who delivered at the Johannesburg B site during the study period were extracted from a database of routinely collected clinical data from consenting patients at the site. These data were described using median (interquartile range) and proportions. Logistic regression was used to determine the association between high VL at delivery and (1) maternal age at delivery and (2) duration on ART.

ETHICS CLEARANCE

This work was approved by the human research ethics committee (HREC) of the University of the Witwatersrand (M1711115) and the faculty of health sciences research ethics committee of the University of Pretoria (50/2018). Patient identity was protected by de-identifying data before analysis. Maternal clinical data were available for study participants from the Johannesburg B site because of a data-sharing agreement routinely used at that facility, HREC clearance number M170778.

RESULTS

Over the period of 10 months, the 4 sites had 8147 live births to WLHIV of whom 2769 (34.0%) had a valid VL result (Table 1) and 4333 (53.2%) neonates had a valid EID result (Table 2). Testing coverage of maternal VL and EID varied considerably across the TOU sites with an overall maximum coverage of 48.6% and 76.0%, respectively (Tables 1 and 2).

The median maternal VL around the time of delivery at all sites was <40 copies/mL, with an overall interquartile range of 0–398 copies/mL. Figure 1 shows the distribution of VLs among women with a detectable VL around the time of delivery by TOU. Of 2769 valid VL results, 1578 (57.0%) were quantifiable with 571 (20.6%) having results of <50 copies/mL. Overall, the proportion of women with a VL ≥50, 50 to <1000, and ≥1000 copies/mL was 36.4% (n = 1007), 13.9% (n = 386), and 22.4% (n = 621), respectively (Table 1). Similar trends in proportions of viraemic women were observed for the 3 Johannesburg units, whereas higher proportions were observed for the Tshwane unit at 45.1%, 16.6%, and 28.5%

TABLE 1. Description of Maternal VL Around the Time of Delivery at 4 TOUs in Gauteng, South Africa

Variables	Total N = 2769	Location of TOU: Johannesburg B, n = 1230	Johannesburg D, n = 693	Johannesburg F, n = 309	Tshwane, n = 537	P
Total live births to WLHIV	8147	2103	3324	1543	1177	
Minimum PoC VL testing coverage*	34.0%	58.5%	20.8%	20.0%	45.6%	<0·001
Maximum PoC VL testing coverage†	48.6%	90.0%	28.2%	28.6%	62.5%	<0·001
VL suppression threshold						<0·001
<50 cps/mL	1762 (63.6%)	815 (66.3%)	445 (64.2%)	207 (67.0%)	295 (54.9%)	
≥50 cps/mL	1007 (36.4%)	415 (33.7%)	248 (35.8%)	102 (33.0%)	242 (45.1%)	
VL suppression threshold						0·001
50 to <1000 cps/mL	386 (13.9%)	161 (13.1%)	92 (13.3%)	44 (14.2%)	89 (16.6%)	
VL suppression threshold						0·001
<1000 cps/mL	2148 (77.6%)	976 (79.4%)	537 (77.5%)	251 (81.2%)	384 (71.5%)	
≥1000 cps/mL	621 (22.4%)	254 (20.7%)	156 (22.5%)	58 (18.8%)	153 (28.5%)	
Quarter of the year‡						<0·001
July–September 2018	862 (34.5%)	448 (41.1%)	144 (22.9%)	96 (34.0%)	174 (34.6%)	
October–December 2018	802 (32.1%)	317 (29.1%)	199 (31.7%)	141 (50.0%)	145 (28.8%)	
January–March 2019	838 (33.5%)	324 (29.8%)	285 (45.4%)	45 (16.0%)	184 (36.6%)	

*Denominator includes the total number of live births to WLHIV during the study period.
†Denominator includes the number of live births to WLHIV occurring on weekdays only during the study period.
‡June 2018, the first month of study initiation is excluded [n = 267 (9·6%) overall].
N, number; cps/mL, copies per millilitre.

for VL ≥50, 50 to <1000, and ≥1000 cps/mL, respectively (Table 1, P = 0.001). The proportion of IU-infected neonates ranged between 0.9% and 1.5% for the Johannesburg units, whereas the Tshwane unit had an IU rate of 2.7% (P = 0.005). When study data were aggregated to the district level to compare IU transmission rates between the 2 districts, a similar trend was noted with 40/3420 (1.2%) for Johannesburg and 25/913 (2.7%) for Tshwane (P = 0.002). Percentage positivity rates calculated from programmatic NHLS HIV PCR data from each site were comparable with overall IU transmission rates, suggesting generalisability (P = 0.705). Percentage neonatal positivity was associated with high maternal VL around the time of delivery. Among 1449 (33.4%) mother–neonate pairs with both a valid PoC VL and EID result, n (%), (95% confidence interval), 3/946 (0.3%) (0.1%–1.0%), 6/187 (3.2%) (1.4%–7.0%), and 25/316 (7.9%) (5·4%–11·5%) IU infections occurred among women

TABLE 2. Neonatal Point-of-Care EID at 4 TOUs in Gauteng, South Africa

Variables	Total, N = 4333	Location of TOU: Johannesburg B, n = 1292	Johannesburg D, n = 1305	Johannesburg F, n = 823	Tshwane, n = 913	P
Total live births to WLHIV	8147	2103	3324	1543	1177	
Minimum PoC EID testing coverage†	53.2%	61.4%	39.3%	53.3%	77.6%	<0·001
Maximum PoC EID testing coverage‡	76.0%	94·5%	53.0%	76.2%	>99.0%	<0·001
n (%) Positivity	65 (1.5%)	19 (1.5%)	14 (1.2%)	7 (0.9%)	25 (2.7%)	0·005
IU transmission, n (%) by VL threshold in mother–neonate pairs tested*	34 (52.3%)	14 (73.7%)	8 (57.1%)	3 (42.9%)	9 (36.0%)	<0·001
<50 cps/mL	3 (0.3%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	2 (2.0%)	
50 to <1000 cps/mL	6 (3.2%)	2 (1.6%)	1 (4.0%)	1 (7.1%)	2 (8.7%)	
≥1000 cps/mL	25 (7.9%)	11 (5.6%)	7 (14.9%)	2 (10.5%)	5 (9.6%)	
Total EID tests <3 days (birth)	8728 (100.0%)	2387 (27.3%)	3369 (38.6%)	1713 (19.6%)	1259 (14.4%)	
% IU transmission (Programmatic)	149 (1.7%)	39 (1.6%)	52 (1.5%)	20 (1.2%)	38 (3.0%)	<0·001

*n = 1449; mothers of twin babies were counted twice as the mother contributed in 2 EID PCR events.
†Denominator includes the total number of live births to WLHIV during the study period.
‡Denominator includes the number of live births to WLHIV during weekdays only during the study period.
N, number; IU, intrauterine.

with a delivery VL threshold of <50, 50 to <1000, and ≥1000 copies/mL, respectively (Table 2, $P < 0{\cdot}001$). All 3 of the IU infections occurring in the VL <50 copies/mL threshold occurred to women with an HIV-1 RNA detectable VL result. A search for previous VL results from the NHLS' DW showed that 2 of these women did not have a documented VL before delivery, whereas 1 woman had a VL ≥1000 3 months before delivery.

Proportions of high maternal VL remained constant during the study period, suggesting similarity in participants tested throughout the implementation period despite low testing coverage (Table 3). Although there was uniformity in the proportion of women with high VLs in the Johannesburg sites (Table 3), women who received their PoC HIV VL test in Tshwane were almost 2 times more likely to have a high VL compared with the site in Johannesburg F [AoR = 1·88, 95% CI: (1.31–2.71)].

Results of the subanalysis of demographic and clinical characteristics of women who delivered at the Johannesburg B site showed that high VL at delivery was predicted by younger maternal age: (age <25 years, n = 191/1129), [AoR = 2.17, 95% CI: (1.13–4.18)] and shorter duration on ART: (on ART for <3 months, n = 61/375), [AoR = 4.11, 95% CI: (2.20–7.66)].

DISCUSSIONS

These findings are among the first documenting maternal VL burden around the time of delivery across multisite, high-volume obstetric units in South Africa. Approximately 20% of women delivering across the 4 TOUs in Gauteng had a VL ≥1000 copies/mL with 36.4% having a VL of ≥50 copies/mL. Among mother–neonate pairs tested, higher maternal VL around the time of delivery was associated with higher IU transmission rates. Although women delivering in the Johannesburg sites had similar VL profiles, higher proportions of viraemic women were seen at the Tshwane site. A similar trend was observed for the neonatal IU transmission rate, which ranged from 0.9% to 1.5% in the Johannesburg sites but was 2.7% in Tshwane. Overall and site-specific IU transmission rates approximated programmatic IU transmission rates, suggesting generalisability of these findings to these sites. Data to investigate the reasons for the statistically significant differences observed in both the proportion of viraemic women and percentage IU transmissions between the Johannesburg and Tshwane sites were not available. We postulate that the Tshwane site may have provided care for younger women as well as treated a higher proportion of migrant patients who are more likely to have poorer treatment outcomes.[27,28] Our findings suggest that maternal VLS rates at the time of delivery are likely to vary between health districts, even within the same province. By monitoring maternal VL testing coverage and suppression rates at time of delivery, districts requiring targeted interventions to improve antenatal care can be identified to further reduce MTCT of HIV.

The 2017 National Antenatal Sentinel HIV survey confirmed that the PMTCT program has reached the first and second UNAIDS 90-90-90 targets for antenatal clients, in that 90% of all pregnant WLHIV know their status and 90% of these are on ART.[29] In spite of very high ART coverage during antenatal care in the public sector, our findings reveal suboptimal maternal VLS at time of delivery. Monitoring maternal VL during pregnancy and delivery instead of antenatal ART coverage, which fails to take duration of ART into account, may provide a better indicator as South Africa works toward eMTCT. In fact, because VLS before pregnancy is important for eMTCT, monitoring VLS of all women of childbearing potential is imperative. The proportion of viraemic (VL ≥1000 copies/mL) women at time of delivery was much higher than has been reported for WLHIV on ART in general of ≈ 10%.[30] This likely reflects the effect of new diagnoses and recent ART initiation during pregnancy, particularly among younger women. According to the DHIS in 2018, more than one-third of pregnant WLHIV were initiated on ART at their first antenatal visit and a similar proportion (34%) presented for their first antenatal clinic visit after 20 weeks of age. Thus, pregnant WLHIV often present for care after the first trimester with limited time to achieve VLS before delivery. The availability of maternal VL PoC testing during antenatal care may reduce the time to achieving VLS in pregnancy by reducing the time from sampling to result and improving the result return rate among virologically unsuppressed WLHIV.

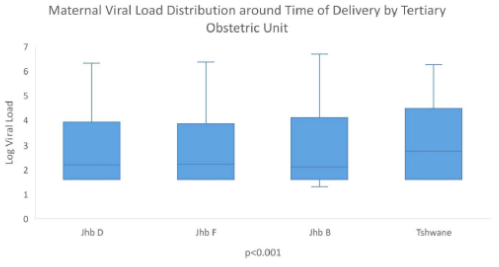

FIGURE 1. Distribution of maternal VL among women with detectable VL around the time of delivery by TOU, n = 1578 (57·0%) of maternal PoC VL results comprising 1007 VL ≥50 copies/mL and 571 VL <50 copies/mL but detectable. VL results "HIV less than detectable" were assigned values of 0 (n = 1191). Jhb, Johannesburg.

TABLE 3. Factors Associated With High Viral Load (VL ≥1000 Copies/mL) Around the Time of Delivery at 4 TOUs in Gauteng, South Africa

Variable	N (%)	Univariate OR (95% CI)	P	Adjusted OR (95% CI)	P
Quarter of the year*					
July–September 2018	197 (35.6%)	Reference	Reference	Reference	Reference
October–December 2018	183 (33.1%)	0·99 (0.79–1.25)	0.99	1.01 (0.80–1.20)	0.95
January–March 2019	173 (31.3%)	0·88 (0.70–1.11)	0.27	0·84 (0.67–1.07)	0.16
Location of TOU					
Johannesburg F	58 (9.3%)	Reference	Reference	Reference	Reference
Johannesburg D	156 (25.1%)	1·26 (0.90–1.76)	**0.18**	1.34 (0.93–1.97)	0.11
Tshwane	153 (24.6%)	1·72 (1.22–2.43)	**0002**	1.88 (1.31–2.71)	**0.001**
Johannesburg B	254 (40.9%)	1·13 (0.82–1.55)	0.46	1.18 (0.84–1.65)	0.35

*June 2018, the first month of study initiation is excluded from this analysis [n = 267 (9·6%) overall]. Level of statistical significance is 0.20 for univariate ORs and 0.05 for adjusted ORs.
OR, odds ratio; N, number; mL, milliliter.

Because the VL testing coverage was poor, the effect of targeted testing of high-risk mothers on our findings cannot be excluded. We may have disproportionately enrolled unbooked mothers, sick mothers with high VLs, or mothers with ART adherence issues. However, we found that the proportion of viremic women remained constant throughout the implementation period within each site. This suggests that despite low coverage, women included in the study were similar at each site or selection bias was uniform throughout implementation. Although most pregnant women presenting in labor wards had maternity case records with them around the time of delivery, few had documented VL results. As a result, clinical staff were less likely to be alerted to women with high VL results and unlikely to have selected women who were likely to have high VLs for PoC testing. Clinical staff also had the option to access PoC HIV VL testing on women if clinically indicated without enrolling them in the study and did not have to actively select women with high VL into the study. Finally, there were no provisions in the current PMTCT guidelines recommending that mothers with high VLs be managed in TOUs. WLHIV routinely obtain HIV care in primary health care facilities and are not referred for HIV management to TOUs. Therefore, it is unlikely that virologic profiles of women who participated in this study would differ from the surrounding primary health care facilities.

We present findings based on a single VL measurement at delivery. We did not have historic VL measurements to understand the evolution of virologic control of these women during pregnancy. As a result, we could not ascertain the VL patterns during pregnancy that culminated in neonatal infection. Myer et al found that episodes of viremia occurred frequently and were common in a cohort of women initiating ART during pregnancy in routine antenatal settings in the Western Cape.[31,32] This suggests that pregnant and postpartum WLHIV require close VL monitoring throughout pregnancy and during breastfeeding to minimize the risk of transmission. A follow-up study, describing the evolution of virologic control in pregnant and postpartum WLHIV at a national level, would be helpful to develop evidence-based VL monitoring algorithms. At the program level, individual monitoring of every pregnant and postpartum woman may go a long way toward eMTCT using HIV VL test data stored in the NHLS DW. Results for action reports such as the ones currently used for linking HIV PCR-positive infants to care[9] can be used by clinicians for WLHIV during pregnancy and postpartum to rapidly achieve VLS and avert transmission.

If the country is to achieve eMTCT, urgent prioritization of (1) VL monitoring, (2) ART adherence support, and (3) intervention for pregnant and breastfeeding WLHIV with unsuppressed VLs will be required.

CONCLUSIONS

Despite >95% antenatal ART coverage of pregnant WLHIV, approximately a third of WLHIV had a detectable VL around the time of delivery, thereby increasing risk of vertical transmission of HIV. Among mother–neonate pairs with valid PoC test results, 91% of IU infections occurred where maternal VL at the time of delivery was ≥50 copies/mL. Closer monitoring of VLS rates among pregnant and breastfeeding WLHIV may advance the PMTCT program's prospects of achieving eMTCT and will be more informative than ART coverage rates. Maternal PoC VL

Our data are limited by lack of information on ART status, ART drug regimens, time on ART, and previous VL results among study participants. These are important predictors of virologic response, which we could not ascertain in most of our study population.[16–18] However, results of the Johannesburg B site subanalysis confirmed what is already known. Younger maternal age and shorter duration on ART were significantly associated with high VL at delivery.[16] Regardless of patient-level factors, conducting a PoC VL test at delivery within the high-volume TOUs identified a third of women with detectable VLs for intervention. Given the maturity of South Africa's PMTCT program and the need for potential game changers to achieve eMTCT, this study demonstrates the utility of PoC VL around the time of delivery within a high-burden setting.

testing during pregnancy and at delivery may facilitate VLS and reduce MTCT transmission risk. Essentially, improvement in the quality of HIV care among WLHIV is required if South Africa is to achieve eMTCT.

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Appendix 7.1: Maternal HIV viral load testing during pregnancy and postpartum care in Gauteng Province, South Africa (in press)

Date: Oct 19, 2020
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From: "SAMJ" submissions@hmpg.co.za
Subject: Your Submission

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South African Medical Journal

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South African Medical Journal

South African Medical Journal

Maternal HIV viral load testing during pregnancy and postpartum care in Gauteng Province, South Africa.

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Abstract:	Background Pregnant and breastfeeding women living with HIV (WLHIV) are a target population for the elimination of mother-to-child transmission of HIV (eMTCT) however; there is limited data on maternal virologic responses during pregnancy and postpartum period in South Africa. Objectives To review compliance of viral load (VL) testing with national guidelines and suppression rates during pregnancy and up to 9-months postpartum among WLHIV delivering in four tertiary hospitals in Gauteng Province, South Africa. Methods All women who had a point-of-care (PoC) HIV VL test using Xpert® HIV-1 VL (Cepheid, Sunnyvale, California, USA) at delivery from four tertiary obstetric units in Gauteng Province between June 2018 and February 2020 were included. HIV VL tests of eligible women performed within 9-months prior or subsequent to delivery were extracted from the National Health Laboratory Service's Corporate Data Warehouse. Proportions of women delivering who had antenatal & postpartum VL tests performed and their suppression rates were determined and expressed as percentages. Results Of 4 989 eligible WLHIV with median maternal age of 31.1 years, 917 (18.4%) had a VL performed during the antenatal period of whom, 335 (36.5%) had VL ≥50 copies/mL and 165 (18.0%) had VL ≥1 000 copies/mL. At delivery, 1 911 (38.3%) women had a VL ≥50 copies/mL and 1 028 (20.6%) had a VL ≥1 000 copies/mL. Among 627 (12.6%) women with a VL test postpartum, 234 (37.3%) had VL ≥50 copies/mL and 93 (14.8%) had VL ≥1 000 copies/mL. Overall, having a VL performed during the antenatal period was associated with viral suppression at delivery and receiving a VL test postpartum (p-value <0.001). Women with a VL ≥50 copies/mL at delivery, were more likely to be younger and remain virally unsuppressed postpartum (p-value <0.001) compared to women with a VL <50 copies/mL at delivery. Conclusion Less than 5% of WLHIV with a VL at time of delivery received VL monitoring during antenatal and postpartum periods in accordance with national guidelines. More than 80% of WLHIV delivering had no evidence of VL monitoring during the antenatal period and were more likely to be virally unsuppressed at delivery and receive no VL monitoring postpartum. Women with high VL at delivery were more likely to remain virally unsuppressed postpartum. Results emphasize the need for closer monitoring of and rapid reaction to high maternal VL during pregnancy, delivery and postpartum for attainment of eMTCT.

Introduction

Maternal viral load (VL) is closely associated with the risk of mother-to-child transmission of HIV (MTCT).[1-3] Thus, frequent and timely VL testing among pregnant and breastfeeding women living with HIV (WLHIV) is critical to prevent MTCT. This is because there is limited time for identifying women with high VL and instituting interventions, such as switching regimens and/or intensifying adherence support, to ensure VL suppression. The South African Prevention of Mother-to-Child Transmission of HIV (PMTCT) programme has evolved to enable universal HIV testing and antiretroviral therapy (ART) coverage in the public sector. For monitoring treatment response, the PMTCT guidelines since 2015 have recommended a VL test at the first antenatal care (ANC) visit for WLHIV already on ART, irrespective of when the last VL was done.[4] For WLHIV newly diagnosed with HIV during pregnancy, a VL is recommended after three months of ART use. In both groups, six monthly VL monitoring follows throughout pregnancy and the breastfeeding period. In November 2019, the guidelines were revised to include a VL at delivery for all WLHIV, and the VL threshold was lowered from ≥1 000 to ≥50 copies/mL for instituting intensified adherence support and/or regimen changes.[5]

Despite the existence of a robust PMTCT policy framework, minimal attention has been placed on maternal VL monitoring during pregnancy and the postpartum period in South Africa.[2] Previous reports have found VL testing coverage as low as 30% during pregnancy or the breastfeeding period[6], with frequent disengagement from care during the postpartum period particularly among WLHIV newly initiating ART during pregnancy.[7-8] Furthermore, approximately 20% of maternal VLs were ≥1 000 copies/mL during antenatal and postpartum care[9], while up to 37% of pregnant WLHIV have VL ≥50 copies/mL at delivery in the public health sector.[10-12] This has important implications for vertical transmission, as elimination of mother-to-child transmission of HIV (eMTCT) requires sustained suppression of maternal VL at <50 copies/ml throughout pregnancy, delivery and the breastfeeding period. The foregoing suggests that the programme is far from achieving UNAIDS 90-90-90 and eMTCT targets.[13-14]

South Africa's public health sector provides routine HIV VL testing via a well-established, centralized laboratory network which is accessible to 4 300 ANC facilities nationally.[15] However, delays exist from specimen collection to testing and ultimately the return of results to patients.[2] Point-of-care (PoC) HIV VL has been proposed as a game changer for fast-tracking eMTCT in South Africa. Point-of-care VL testing can reduce gaps along the VL monitoring cascade by accelerating return of results to patients and facilitating prompt clinical management in cases with elevated maternal VL.[16-18] Previous reports suggest that PoC HIV VL technologies have a place within routine settings in South Africa. However, scale up needs to complement existing laboratory-based systems and address site-specific health system level factors.[15]

This article reviews compliance of VL testing with national guidelines and suppression rates during the antenatal period and up to nine months postpartum among WLHIV who received a PoC HIV VL at delivery at four tertiary hospitals in Gauteng Province, South Africa.

Methods

Between June 2018 and February 2020, PoC HIV VL testing was piloted at four tertiary obstetric units in Gauteng Province- three in the City of Johannesburg and one in Tshwane District. All pregnant WLHIV presenting at labour or postnatal wards were eligible for PoC HIV VL testing using Xpert® HIV-1 VL (Cepheid, Sunnyvale, California, USA). Specimen collection was performed by nurses and doctors as part of routine care, while testing was

performed by trained PoC operators onsite. Testing was performed on weekdays between 08h00-16h00. No clinical details, such as time of first HIV diagnosis, PMTCT regimen, ANC attendance, were recorded. All women who received a PoC HIV VL test at delivery were included in the study. For each PoC HIV VL that was performed, a corresponding sample was sent for routine testing to the National Health Laboratory Service (NHLS), with the two samples sharing the same laboratory barcode. Prior and subsequent HIV VL tests associated with the same patient, as per the NHLS' Corporate Data Warehouse (CDW) generated unique patient identifier, were extracted from the NHLS CDW. HIV VL test data extracted included VLs performed up to nine months prior to and post the delivery HIV VL. Viral loads performed up to nine months prior to delivery were used as a proxy for VL monitoring during the antenatal period. Record linkage within the NHLS CDW relied on a validated probabilistic patient-linking algorithm which uses patient demographics (name, surname, date of birth, etc) for linking test records to unique individuals.[19]

Study outcomes and analysis

The analysis evaluated proportions of women who received a VL test during the antenatal period, at delivery and within nine months postpartum, expressed as percentages. Eligible VLs analyzed included any VL performed within nine months pre- and post-delivery. Proportions of pregnant WLHIV with a documented VL and proportions of VL suppression during the antenatal period, at delivery and postpartum were calculated. Analyses were stratified by i) receipt of PoC HIV VL result prior to discharge from hospital or not, to determine the impact of PoC HIV VL testing on rate of retention postpartum and ii) maternal VL ≥50 copies/mL versus VL <50 copies/mL at time of delivery. The Pearson's Chi squared test was used to test for associations between categorical variables, and Fischer's exact in the case of sparse data. Ethics approval for the study was obtained from the Wits Human Research Ethics Committee (M1711115) and from the Faculty of Health Sciences Research Ethics Committee of the University of Pretoria (50/2018).

Results

A total of 4 989 pregnant WLHIV received PoC HIV VL testing at time of delivery from the four tertiary obstetric units between June 2018 and February 2020. Among these, 3 671 (73.6%) women received their PoC HIV VL result prior to discharge from the hospital and 1 318 (26.4%) did not. Median maternal age was 31.1 years (interquartile range: 26.6-35.6) (Table 1). A total of 917 (18.4%) women had a documented VL during the antenatal period of which, 335 (36.5%) had a VL ≥50 copies/mL and 165 (18.0%) had a VL ≥1 000 copies/mL (Fig. 1). At delivery, 1 911 (38.3%) women had a VL ≥50 copies/mL and 1 028 (20.6%) had a VL ≥1 000 copies/mL. A total of 627 (12.6%) women had a documented VL within nine months postpartum, of which 234 (37.3%) had a VL ≥50 copies/mL and 93 (14.8%) had a VL ≥1 000 copies/mL (Table 1). Women with a documented VL during the antenatal period versus those without, were more likely to i) have VL <50 copies/mL at delivery, 652 (71.1%) versus 2 426 (59.6%); p value <0.001 and ii) have a documented VL postpartum, 216 (23.6%) versus 411 (10.1%); p value <0.001, respectively. However, VL suppression postpartum was not associated with having a VL performed during the antenatal period (p value = 0.478). Overall, 216 (4.3%) of 4 989 women received VL monitoring during the antenatal period, at delivery and within nine months postpartum.

Receipt of a PoC VL result before discharge from the hospital was associated with having a VL test performed within nine months postpartum. However, the association did not reach statistical significance (p value = 0.055, Table 1). A significant proportion of younger women (age <25 years) had a VL ≥50 copies/mL at time of delivery (Table 1). When compared to

women with VL <50 copies/mL, women with VL ≥50 copies/mL at time of delivery had fewer VLs during the antenatal period (265/1 911 (13.8%) versus 652/ 3 078 (21.2%); p value = 0.001) and tended to have unsuppressed VLs if they had a VL during the antenatal period (VL ≥50 copies/mL for 220/265 (83.0%) versus 115/652 (17.6%) women, p value <0.001) (Fig. 1). Rates of postpartum VL monitoring were similar between the two groups at 251 (13.1%) for women with a VL ≥50 copies/mL and 376 (12.2%) for women with a VL <50 copies/mL at time of delivery (p value = 0.341). However, women with VL ≥50 copies/mL at time of delivery were more likely to remain unsuppressed at postpartum follow-up compared to women with VL <50 copies/mL at time of delivery (Fig. 1).

Discussion

We present findings from a review of compliance to national VL testing guidelines and suppression rates during the antenatal and postpartum periods in Gauteng Province. Less than 20% of pregnant WLHIV had evidence of VL monitoring during the antenatal period, with 37% of these women having VL ≥50 copies/mL prior to delivery. At delivery, 38% and 21% of the women had VL ≥50 and VL ≥1 000 copies/mL, respectively. Overall, the rate of VL monitoring within nine months postpartum was 13% and 37% of women with a VL test within nine months postpartum had VL ≥50 copies/mL. Women with evidence of VL monitoring during the antenatal period were more likely to be virally suppressed at delivery and receive VL monitoring during the postpartum period. We observed that a significant proportion of women aged <25 years had VLs ≥50 copies/mL at delivery and that women with VL ≥50 copies/mL at delivery were less likely to be virally suppressed at postpartum follow-up compared to women with VL <50 copies/mL at delivery. Since similar proportions of VL ≥50 copies/mL were observed during the antenatal period (37%), delivery (38%) and within nine months postpartum (37%), findings show that a similar proportion of women are transitioning the care continuum with unsuppressed VLs. In which case, the programme is failing to identify distinct groups of women with specific needs that require targeted packages of care for maternal VL suppression. However, VL data was too few to determine the proportion of women consistently unsuppressed at all three time points.

Elimination of MTCT requires sustained maternal VL suppression from conception through pregnancy to the end of the breastfeeding period. Over 80% of women in our cohort had no evidence of VL monitoring during the antenatal period. Given the small window of opportunity for intervention between detecting high maternal VL during the antenatal period and time of delivery, it is not surprising that 40% of these women had VL ≥50 copies/mL at delivery. Findings speak to the need for improved implementation of frequent maternal VL monitoring and rapid reaction to elevated maternal VL during pregnancy and postpartum period. South Africa already has a robust policy framework that provides for optimal monitoring of maternal VL during pregnancy. What is required are systems for improving clinical management of pregnant and postpartum WLHIV within the PMTCT programme including PoC VL testing.[15] Point-of-care VL utilization varied across our study sites as previously reported [15] and these data show that approximately one in three women who received a PoC VL test at delivery did not receive their result prior to discharge from the hospital, suggesting suboptimal utilization. Nonetheless, higher proportions of VL monitoring in the postpartum period were seen in women who received their delivery PoC HIV VL result prior to discharge from the hospital than those who did not. Although the difference was not clinically relevant (11% versus 13%), the finding demonstrated the potential of PoC VL testing in improving maternal VL testing and subsequent retention in care postpartum within routine settings. This is particularly important in the current context of very low maternal VL testing coverage within the national PMTCT programme, such that any intervention that improves VL testing coverage is welcome.

However further research is required to explore this association as findings may be biased by underlying health system and patient level factors which were beyond the scope of this study.

Evidence from different studies show that approximately 30%-37% of women delivering in the public sector have VL ≥50 copies/mL at time of delivery.[9-11] We present similar findings for maternal viraemia at delivery and within nine months postpartum. These proportions are unacceptably high if the programme is in pursuit of eMTCT, especially considering recommendations for extended breastfeeding for two years postpartum. We found that women who had unsuppressed VLs at time of delivery, continued to be unsuppressed during the postpartum period. Even more concerning was the observed high rate of absent VL monitoring within nine months postpartum amongst the cohort. This places HIV-exposed infants at a higher risk of MTCT during breastfeeding.[20-22] Poor monitoring of maternal VL during the postpartum period undermines the benefits of high ART coverage prior to delivery by compounding the risk of MTCT in the postnatal period. These findings emphasize the need for on-going patient support and improved systems for monitoring patient care during pregnancy and postpartum period in order to achieve eMTCT. Until clinical databases can assume this role, routine near real-time surveillance of maternal VL during pregnancy, delivery and postpartum periods using the NHLS laboratory database can fast-track attainment of eMTCT and the third 90 in this population. The revised PMTCT guidelines of 2019 make provision for accurate, national surveillance of maternal VL during pregnancy, at delivery and the postpartum period by introducing the electronic gate keeping (EGK) codes C#PMTCT and C#DELIVERY to distinguish maternal VL testing at these three time points.[5] The EGK codes are meant to be captured on standard laboratory requisition forms for specimens submitted to and processed by the NHLS. As with other policy recommendations, the success of this initiative depends on uptake and implementation by stakeholders.

At patient level, investing in patient support services may sensitize mothers on the importance of VL monitoring and empower them to take charge of their own health and health care, for example young mothers and women who are struggling with adherence to treatment. The success of the PMTCT programme to date is largely attributable to implementation of broad-based and programme-level interventions. These interventions were necessary and are still relevant. However, achieving eMTCTrequires a further shift towards focusing on case management during pregnancy and postpartum period. This may explain the constant figure of approximately 37% of women that remain unsuppressed throughout the continuum of care in this study. These are probably women with specific needs that are not addressed by programme-level interventions and require extra services. While this approach may be time- and resource-intensive, the PMTCT programme can leverage on services provided by 'MomConnect' and the community health care worker programme to address such needs.[25] MomConnect is a mobile phone based health initiative of the South African National Department of Health that sends targeted health promotion messages to pregnant women (regardless of HIV status) accessing antenatal care in the public health sector. The targeted health messages aim at improving both maternal and infant health. [23] Subscription to the service is on a voluntary basis and is free of charge.

Interpretation of our findings requires consideration of certain limitations. We relied on the national laboratory database for VL testing patterns throughout the continuum of PMTCT care for the study cohort. However, the laboratory database is not a clinical longitudinal cohort management system. The VL testing cascade generated from laboratory data is based on availability of VL testing according to HIV monitoring guidelines. Therefore, some women may be in care but not receiving appropriate HIV testing. In addition, the laboratory database may be inaccurate for longitudinal cohort monitoring as, in the absence of a unique identifier,

record linkage relies on probabilistic matching of patient demographic information. Therefore, some VL results may not have been linked to study participants due to inconsistent documentation of demographics (for example due to data capturing error and or surname changes due to marriage) which would cause the patient linking algorithm to fail to link VL results belonging to the same patient. This is particularly worth noting considering pregnant women often attend multiple facilities during the antenatal period, delivery and postpartum[24] and each facility may capture their personal identifiers differently. However, a manual search for longitudinal VL test results for 200 randomly selected participants was performed from the Laboratory Information System (LIS). The manual search did not yield additional VL data to results obtained from the patient linking algorithm. This suggests reasonable performance of the linking algorithm in finding most of the HIV VLs performed on each patient, thereby validating the study findings. However, the use of markers specific for maternal VL monitoring during pregnancy and breastfeeding period, such as the recommended EGK codes, is anticipated to provide accurate surveillance data from the laboratory database in the near future.

Another limitation includes the lack of clinical information for study participants. Data on maternal ART status during the antenatal period was not available to the study to determine timing of first VL and or the impact of ART duration on maternal viraemia during the antenatal and postpartum periods. Lastly, considering the low maternal VL testing coverage during both the antenatal and postpartum periods, testing may have been biased towards unsuppressed women. This may explain why women with unsuppressed VLs during pregnancy tended to be unsuppressed during the postpartum period. Furthermore, the few VL data in this study limited a longitudinal analysis of maternal VL evolution.

Conclusion

Less than 5% of WLHIV enrolled in this study received VL monitoring during antenatal and postpartum periods according to national guidelines. Approximately one fifth of women had evidence of VL monitoring during the antenatal period. Women living with HIV who did not have VL monitoring during the antenatal period were more likely to be virally unsuppressed at delivery and receive no postpartum VL monitoring. Women with high VL at delivery were more likely to remain virally unsuppressed postpartum. These results emphasize the need for closer monitoring of and urgency in responding to elevated maternal VL during pregnancy, at delivery and postpartum for the attainment of eMTCT in South Africa.

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Authors' contributions

GGS, FM, AHM conceived study design and selected indicators for analysis. GGS and FM acquired the data. FM, AHM, TK and GGS analysed/interpreted the data. FM and AHM wrote the article. TK and GS provided critical revision and final approval.

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Competing Interests

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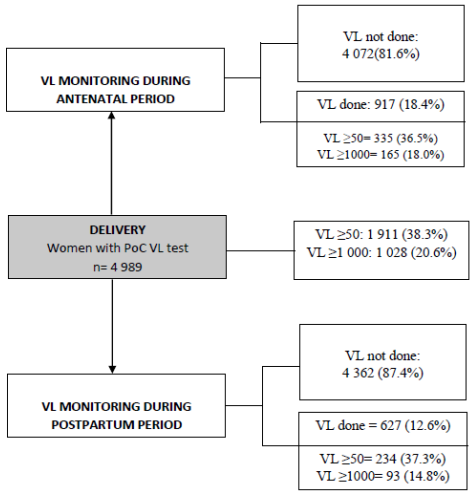


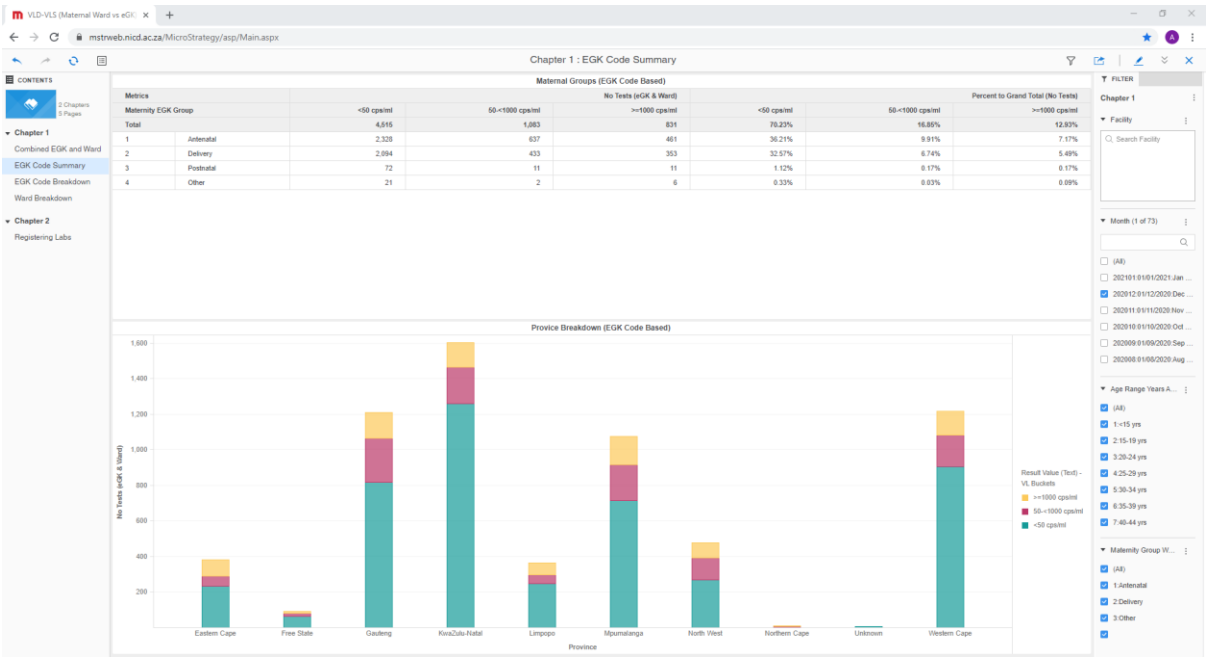
Figure 1. Compliance of VL testing and rates of suppression amongst pregnant and postpartum women living with HIV amongst the cohort.
Abbreviation: PoC point-of-care, VL viral load in copies/mL

Table 1: Demographic and clinical characteristics of WLHIV who received a PoC HIV VL test at delivery from four tertiary obstetric units in Gauteng Province, June 2018-February 2020.

Variables	Total N=4 989	PoC Result receipt at delivery			PoC HIV VL category at delivery (*copies/mL*)		
		Not received n=1 318	*Received n=3 671*	P-value	*VL <50 n=3 078*	*VL ≥50 n=1 911*	P-value
Maternal age at delivery				0.416			**<0.001**
Median (years)	*31.1 (26.6-35.6)*	*31.0 (26.2-35.4)*	*31.1 (26.5-35.5)*	*0.402*	*32.2 (27.6-36.1)*	*29.8 (25.1-34.6)*	**<0.001**
<25	616 (12.3%)	139 (10.5%)	477 (13.0%)		296 (9.6%)	320 (16.7%)	
25-34	1 855 (37.2%)	377 (28.6%)	1 478 (40.3%)		1 148 (37.3%)	707 (37.0%)	
35-44	990 (19.8%)	200 (15.2%)	790 (21.5%)		692 (22.5%)	298 (15.6%)	
≥45	16 (0.3%)	2 (0.2%)	14 (0.4%)		11 (0.4%)	5 (0.3%)	
missing[†]	1 512 (30.3%)	600 (45.5%)	912 (24.8%)		931 (30.2%)	581 (30.4%)	
VL test during antenatal period (ANC)							
VL done	917 (18.4%)	186 (14.1%)	731 (19.9%)	**<0.001**	652 (21.2%)	265 (13.9%)	**<0.001**
VL not done	4 072 (81.6%)	1 132 (85.9%)	2 940 (80.1%)		2 426 (78.8%)	1 646 (86.1%)	
VL at ANC (copies/mL)				0.663			**<0.001**
Median[*] (IQR)	*20 (0-222)*	*20 (0-423)*	*20 (0-182)*	*0.158*	*20 (0-28)*	*718 (0-14 059)*	**<0.001**
<50	582 (63.5%)	113 (60.8%)	469 (64.2%)		537 (82.4%)	45 (17.0%)	
50-<1 000	170 (18.5%)	36 (19.4%)	134 (18.3%)		75 (11.5%)	95 (35.9%)	
≥1 000	165 (18.0%)	37 (19.9%)	128 (17.5%)		40 (6.1%)	125 (47.2%)	
VL test within 9 months postpartum				**<0.007**			0.341
VL done	627 (12.6%)	138 (10.5%)	489 (13.3%)		376 (12.2%)	251 (13.1%)	
VL not done	4 362 (87.4%)	1 180 (89.5%)	3 182 (86.7%)		2 702 (87.8%)	1 660 (86.9%)	
VL within 9 months postpartum (copies/mL)				0.055			**<0.001**
Median (IQR)	0 (0-66)	0 (0-70)	20 (0-66)	0.092	0 (0-20)	107 (20-4 697)	**<0.001**
<50	393 (62.7%)	83 (60.1%)	310 (63.4%)		322 (85.6%)	71 (28.3%)	
50-<1 000	141 (22.5%)	26 (18.8%)	115 (23.5%)		46 (12.2%)	95 (37.9%)	
≥1 000	93 (14.8%)	29 (21.0%)	64 (13.1%)		8 (2.1%)	85 (33.9%)	

[*]Zero values were assigned for VL values were target was not detected; the value of the lower limit of quantification was assigned where HIV RNA was detected but below the lower limit of quantification of the VL assay. [†]Missing age category excluded from bivariate analysis.
Abbreviation (s) WLHIV women living with HIV; PoC point of care; VL viral load, IQR interquartile range, ANC antenatal care, mL millilitre.

Appendix 8.1 Maternal VL suppression dossier report using EGK codes and ward type



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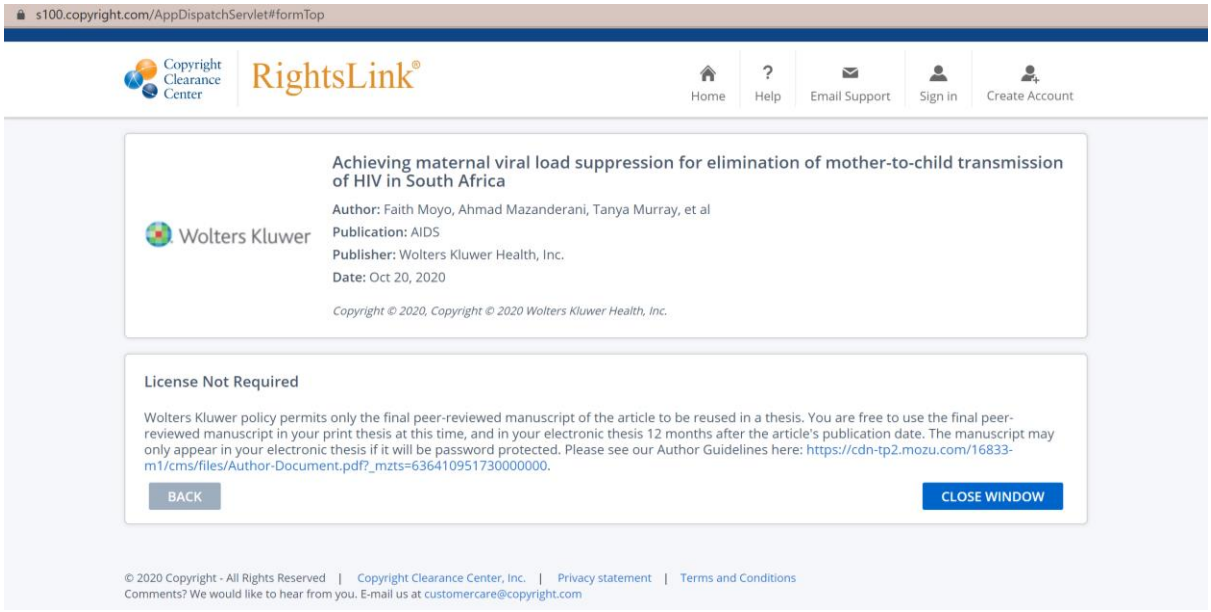
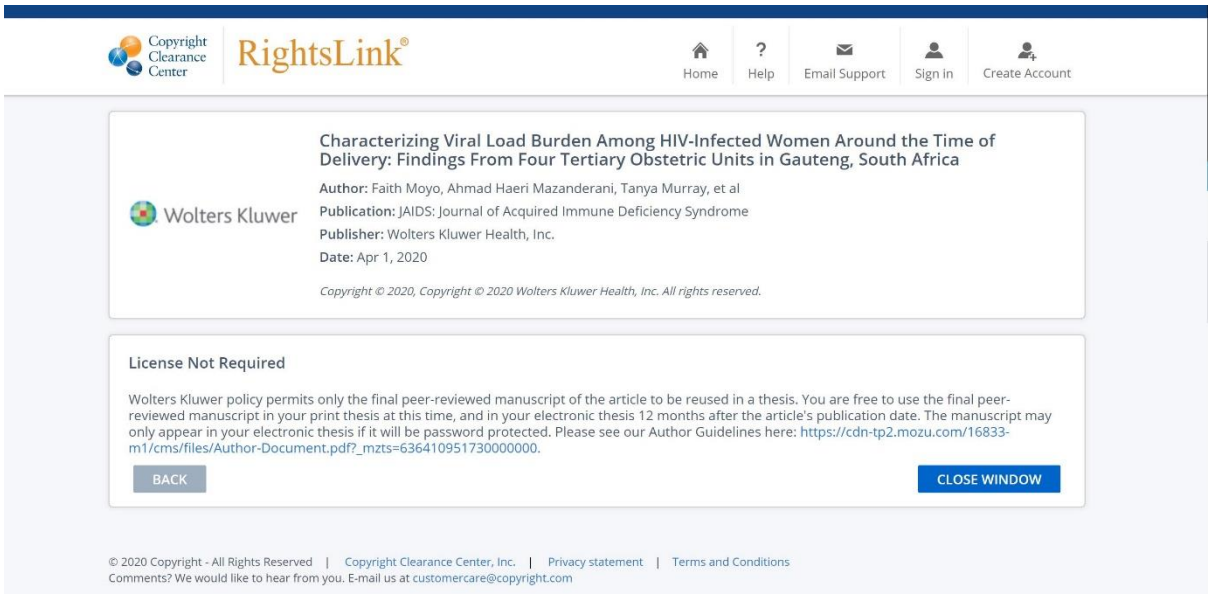
1. Achieving maternal viral load suppression for elimination of mother-to-child transmission of HIV in South Africa



2. Characterizing viral load burden among HIV-infected women around the time of delivery: Findings from four tertiary obstetric units in Gauteng, South Africa



3. The geographic distribution of priority population groups for the elimination of mother-to-child transmission of HIV in South Africa

Thu 2020/12/03 1:21 AM

noreply@salesforce.com on behalf of plosone <plosone@plos.org>

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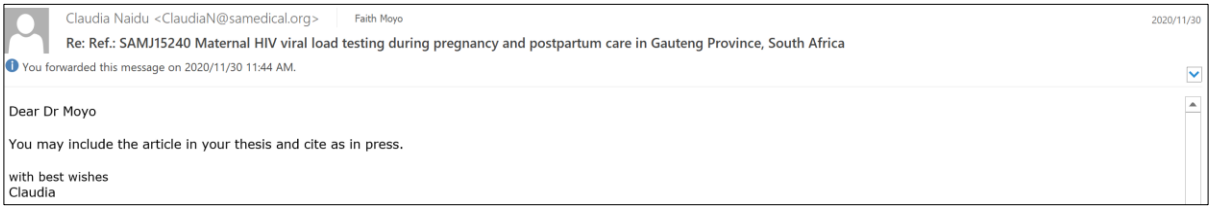
4. Maternal HIV viral load testing during pregnancy and postpartum care in Gauteng Province, South Africa



Claudia Naidu <ClaudiaN@samedical.org> Faith Moyo 2020/11/30

Re: Ref.: SAMJ15240 Maternal HIV viral load testing during pregnancy and postpartum care in Gauteng Province, South Africa

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Dear Dr Moyo

You may include the article in your thesis and cite as in press.

with best wishes
Claudia

Appendix 8.3: Declaration of student's contribution to articles and agreement of co-authors

I **Faith Moyo**, student number 569935 declare that this Thesis is my own work and that I contributed adequately towards the below published research articles which form part of my Thesis.

Signature of student..... Date 27/01/2021

Name of Supervisor: Prof Gayle Sherman Signature of Supervisor.....

Date 27/01/21

Co- author agreement

By signing this declaration, the co-authors listed below agree to the use of the article by the student as part of her Thesis. In cases where the student is not the 1st author of a published article, the primary supervisor must explain (under comments) why the student is entitled to the to use the paper for her degree purposes.

Article 1

The geographic distribution of priority population groups for the elimination of mother-to-child transmission of HIV in South Africa. **Journal name, year, volume and page numbers:** Plos One 2020, 15: e0231228.

Author	Name	Signature	Date
1st	Moyo Faith		27/01/2021
2nd	Ahmad Haeri Mazanderani		01/12/2020
3rd	Kufa Tendesayi		27/01/2021
4th	Sherman Gayle G		27/01/21

Article 2

Achieving maternal viral load suppression for elimination of mother-to-child transmission of HIV in South Africa. **Journal name, year, volume and page numbers:** AIDS 2020, doi: 10.1097/QAD.0000000000002733 (published ahead of print).

Author	Name	Signature	Date
1st	Moyo Faith		27/01/21
2nd	Ahmad Haeri Mazanderani		27/01/21
3rd	Sherman Gayle G		27/01/21
4th	Kufa Tendesayi		27/01/21

Article 3 Characterizing viral load burden among HIV-Infected women around the time of delivery: Findings from four tertiary obstetric units in Gauteng, South Africa. **Journal name, year, volume and page numbers:** J Acquir Immune Defic Syndr. 2020,83:390–396.

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1st	Moyo Faith		27/01/21
2nd	Ahmad Haeri Mazanderani		01/12/2020
3rd	Murray T		01/12/2020
4th	Karl-Gunter Technau		30 Nov 2020
5th	Carmona S		30 Nov. 2020
6th	Kufa Tendesayi		27/01/2021
7th	Sherman Gayle G		27/01/21

Article 4 Maternal HIV viral load testing during pregnancy and postpartum care in Gauteng Province, South Africa. **Journal name, year, volume and page numbers:** S Afr Med J, 2020 (Accepted for publication 19 October 2020)

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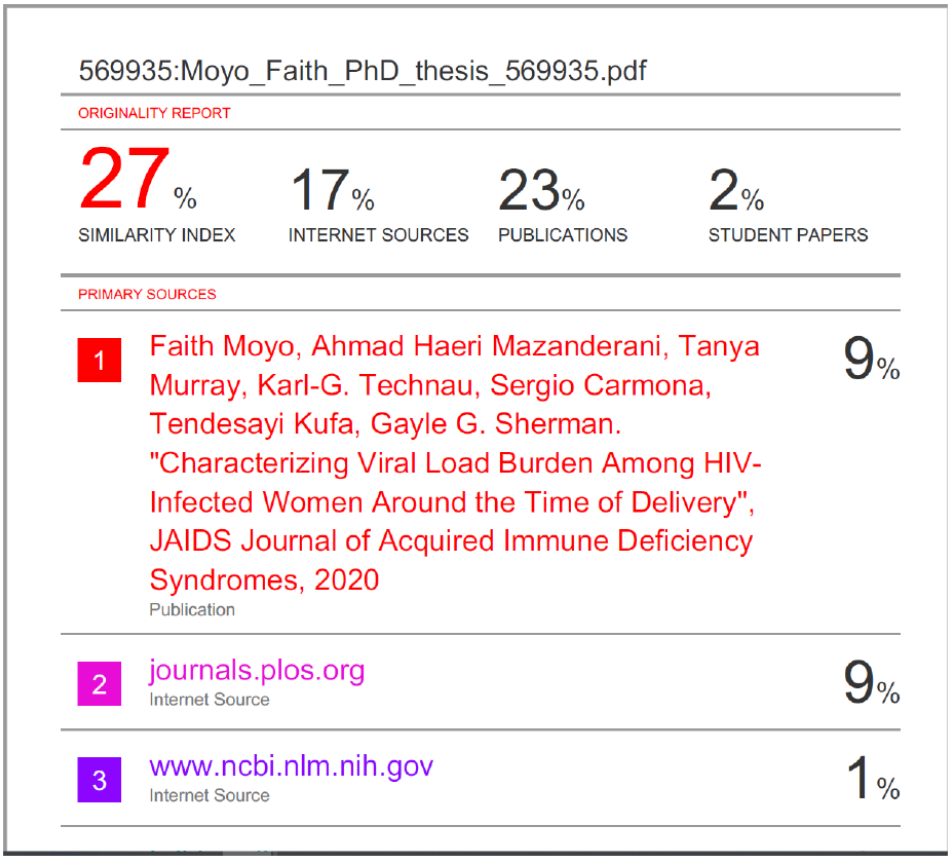
1st	Moyo Faith		27/01/2021
2nd	Ahmad Haeri Mazanderani		01/12/2020
3rd	Kufa Tendesayi		27/01/2021
4th	Sherman Gayle G		27/1/21

Appendix 8.4 Turn-it-in Report



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