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Strengthening maternal and child healthcare

PHANGISA STUDY, EHLANZENI

BRIEF REPORT

1 March 2022

KEY RISK FACTORS FOR PERIPARTUM AND POSTPARTUM VERTICAL HIV TRANSMISSION IN THE CONTEXT OF PMTCT OPTION B+ IN A RURAL DISTRICT IN SOUTH AFRICA
EHLANZENI DISTRICT, MPUMALANGA

saMRC advancinglife

CONDUCTED BY:

HEALTH SYSTEMS RESEARCH UNIT/HIV PREVENTION RESEARCH UNIT SOUTH AFRICAN MEDICAL RESEARCH COUNCIL

IN COLLABORATION WITH:

National Institute of Communicable Diseases
Montpellier University
University of Bergen
Queen Mary University of London
University of Liverpool
Academy for Quality Healthcare
Right-to-care
Rob Ferreira Regional laboratory
Ehlanzeni District

FUNDED BY:

SA NATIONAL DEPARTMENT OF HEALTH

ISBN:

978-1-928340-61-4

RECOMMENDED CITATION: Nobubelo Ngandu, Thandiwe Mbira, Vundli Ramokolo, Witness Chirinda, Nobuntu Makhari, Natasha Titus, Mark Goosen, Adrian Puren and Ameena Goga for the scientific collaborators. KEY RISK FACTORS FOR PERIPARTUM AND POSTPARTUM VERTICAL HIV TRANSMISSION IN THE CONTEXT OF PMTCT OPTION B+ IN A RURAL DISTRICT IN SOUTH AFRICA. South African Medical Research Council, March 2022. Report number: 978-1-928340-61-4. Available from www.samrc.ac.za

ACKNOWLEDGEMENTS

SAMRC team
Principal Investigators: Dr Nobubelo Ngandu, Prof Ameena Goga
Project coordinator: Mrs Nobuntu Makhari
Administration: Ms Lucille Heyns, Mathokwa Choeu
Scientists: Dr Witness Chirinda, Dr Vundli Ramokolo,
Data quality control: Ms Natasha Titus, Ms Thandiwe Mbira, Ms Khanya Mohlabi
Field Team leaders: Mantjane Mogorosi, Nozipho Ntshobodi
Study nurses: Ms Chairmaine Mabunda, Mr Damiano Phiri, Ms Dudu Mathebula, Ms Emeldah Nxumalo, Ms Idah Nsingwane, Ms Siciniseko Nsingwane, Ms Maria Shai, Sr Ruth Makhuhleni, Sr Maggie Mhango

Ehlanzeni District (PMTCT)
Ms Nomsa Sithole, Ms Thoko Tsela

District support & partners
AQUAH – Dr Lesego Mawela
Right-to-Care – Dr Christi Jackson

Rob Ferreira regional Lab
Mr Moeletsi Lebeko
Mr Isaac Mofokeng
Rob Ferreira staff

NICD
Prof Adrian Puren, Dr Mark Goosen, Ms Zinhle Brukwe, Ms Beverley Singh, Ms Ewalde Cutler

Scientific collaborators
Prof Carl Lombard (Chief Biostatistician, SAMRC)
Prof Philippe van de Perre (Montpellier University, France)
Prof Thorkild Tylleskar (University of Bergen, Norway)
Prof Andrew Prendergast (Queen Mary University of London /Zvitambo MCH Institute)
Dr Catriona Waitt (University of Liverpool, UK)

saMRC advancinglife
NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service
health
Department:
Health
REPUBLIC OF SOUTH AFRICA

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LIST OF ABBREVIATIONS

ANC	–	antenatal care
ART	–	antiretroviral
CHC	–	community healthcare centers
DBS	–	Dried blood spot specimens
HEI	–	HIV-exposed infants
HIV	–	Human Immunodeficiency Virus
MTCT	–	mother-to-child transmission of HIV
PrEP	–	Pre-Exposure Prophylaxis
PMTCT	–	prevention of mother-to-child transmission of HIV
UNAIDS	–	United Nations AIDS program

1. INTRODUCTION

The sub-regional variation in maternal HIV exposure and vertical transmission rates are the current stumbling block against progress towards meeting targets for eliminating mother-to-child transmission of HIV (MTCT) in South Africa [1, 2]. Understanding factors associated with high risk of MTCT at district level will assist with the design of high impact and context-specific interventions.

2. STUDY OBJECTIVES

We set out to describe and understand the primary risk factors for MTCT in Ehlanzeni district, to recommend interventions relevant to the local context.

Primary objective:

(i) To measure the prevalence of maternal viral load non-suppression and determine associated factors, and understand what interventions are needed to achieve the UNAIDS targets of viral suppression amongst pregnant and postpartum women.

Secondary objectives:

(i) To identify any missed opportunities for HIV diagnosis in mothers and HIV-exposed infants
(ii) To understand feeding practices and antiretroviral prophylaxis coverage amongst HIV-exposed infants
(iii) To understand knowledge and perceptions about Pre-Exposure Prophylaxis (PrEP)

3. METHODS

3.1 STUDY DESIGN AND SAMPLE SIZE

A facility-based cross-sectional study was conducted in 8 largest community healthcare centers (CHC) across the Ehlanzeni district: KaNyamazane, Nelspruit CHC, KaBokweni CHC, and Phola Nsikazi CHC in Mbombela sub-district; Naas and Mangweni in Nkomazi sub-district; Thulamahashe CHC and Dwarsloop CHC in Bushbuckridge sub-district. A sample size needed for a district-level estimate of viral load non-suppression was used with a 5% precision. The sampling approach was designed to fairly represent participants from various stages of the peripartum and postpartum phase of the prevention of MTCT (PMTCT) cascade. That is, five study groups of 200 HIV-positive women each: third trimester of pregnancy, and four postpartum groups of mothers with biological children aged 0-14 weeks, 15-26 weeks, 6-11 months and 12-24 months. HIV-negative mothers with their biological children were enrolled at 15-26 weeks and 12-24 months targeting sample sizes of 400 in each group, to compare infant feeding practices and PrEP knowledge. The summary of inclusion criteria is shown in **Figure 1**.

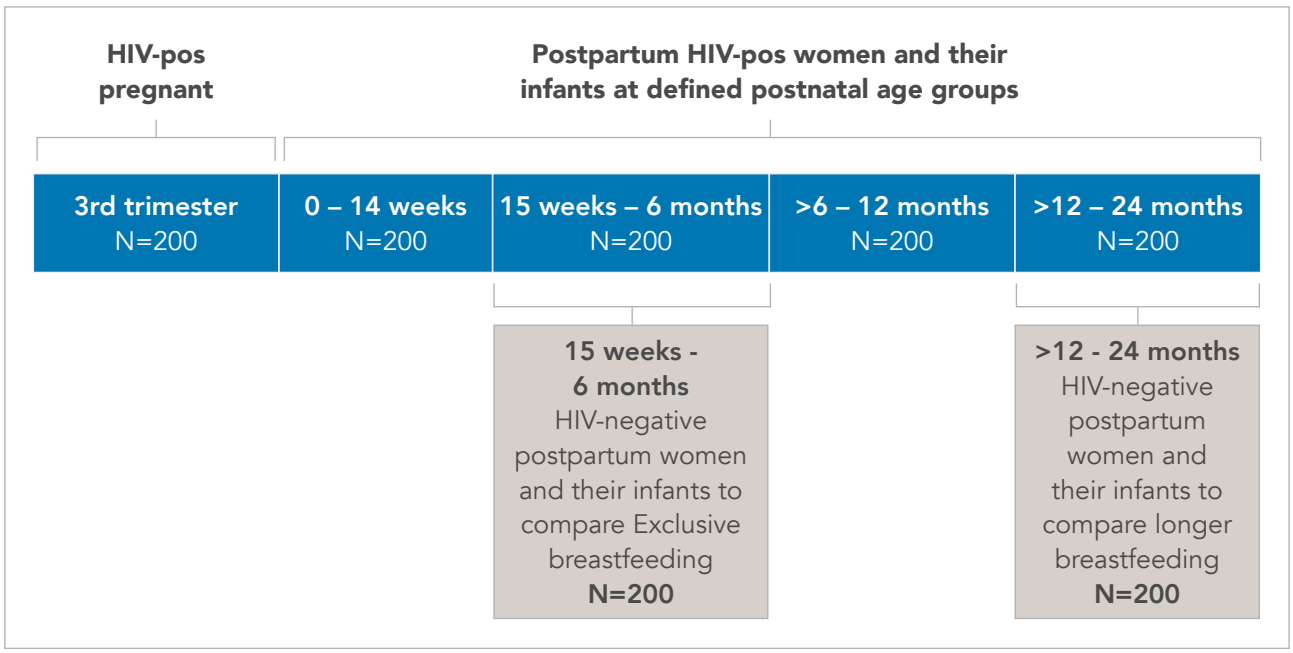

Figure 1: Summary of inclusion criteria of study participants. HIV-pos = HIV-positive

ETHICS APPROVAL was obtained from the South African Medical Research Council ethics committee (Protocol EC002-2/2019). Complete informed signed consent was obtained from eligible women before any data were collected.

Picture: data collector training session conducted by Nelspruit Lancet staff

3.2 DATA COLLECTION & LABORATORY PROCEDURES

Data collection and laboratory processes are summarized in **Figure 2** below.

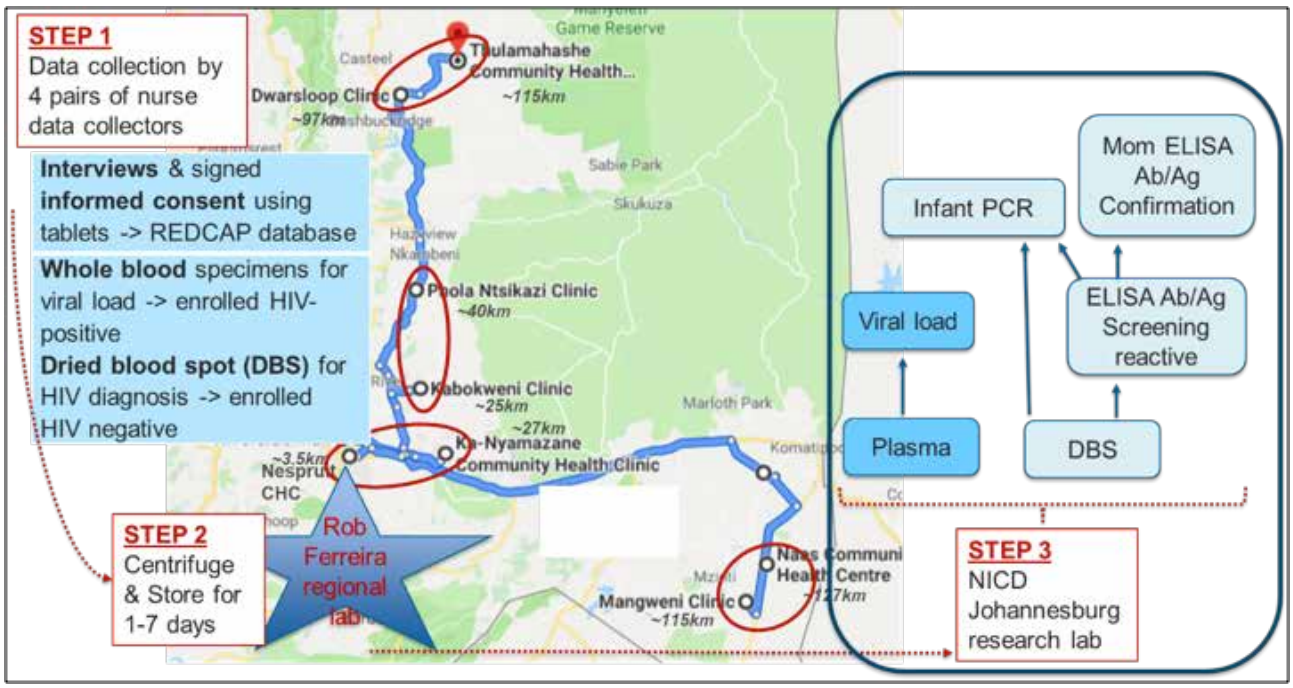

Figure 2: Data collection pipeline - Data was collected during September 2019 to December 2019

STEP 1: Data collection involved 20-30 minutes interviews to collect basic demographic and HIV-related clinical histories, captured directly onto electronic tablets linked to a REDCAP database. Whole blood was collected from all participants enrolled as HIV-positive (mothers or infants). Dried blood spot specimens (DBS) were collected from all mothers enrolled as HIV negative or unknown HIV status. DBS was taken from infants whose mothers were enrolled as HIV-positive. No blood samples were taken from infants whose mothers were enrolled HIV-negative or infants who had been pricked for routine HIV care within the past four weeks (regardless of maternal HIV status).

STEP 2: All blood samples were couriered to a local regional lab (Rob Ferreira) within 3-10 hours on the same day of blood draw, where whole blood was centrifuged to separate and store plasma at -20 degrees Celsius. DBS samples were stored below 8 degrees celsius. All stored samples were couriered to the research lab every Monday (i.e., within 3-7 days from day of blood draw).

STEP 3: Whole blood plasma samples were used for the HIV-1 viral load assays which were performed using the Roche COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test, version 2.0 (Roche Diagnostics GmbH, Mannheim, Germany).
HIV diagnosis of the mothers from DBS samples was performed using the Genscreen Ultra HIV Ag-Ab (Bio-Rad, Marnes-la-Coquette, France) kit for screening assays and the Murex HIV Ag/Ab Combination (DiaSorin S.p.A., Dartford, UK) for confirmatory assays.
HIV diagnosis of infants from DBS samples was performed using the Roche COBAS® AmpliPrep/ COBAS® TaqMan® HIV-1 Qualitative Test, version 2.0 (Roche Diagnostics GmbH, Mannheim, Germany). All assays were performed according to the manufacturer's instructions.

3.3 DATA ANALYSES

Data were cleaned and analyzed using the STATA SE 2014 software. Proportions were calculated to report the prevalence of each outcome variable. Chi-squared tests were conducted to assess the distribution of an outcome variable by various exposure factors including socio-demographic characteristics and use of PMTCT, antenatal and postnatal services.

Logistic regression models were used to identify exposure factors significantly associated with each outcome variable. A p-value less than 0.05 was considered to indicate a significant result.

All analyses were adjusted for survey design and sample size realization to report district-level estimates.

4. RESULTS and DISCUSSIONS

4.1 SUMMARY OF STUDY POPULATION

A total of 971 women were enrolled in the study, of which 304 were HIV-negative and 667 were HIV-positive (of which 187 were in the third trimester). HIV-positive average sample realization was 66.5% ranging between 43% and 94% (**Figure 3, Appendix Table A1**). HIV-negative sample realization average was 38%. The sample size was generally influenced by infant vaccination points resulting in fewer participants where the required child postnatal age-group did not overlap with routine vaccination points. At facility level, clinics situated in the most remote rural locations, particularly in Bushbuckridge subdistrict achieved the lowest sample size. Viral load was successfully performed in 8% fewer samples (N=612) compared to the number of interviews done due to insufficient plasma from 55 samples. All postpartum women were enrolled with their biological child with an age corresponding to the postpartum stages listed in Appendix Table A1. Therefore, a total of 304 infants unexposed to HIV and 480 HIV-exposed infants (HEI) were enrolled. A total of 10 out of 480 HEI infants were HIV-positive at enrolment. Out of the remaining HEI infants, 383 had not been pricked within the preceding four weeks and hence eligible for a study DBS sample for HIV diagnosis (**Figure 3**). No samples were taken from unexposed infants.

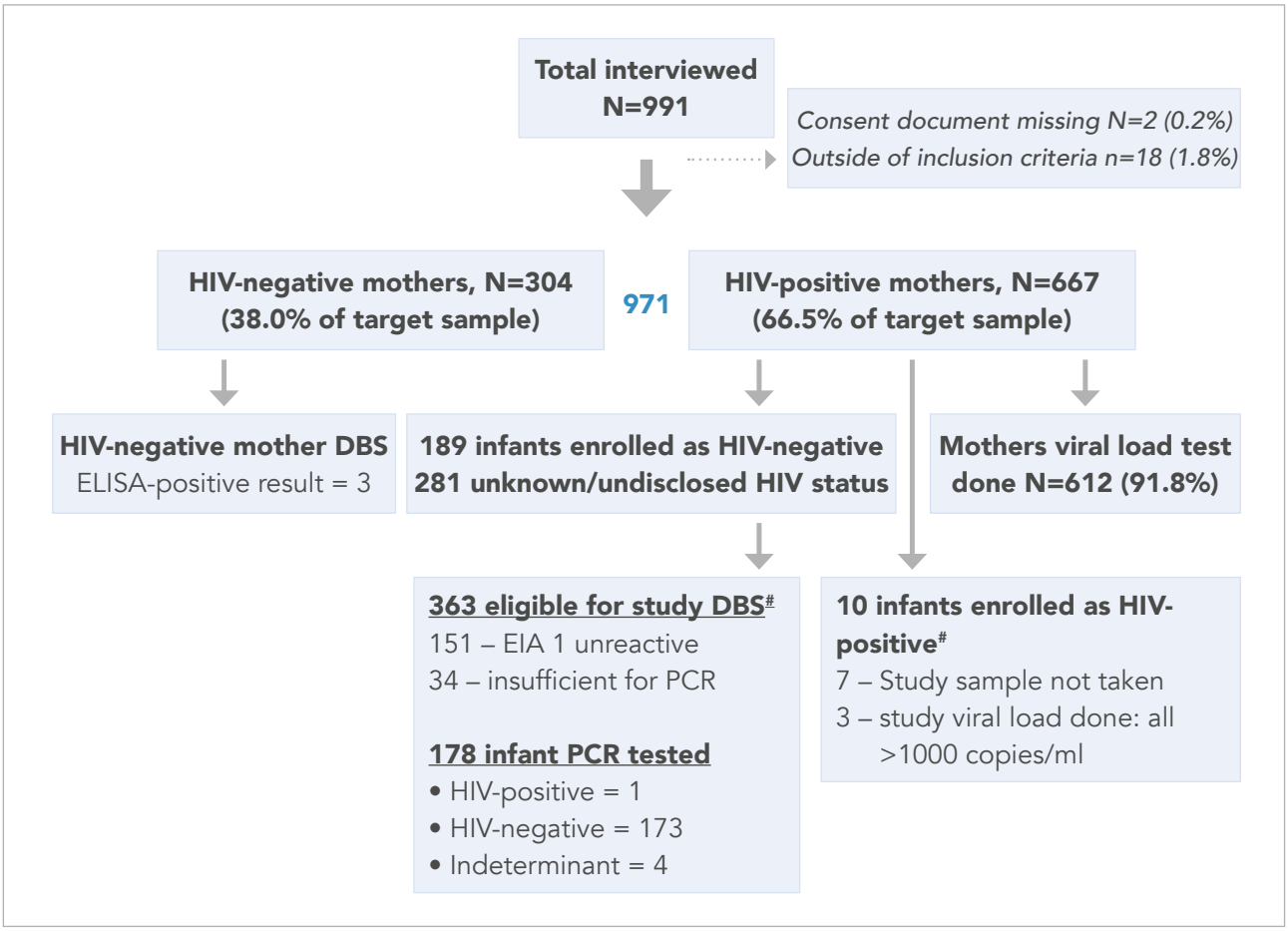

Figure 3: Summary of study sample. #Infant study samples only taken if infant was not pricked routinely within the past 4 weeks.

The summary of basic characteristics of the enrolled participants is presented in **Figure 4**. Maternal age ranged between 15 and 46 years with a median of 29 years and interquartile range: 24-34 years. Half of the participants (53.5%) had completed grade 8-12 of education, 40% had completed a post matric certificate or diploma or higher and about 6% had not more than grade 7 education achieved. Most (61.9%) women reported never being married nor cohabiting while 38.1% were married or cohabiting. Half of the women (49.9%) dependent on another person (a spouse, parent or relative) for their main source of income, a quarter dependent on government grants and nearly another quarter were employed or self-employed.

Early uptake of the first antenatal care visit (ANC-1) by 20 weeks gestation was very high with 65.3% women taking ANC-1 by 12 weeks gestation and 26.7% taking ANC-1 between 13-20 weeks gestation. Nearly three quarters of the participants has at least 5 ANC visits during pregnancy. However, 56.1% reported an unplanned pregnancy for the current child and 31.0% did not know the HIV status of their male partner while over a quarter (26.3%) knew their partner was HIV-positive and 42.7% knew their partner was HIV-negative. Self-reported condom use appeared to be high, nearly half of the women reporting always using condoms.

Amongst HIV-positive women alone, over a quarter (27.1%) received their HIV diagnoses after enrolling into antenatal care, 86.5% were on ART for more than 12 months and 80.5% were still on first-line ART regimen.

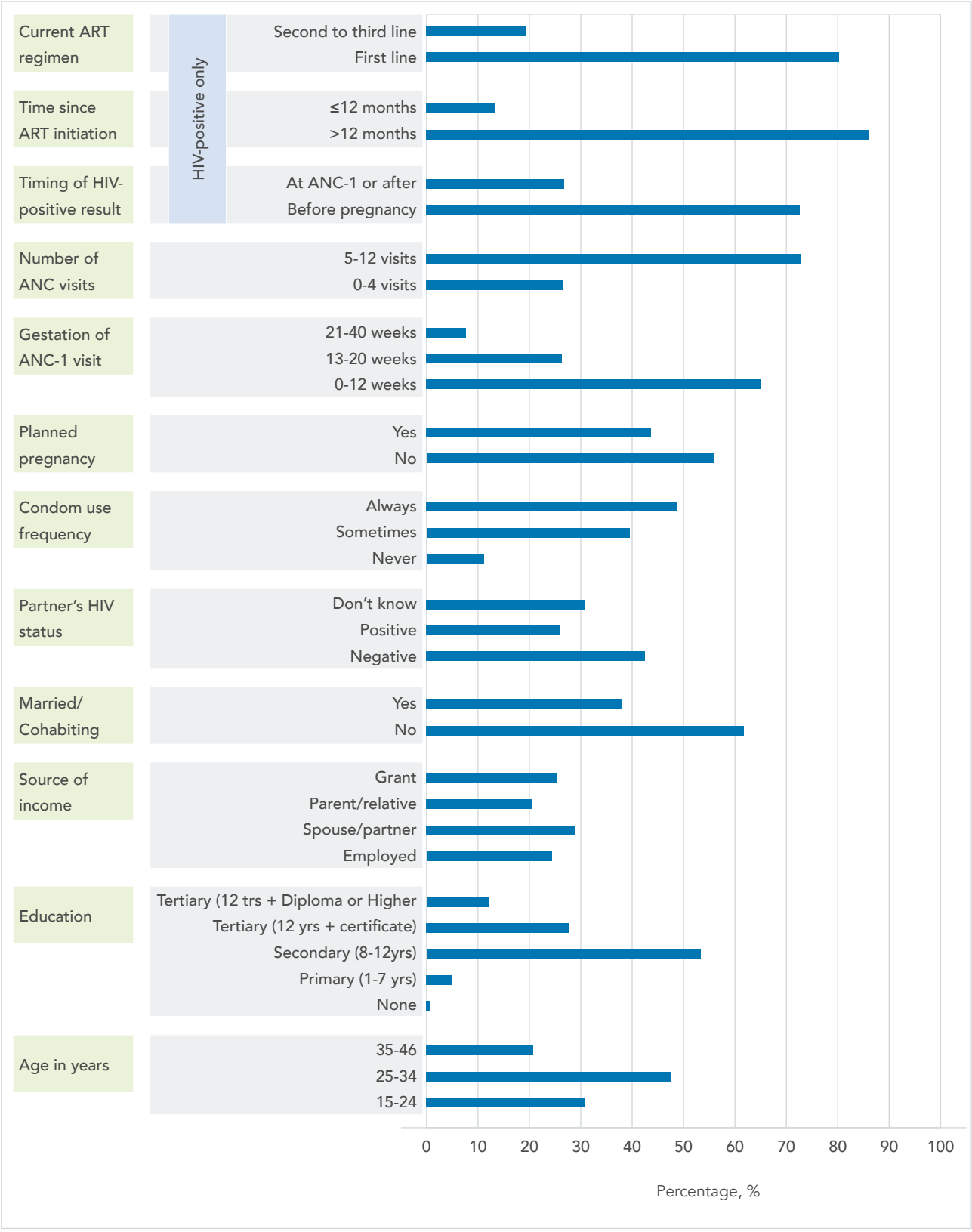

Figure 4: Characteristics of study population at enrolment

In the postnatal sample of 784 infants, age ranged from 0 to 104 weeks old with a median of 39 weeks and interquartile range: 18-69 weeks. The proportion of infants who were born with low birth weight (<2.5kg) was 9.6%.

4.2 MATERNAL VIRAL LOAD NON-SUPPRESSION AND ASSOCIATED FACTORS - Objective1

The results in this section were published in March 2022 (https://bmjopen.bmj.com/content/12/3/e058347)

Out of the 612 viral load tests done, 14.7% were virally non-suppressed, 13.8% had low-level viraemia (VL 50-1000 copies/mL) and 71.5% had policy-defined undetectable (<50 copies/mL) viral load (**Figure 5-A**).

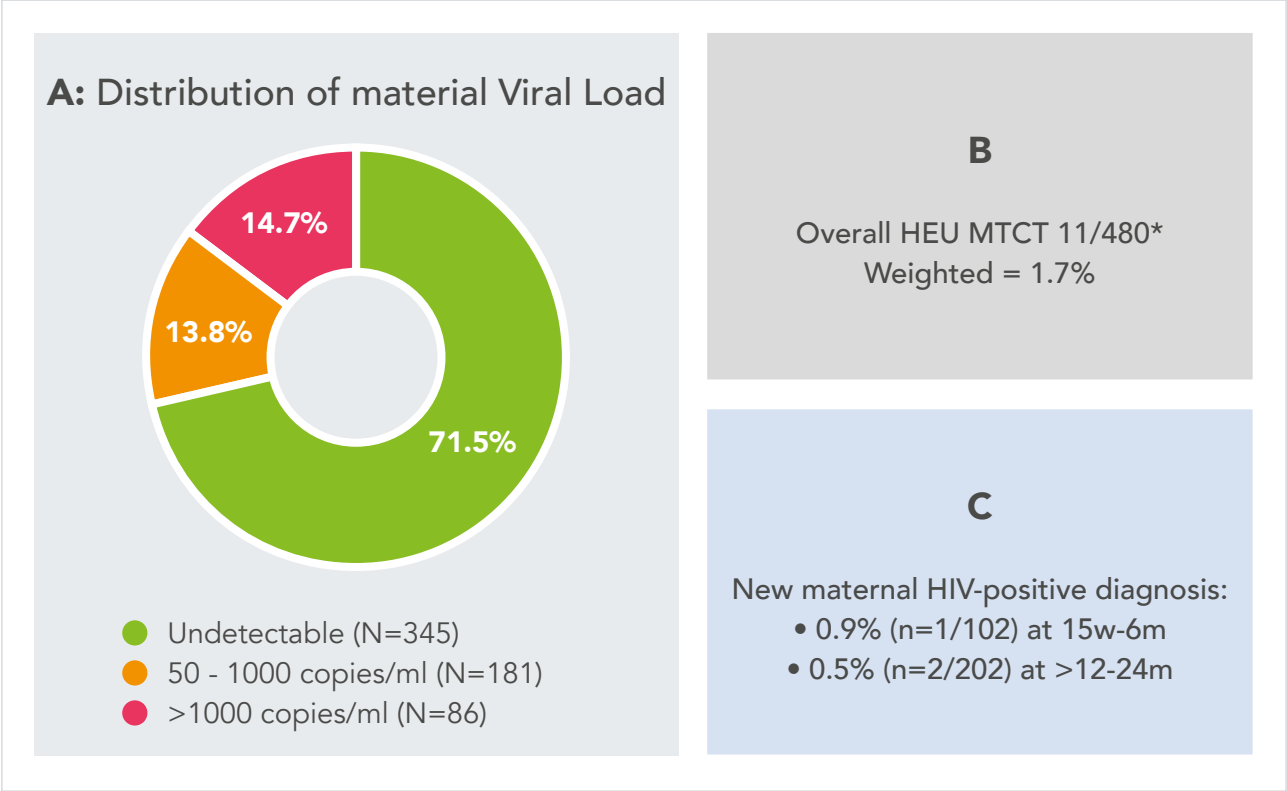

*Figure 5. A: Observed distribution of maternal viral load amongst all HIV-positive women with a viral load result, B: *MTCT calculated from infants who were HIV-exposed at enrolment, and C: postnatal maternal HIV-positive diagnoses rate.*

The detailed prevalence of maternal viral load (mVL) non-suppression by study population characteristics is provided in **Appendix -Table A2**. The proportion of viral load non-suppression (VL>1000 copies/mL) was significant when women were grouped by their source of income, duration on ART or ART regimen. The proportion of viral load non-suppression was higher amongst women who depended on a parent/relative (24%) or spouse/partner (19%) as their main source of income compared to women relied on their own income either obtained from government grants or employment (~8%-11%) (p-value= 0.018) . The proportion of viral load non-suppression was also higher amongst women who had been on ART for no more than one year compared to those who had been on ART for more than 12 months (21.4% versus 12.5%, respectively, p-value=0.029). The proportion of viral load non-suppression was 16.5% amongst women on first line ART regimen compared to 7.7% amongst those on second/third line regimen (p-value=0.016). None of the infant related postnatal PMTCT characteristics appeared to distinguish women by prevalence of viral load non-suppression.

The regression model to investigate factors which strongly predict women who are likely to have viral load non-suppression identified four maternal characteristics with strong associations (**Table 1- Adjusted Odds ratio p-values<0.05**) and two characteristics with weak associations (**Table 1- Odds ratio p-values<0.05**). No infant-related characteristics were significantly associated with maternal viral load in this sample. We associations indicate that women who **recently initiated ART** (no more than 12 months on ART) and women who **did not know the HIV status of their male partner** were more likely to have viral load above 1000 copies/ml compared to their counterparts. Strong associations indicated that **women younger** than 25 years were more likely to be virally unsuppressed compared to women older than 34 years of age; women on **first line regimen** were more likely to be virally unsuppressed compared to women on second or third line regimen; **married/cohabiting** women were more likely to be virally unsuppressed compared to the rest of the women; and women with excessively high BMI (40.0-80.0) were LESS likely to be virally unsuppressed compared to women who had healthy BMI of 18.5 – 24.9.

Table 1: Factors associated with maternal viral load non-suppression among all HIV-positive women

N = 612	Odds Ratio [95% Confidence Interval]	p-value	Adjusted Odds Ratio [95% Confidence Interval]	p-value
Time since ART initiation				
>12 months	ref			
≤12 months	1.9 [1.1, 3.4]	**0.031**	1.7 [0.8,3.6]	0.126
Current ART regimen				
2nd/3rd line or unknown	ref			
First-line	2.4 [1.2, 4.8]	**0.018**	2.3 [1.1,4.6]	**0.026**
Age in years				
35 - 46	ref			
25 - 34	1.4 [0.7,2.8]	0.376	1.1 [0.5,2.4]	0.733
15 - 24	2.6 [1.1,6.2]	**0.029**	2.6 [1.1,6.4]	**0.037**
BMI				
18.5 - 24.9	ref			
13.0 - 18.4	0.7 [0.1, 3.8]	0.689	0.8 [0.2,4.4]	0.8146
25.0 - 29.9	1.4 [0.7,2.8]	0.379	1.4 [0.6,2.9]	0.415
30.0 - 39.9	0.5 [0.3,1.0]	0.051	0.5 [0.3,1.1]	0.089
40.0 - 80.0	0.4 [0.2,1.2]	0.112	0.3 [0.1,0.9]	**0.028**
Married/Cohabiting				
No	ref			
Yes	1.6 [0.8, 2.8]	0.124	1.9 [1.0,3.7]	**0.042**

N = 612	Odds Ratio [95% Confidence Interval]	p-value	Adjusted Odds Ratio [95% Confidence Interval]	p-value
Partner's HIV status				
Negative	ref			
Positive	1.9 [0.9,4.3]	0.101	1.9 [0.9,4.1]	0.096
Don't know	2.3 [1.2,4.7]	**0.020**	2.1 [0.9,4.8]	0.080
Condom use frequency				
Never	ref			
Sometimes	0.8 [0.3,1.9]	0.579	0.8 [0.3,2.0]	0.628
Always	1.2 [0.6,2.6]	0.583	1.1 [0.6,2.1]	0.769
Household gross income/month				
>R3200	ref			
R3200 or less/none	0.6 [0.3, 1.1]	0.099	0.6 [0.4,1.0]	0.073

Significant p-values from logistic regression test of association between mVL and independent variables are in bold font

DISCUSSION

The prevalence of mVL<1000 copies/mL in this rural South African district was estimated at 85.3%, and is still below the UNAIDS 2020 and 2030 targets of 90% and 95%, respectively, amongst persons on ART[3, 4]. However, the district is performing well when compared to the national average VL suppression prevalence of 79.5%, reported in the 2017 South Africa national antenatal survey estimate [2]. But it appears to perform lower than an urban setting (91%) within South Africa[5]. The increased risk of high viral load among women on first line ART regimen could a combination of the observed effect of recent ART initiation, efavirenz-based first-line ART which has been observed to delay viral suppression[6], high risk of drug resistance in rural South Africa population[7], long 6-months window of routine follow-up visits when viral load is less than 1000copies/ml [8], thus giving too much time to have higher unnoticed viral load fluctuations before the next routine visit. The observed association with young women and adolescents is uncommon and indicates that more work still needs to be done to support this highly vulnerable group.

The high prevalence of unsuppressed VL observed amongst women who depended on a spouse or other family member could be related to the high proportion of women not knowing the HIV status of their mail partner. Other previous work in Mpumalanga province showed that non-disclosure of HIV status increased the risk of poor ART adherence[9]. Partner disclosure in another African setting showed improved healthcare outcomes amongst women and their children[10]. More work is needed to encourage partner HIV disclosure in this community.

The protective association with high BMI is unclear and requires further proper investigation.

4.3 ESTIMATING MISSED OPPORTUNITIES FOR HIV DIAGNOSIS FOR MOTHERS AND INFANTS - Secondary Objective i

Out of the 363 infants who were eligible for a study PCR test, only 1 had a positive result. The total weighted PCR-positivity rate in the study sample, including 10 infants enrolled with a known HIV-positive status was 1.7% (**Figure 5B**).

A total of 3 out of 304 women enrolled HIV-negative (or with unknown HIV status), had an HIV-positive diagnosis in the study and the weighted maternal positivity rate was 1.0% (**Figure 5C**). This positivity rate was 0.9% and 0.5% at the 15weeks-6months and 12-24 months postnatal stages, respectively.

DISCUSSION

Only 1 infant had a positive PCR test result in the study indicating that coverage of routine early infant diagnosis in the study clinics was high. Although the missed opportunities for diagnosis of postpartum women appear to be very low, a large and appropriately powered sample size is required to provide a reliable estimate.

4.4 UNDERSTAND FEEDING PRACTICES AND INFANT ANTIRETROVIRAL PROPHYLAXIS COVERAGE- Secondary Objective ii

Box A: Overview of infant feeding practices and antiretroviral prophylaxis coverage at different postnatal stages

	0 - 14 weeks	15 weeks - 6 months		>6 - 12 months	>12 - 24 months	
FEEDING:	HE, N=144	HE, N=85	Unexposed, N=102	HE, N=135	HE, N=116	Unexposed, N=202
currently breastfeeding	75.0%	**67.8%**	**80.2%**	55.3%	**29.7%**	**39.3%**
infant formula - ever	50.6%	55.7%	45.9%	60.3%	**72.2%**	**54.0%**
water - ever	28.0%	62.2%	62.3%			
counter/trad meds - ever	22.3%	52.1%	48.2%			
solids - ever	9.2%	45.1%	46.7%			
Current prophylaxis	68.50%	28.50%		13.40%	8.70%	

INFANT FEEDING PRACTICES: Three quarters of HIV-exposed infants aged 0-14 weeks were being breastfed and half of these infants were already taking formula milk. At 6 months, although breastfeeding remains high with two thirds of HIV-exposed infants being breastfed, this is lower than 80% observed for unexposed infants. Other types of feeding such as formula and solids are the same at 6 months. After 1 year of age, more HIV exposed infants appeared to still be taking formula milk and a around 30% were still being breastfed.

INFANT PROPHYLAXIS COVERAGE: This study was conducted when antiretroviral prophylaxis was universally issued during the first 6 weeks of life alone. Longer duration of infant prophylaxis was issued for infants at high risk of infection. The coverage of around 68% amongst infants 0-14 weeks is therefore acceptable. It is encouraging that some infants were still on prophylaxis (more than 90% on nevirapine) after 14 weeks and some until one year of age and above, indicating that there were some considerations to support infants at high risk of HIV infection.

Box B: Exclusive and extended breastfeeding amongst mothers with VL≤ 1000 copies/mL versus mothers with VL<1000 copies/mL

	VL≤1000		VL>1000		
	N	% [95% CI]	N	% [95% CI]	P-value
Current exclusive BF at 0-6 months					0. 105
Yes	59	32.3 [22.0, 44.6]	4	10.5 [2.1, 39.4]	
No	123	67.7 [55.5, 78.0]	17	89.5 [60.6, 97.9]	
Current extended BF at >12-24 months					0.786
Yes	17	18.9 [11.6, 29.1]	3	23.1 [7.4, 52.9]	
No	48	51.0 [35.1, 66.5]	8	51.6 [27.3, 75.3]	
No response	30	30.2 [14.9, 51.9]	4	25.2 [10.2,50.0]	

Exclusive breastfeeding was defined as breastfeeding with or without intake of over-the-counter medicines but no water, formula milk or solids. Less than a third of HIV-exposed infants aged 0-6 months oldy were currently exclusively breastfed. About a fifth of HIV-exposed infants older than one year of age were still breastfeeding. The prevalence of exclusive breastfeeding at 0- 6 months and of breastfeeding beyond one year postpartum was not significantly different between women with **VL≤1000** and those with **VL>1000**.

Box C: Exclusive and extended breastfeeding amongst HIV-exposed infants versus unexposed infants

	HIV-exposed		Unexposed		
	N	% [95% CI]	N	% [95% CI]	P-value
Current exclusive BF at 15weeks -6m					0.450
Yes	14	19.6 [9.1, 37.3]	12	13.9 [6.9, 26.1]	
No	71	80.4 [62.7, 90.9]	90	86.1 [73.9, 93.1]	
Current extended BF at >12-24 months					0.008
Yes	24	18.0 [10.5, 29.0]	73	38.0 [35.2, 40.7]	
No	57	56.3 [35.1, 75.5]	114	52.7 [43.8, 61.5]	
No response	35	25.7 [8.4, 56.7]	15	9.3 [4.2, 19.5]	

Continued exclusive breastfeeding around 6 months alone, was low and below 20% regardless of HIV exposure status. There was no significant difference between HIV-exposed and unexposed infants in the prevalence of continued exclusive breastfeeding around 6 months. Breastfeeding beyond one year of age was significantly lower amongst HIV-exposed infants and below 20%, compared to unexposed infants where nearly 40% of infants were still breastfeeding.

DISCUSSION

In this district, breastfeeding during the first 6 months postpartum is high and reaches 80% but decreases after one year postpartum to around a third. Amongst HIV-exposed infants alone, breastfeeding prevalence tends to decrease earlier after 14 weeks to two thirds around 6 months postpartum and to below a third after 12 months postpartum. Maternal viral load level did not influence breastfeeding practices significantly, however maternal HIV status influenced breastfeeding status after one year postpartum. There were twice as more unexposed infants still breastfeeding after one year postpartum compared to HIV-exposed infants.

These results reflect three possible practices in the district. The first is that there is likely good promotion of uniform exclusive breastfeeding practices during the first 6 months postpartum regardless of maternal HIV status. This affirms that the healthcare providers follow the currently recommended infant feeding guidelines which seek to promote equal breastfeeding amongst all infants. The second is that women are given similar feeding messages regardless of HIV Viral load status. This also reflects that efforts are in place to ensure that women who present with high viral loads are supported accordingly to ensure viral suppression is achieved and reduce the risk of vertical transmission. The third, is that there is hesitancy to breastfeed for a longer period of time amongst HIV-positive women.

Recommendation: *The implementation of infant feeding practices during patient-healthcare worker interactions needs to be reviewed.* With the current PMTCT policy which monitors maternal viral load more frequently, hence likely to ensure sustained viral suppression, plus the approval of *longer duration of infant prophylaxis*, it should be feasible to strengthen feeding counselling and support women to breastfeed beyond 6 months and one year with lowest risk of vertical HIV transmission

through breastmilk and maximize long-term health benefits on the child (*Davis 2016, Liu 2015, Kuhn 2013*). Very early mixed feeding also needs to be addressed given its association with the increased risk of MTCT when viral load is unknown or unsuppressed (*Woldesenbet 2017, Kuhn 2013*).

4.5 KNOWLEDGE AND PERCEPTIONS ABOUT PREP - Secondary Objective iii

Knowledge and perceptions about PrEP were investigated among both HIV-positive and HIV-negative women (Figure 6). Only 10.0% of women reported to ever have heard about PrEP, and 15.4% of comprised HIV-negative women and 16.6% of HIV-positive women. Of those who already knew about PrEP about 70% had heard about it from clinic/healthcare workers and over 95.0% knew that it was for preventing HIV infection. Condom use was less frequent regardless of PrEP knowledge, with less than half of women reporting frequent use. There was a tendency for more HIV-negative women (61.5%) compared with HIV- positive women (36.2%) to think that their sexual partners would consider taking PrEP (p=0.089).

More than 90% of HIV-negative women perceived that they would not have problems adhering to a daily dose of PrEP, particularly if there are no side effects. The clinic was the most preferable provider for PrEP drugs. However, several perceived challenges with taking PrEP were raised, the commonest being drug side effects (63.2%) followed by adherence challenges (22.6%). At least 65.3% women thought that adequate PrEP use could be supported through counseling and knowing side effects.

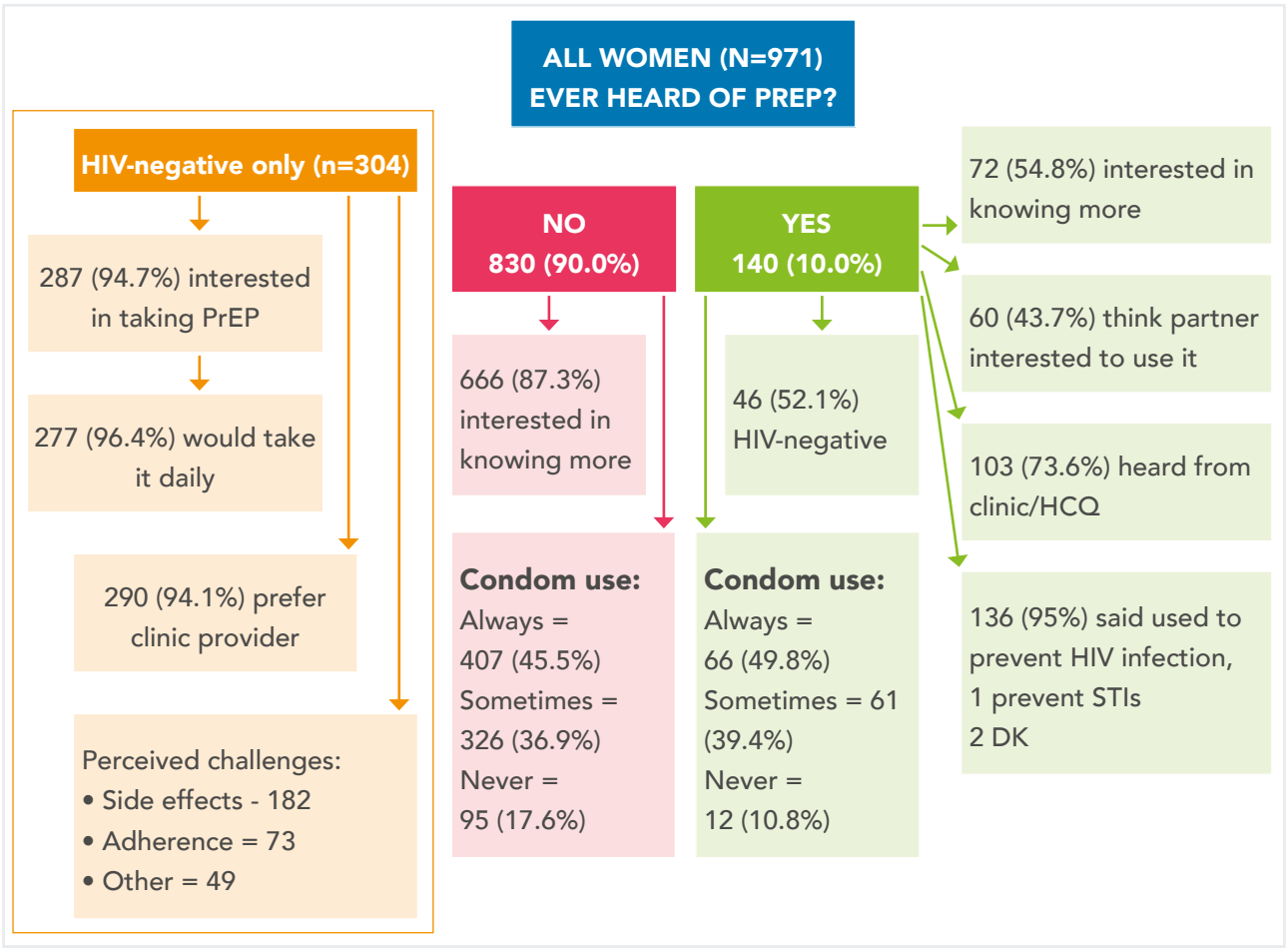

Figure 6: Summary of knowledge and perceptions about PrEP

DISCUSSION

Lack of knowledge about PrEP amongst HIV positive and negative postpartum women in this rural district is high and considerations to make PrEP available and increase its awareness are needed urgently, given that Ehlanzeni is one of South Africa's priority districts for reducing HIV incidence in mothers and eliminating vertical HIV transmission. Our findings highlight several lessons for designing programmes to rollout PrEP in Ehlanzeni district, that fall within three domains of the RE-AIM framework for implementation science, i.e. REACH and MAINTENANCE (both operationalized at individual level) and ADOPTION (operationalized at healthcare provider and program levels)[11].

Reach: Our results show that there is a high need for PrEP amongst breastfeeding (and pregnant) women in Ehlanzeni. The high prevalence of not knowing a partner's HIV status combined with infrequent condom use, in a culture where breastfeeding practice is high raises concerns with eliminating vertical HIV transmission. A total of 27% of HIV-positive women in our study were diagnosed HIV-positive for the first time during the first ANC visit and many had unplanned pregnancies, indicating the high need for PrEP pre-conception. These data also highlight a great need to increase the awareness of PrEP, how it should be used with other interventions such as condoms and make it accessible to male partners of pregnant and breastfeeding women. The role of unknown partner's HIV status, amongst other factors, in elevating HIV risk during pregnancy and breastfeeding has previously been reported in the same province[12]. This further emphasizes the need to make PrEP widely available in the wider community outside of healthcare facilities.

Maintenance: Successful PrEP implementation would require continued support activities to keep the demand high amongst those who need it most. Based on this study, such activities should include counselling with focus on safety concerns and motivational mobile messaging, all coupled with family support and partner involvement. Ongoing safety monitoring would be needed to support existing evidence for pregnant and breastfeeding women[13].

Adoption: In this survey, most women preferred a facility-based delivery model for accessing PrEP. Guidelines for implementing PrEP in South Africa already exist[14] and for Ehlanzeni, these can be integrated to the existing antenatal and postnatal routine HIV prevention care. This approach will likely reach many high-risk pregnant women given that a high proportion enroll early for the first ANC visit. However, due to generally lower retention in care during the postpartum period, healthcare facility-based delivery of PrEP will not offer sufficient coverage. Other client-centered innovative approaches outside of the healthcare facility, e.g. education institutions to benefit younger women and community-based access to lure male-partner involvement, will need to be put in place to make PrEP widely accessible to all who need it[15].

5. MAIN STUDY LIMITATIONS

The study has selection bias of biological mothers who attend clinic with their infants and hence might be under-estimating mVL non-suppression prevalence by excluding those women who assign child postnatal care activities to other caregivers. HIV-negative women were also less frequently identified visiting the clinics, thus affecting the sample size attainment.

The cross-sectional design of the study did not allow us to understand:

- the exact duration of infant prophylaxis intake and the characteristics of infants who were offered extended prophylaxis.
- the time-sequence relationship between the duration of infant prophylaxis versus the duration of exclusive breastfeeding and the duration of unsuppressed maternal viral load. Such longitudinal data would make it possible to investigate whether there is sufficient support for safe breastfeeding to reduce the risk of HIV transmission through breastmilk.

The facility-based recruitment is efficient but likely captures infants during the vaccination age points and hence excludes mother-infant pairs with infants who are in the age-bands which do not have routine vaccination activities during the time of the study.

Picture: During training of data collectors by Nelspruit Lancet - understanding tools for blood draw

6. STUDY RECOMMENDATIONS FOR POLICY CONSIDERATIONS

KEY OBSERVATIONS	POLICY IMPLICATIONS
ON MATERNAL HIV VIRAL LOAD • Viral load suppression amongst pregnant and breastfeeding women is 71% (for viral load below 50 copies/ml) and 85% (for viral load below 1000 copies/mL) and has not reached the WHO/UNAIDS target of 95% either way. • High viral load >1000 copies/mL is associated with gaps in monitoring and supporting women on first line antiretroviral regimens. • Close to 70% of women living with HIV breastfeed their infants sometime during the first two years • Young and adolescent women still at high risk of unsuppressed viral load.	These results provide strong evidence that monitoring viral load suppression should be performed more frequently than 6 months to provide timeous and informed antiretroviral treatment counselling and management. The results therefore, encourage the new 2019 PMTCT guidelines which are recommending frequent viral load visits, to strength the implementation of this policy and follow-on with periodic monitoring and evaluation of impact. Complimentary infant prophylaxis like injectables can be considered to reduce infection risk when achieving sustained viral load suppression throughout breastfeeding is challenging. Adolescent-friendly healthcare provision needs to be prioritized.
ON MATERNAL HIV DIAGNOSES • New HIV-positive diagnoses observed during the antenatal period are still high, over 25%. • HIV-positive diagnosis is still observed among postnatal mothers.	Earlier uptake of the first antenatal care visit needs to be improved to ensure earlier uptake of ART amongst HIV-positive pregnant women without prior HIV diagnoses. Systematic monitoring of HIV diagnoses in pregnant and postpartum mothers is needed to identify and distinguish gaps between new incidence cases already in care and previously undiagnosed late enrollers into care.
ROLE OF MALE PARTNERS • Women who depend on their male partners for income and those who do not know their male partner's HIV status are at high risk of poor HIV clinical outcomes	Innovative ways to integrate male partner participation in PMTCT is needed. Safer sex counselling and support services need to be strengthened with the PMTCT program to also support women who are not able to involve their male partners.

KEY OBSERVATIONS	POLICY IMPLICATIONS
INFANT FEEDING AND PROPHYLAXIS COVERAGE • Breastfeeding for an extended period, beyond 12 months as recommended by WHO [16], appears to be quite low and the same between HIV-positive and HIV-negative women.	Social science work is needed to understand why women in the district do not breastfeed for the minimum recommended duration. Current recommendations for longer infant prophylaxis and frequent viral load monitoring are an opportunity to encourage virally suppressed HIV-positive women to breastfeed for longer.
PREP • Knowledge about PrEP is poor amongst PMTCT clients in this district • This could be the case across many rural and remote districts	The district is recommended to participate in the current PrEP campaigns and integrate it into routine PMTCT services and other community-access points. Innovative ways to reach marginalized settings and educate them about PrEP using messages understandable to the local cultural context are needed.

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8. ACKNOWLEDGEMENTS TO EHLANZENI COMMUNITY

THE RESEARCH TEAM IS THANKFUL TO THE:

DEDICATED **STUDY NURSES** (DATA COLLECTORS) AND THEIR SUPERVISORS MOST OF WHOM LEFT THEIR HOMES TO WORK IN REMOTE CLINICS FOR 12 WEEKS.

FACILITY MANAGERS AND **STUDY PARTICIPANTS** FOR WELCOMING AND SUPPORTING THE STUDY

ROB FEREIRRA REGIONAL LAB MANAGERS FOR THEIR PATIENT SUPPORT IN HANDLING STUDY SAMPLES ON A DAILY BASIS

NELSPRUIT LANCET LABORATORIES FOR PROVIDING TRAINING ON BLOOD COLLECTION

AQUAH FOR OFFICE ACCOMODATION THROUGHOUT THE DATA COLLECTION PERIOD

RIGHT-TO-CARE FOR EARLY STUDY DISCUSSIONS AND SUPPORTING WITH SPACE PROVISION WITHIN CLINICS

DISTRICT AND PROVINCIAL PMTCT MANAGERS FOR THEIR SUPPORT FROM STUDY CONCEPTION TO STUDY COMPLETION

Picture: District support partner offices located with Ehlanzeni district provided office accommodation for the study team

Picture: Nurses practicing DBS blood collection on one another during training offered by Nelspruit Lancet

9. APPENDIX

Table A1: Targeted and realized sample size by study group

Study Group	Mother's HIV status	Target sample size	Sample achieved n(%)	Viral load sample n(%)	Lessons learned from sites with lower sample size achieved
Group 1 (Pregnant women)	Positive	200	187 (94)	176 (88)	Remote rural clinics in Bushbuckridge
Group 2 (Mother and 0-14 weeks old baby)	Positive	200	144 (72)	128 (64)	Clinics where baby rooms are physically distant from other clinic activities
Group 3 (Mother and 15weeks-6 months old baby)	Positive	200	85 (43)	75 (38)	No immunization visit point
Group 3 (Mother and 15weeks-6 months old baby)	Negative	400	94 (23)	n/a	No immunization point. Few HIV-negative biological mothers visited the clinics
Group 4 (Mother and >6-12months old baby)	Positive	200	135 (68)	123 (62)	One immunization point
Group 5 (Mother and >12-24months old baby)	Positive	200	116 (58)	110 (55)	One immunization visit point. Remote rural clinics in Bushbuckridge
Group 5 (Mother and >12-24months old baby)	Negative	400	201 (50)	n/a	One immunization point. Few HIV-negative biological mothers visited the clinics
Overall	Positive	1000	667 (66)	612 (61)	
Overall	Negative	800	304 (38)	n/a	

Table A2: Prevalence of maternal VL non-suppression by study population characteristics

		VL≤ 1000 copies/mL		VL> 1000 copies/mL		p-value
		n	% [95% CI]	n	% [95% CI]	
All		526	85.3 [81.6, 88.3]	86	14.7 [11.7, 18.4]	
Study group	3rd trimester	147	82.9 [76.9, 87.6]	29	17.1 [12.4, 23.1]	0.284
	0 - 14 weeks postpartum	112	85.0 [76.5, 90.8]	16	15.0 [9.2, 23.5]	
	15 - 26 weeks postpartum	70	93.1 [82.5, 97.4]	5	6.9 [2.6, 17.5]	
	27 - 52 weeks postpartum	102	82.5 [71.1, 90.1]	21	17.5 [10.0, 28.9]	
	53 -104 weeks postpartum	95	83.6 [74.5, 89.9]	15	16.4 [10.1, 25.2]	
Maternal socio-demographics and ANC						
Age in years	15 – 24	82	76.5 [65.5, 84.8]	23	23.5 [15.2, 34.5]	0.054
	25 - 34	305	86.2 [80.3, 90.5]	46	13.8 [9.5, 19.7]	
	35 - 46	139	89.5 [82.8, 93.8]	17	10.5 [6.2, 17.2]	
BMI	13.0 - 18.4	17	88.1 [63.0, 97.0]	3	11.9 [3.0, 37.0]	0.075
	18.5 - 24.9	171	84.1 [76.5, 89.6]	29	15.9 [10.4, 23.5]	
	25.0 - 29.9	140	79.4 [70.1, 86.4]	35	20.6 [13.6, 29.9]	
	30.0 - 39.9	157	90.7 [86.6, 93.7]	16	9.3 [6.3, 13.4]	
	40.0 - 80.0	36	92.5 [82.6, 97.0]	3	7.5 [3.0, 17.4]	
Education	None	6	66.5 [31.0, 90.0]	2	33.5 [10.3, 69.0]	0.333
	Primary (1-7 years)	41	94.5 [81.2, 98.5]	3	5.5 [1.5, 18.8]	
	Secondary (8-12 years)	297	84.0 [78.5, 88.4]	50	16.0 [11.6, 21.5]	
	Tertiary- certificate	131	85.8 [78.6, 90.9]	24	14.2 [9.1, 21.4]	
	Tertiary- Diploma/ higher	51	86.7 [70.5, 94.7]	7	13.3 [5.3, 29.5]	
Married/ Cohabiting	No	319	87.7 [83.8, 90.9]	43	12.3 [9.1, 16.3]	0.122
	Yes	207	82.1 [74.7, 87.7]	43	17.9 [12.3, 25.3]	
Income sourcea	Employed	145	88.9 [80.6, 94.0]	18	11.1 [6.0, 19.4]	0.018
	Spouse/partner	153	80.9 [72.6, 87.2]	34	19.1 [12.8, 27.4]	
	Parent/relative	72	75.9 [62.8, 85.4]	18	24.1 [14.6, 37.2]	
	Grant	150	91.3 [85.5, 94.9]	16	8.7 [5.1, 14.5]	
Household monthly gross income	>R3200	215	82.0 [75.9, 86.8]	47	18.0 [13.2, 24.1]	0.097
	R3200 or less/none	310	87.5 [82.8, 91.1]	39	12.5 [9.0, 17.2]	

		VL≤ 1000 copies/mL		VL> 1000 copies/mL		p-value
		n	% [95% CI]	n	% [95% CI]	
Partner's HIV status	Negative	98	91.6 [85.8, 95.2]	12	8.4 [4.8, 14.2]	0.081
	Positive	243	85.0 [79.1, 89.4]	36	15.0 [10.6, 20.9]	
	Don't know	184	82.4 [76.4, 87.2]	38	17.6 [12.8, 23.6]	
Condom use frequencya	Never	43	85.9 [75.4, 92.3]	9	14.1 [7.7, 24.6]	0.235
	Sometimes	200	88.6 [82.6, 92.8]	26	11.4 [7.2, 17.4]	
	Always	280	83.2 [77.5, 87.6]	50	16.9 [12.4, 22.5]	
Planned pregnancy	No	289	86.2 [81.0, 90.2]	41	13.8 [9.8, 19.0]	0.611
	Yes	237	84.3 [77.9, 89.1]	45	15.7 [10.9, 22.1]	
Gestational age at ANC-1 visit	≤12 weeks	335	86.6 [81.8, 90.3]	44	13.4 [9.7, 18.2]	0.443
	13-20 weeks	136	83.2 [76.2, 88.5]	29	16.8 [11.6, 23.8]	
	>20 weeks	55	81.9 [70.9, 89.4]	13	18.1 [10.6, 29.1]	
Number of ANC visitsa	0-4 visits	180	85.1 [79.5, 89.3]	30	14.9 [10.7, 20.5]	0.921
	5-12 visits	345	85.4 [81.1, 88.8]	56	14.6 [11.2, 18.9]	
ART-related factors						
Timing of HIV-positive result	Before pregnancy	394	87.3 [82.6, 90.9]	54	12.7 [9.1, 17.4]	0.086
	At ANC-1 or after	132	79.8 [71.1, 86.4]	32	20.2 [13.6, 28.9]	
Time since ART initiation	>12 months	392	87.5 [83.0, 90.9]	50	12.5 [9.1, 17.0]	0.029
	≤12 months	134	78.6 [70.3, 85.0]	36	21.4 [15.0, 29.7]	
Current ART regimen[a]	2nd/3rd line or unknown	107	92.3 [85.9, 95.9]	12	7.7 [4.1, 14.2]	0.016
	First-line	417	83.5 [79.5, 86.9]	74	16.5 [13.1, 20.5]	
Missed an ART dose last 7 days	No	501	85.7 [82.1, 88.6]	81	14.4 [11.4, 17.9]	0.294
	Yes	25	78.1 [56.0, 90.9]	5	21.9 [9.1, 44.1]	
Facing any ART adherence challenges	No	331	86.3 [81.3, 90.0]	45	13.8 [10.0, 18.7]	0.551
	Yes	195	83.7 [75.8, 89.4]	41	16.3 [10.6, 24.2]	
Infant related factors (postpartum sample only)						
	All	379	85.8 [81.4, 89.4]	57	14.2 [10.6, 18.6]	
Infant HIV status at enrolment	Negative	296	85.4 [80.3, 89.4]	49	14.6 [10.6, 19.7]	0.882
	Positive	9	88.3 [50.1, 98.3]	1	11.7 [1.7, 49.9]	
	Unknown	74	87.5 [72.6, 94.9]	7	12.5 [5.1, 27.5]	
Infant currently on ARV prophylaxisa	No	258	87.0 [81.8, 90.0]	35	13.0 [0.1, 18.2]	0.326
	Yes	119	83.5 [75.3, 89.4]	21	16.5 [10.7, 24.7]	

		VL≤ 1000 copies/mL		VL> 1000 copies/mL		p-value
		n	% [95% CI]	n	% [95% CI]	
Infant ever breastfeda	No	124	82.3 [72.7, 89.1]	22	17.8 [11.0, 27.3]	0.231
	Yes	254	87.4 [82.5, 91.0]	35	12.6 [9.0, 17.5]	
Infant currently breastfeeding	Yes	143	87.5 [81.4, 91.8]	20	12.5 [8.2, 18.6]	0.427
	No	111	87.2 [79.9, 92.1]	15	12.8 [7.9, 20.1]	
	Chose not to disclose	125	82.5 [73.0, 89.2]	22	17.5 [10.8, 27.0]	
Gestational age at birtha	≤37 weeks	56	83.1 [70.9, 90.8]	11	16.9 [9.2, 29.1]	0.466
	38 - 42 weeks	322	86.9 [81.9, 90.7]	45	13.1 [9.3, 18.1]	
Infant birth weighta	Birth weight≥2.5kg	345	86.6 [82.3, 89.9]	47	13.4 [10.1, 17.7]	0.151
	Low birth weight	33	78.4 [61.9, 89.1]	10	21.6 [10.9, 38.1]	

ANC – antenatal care; ART-antiretroviral; BMI- Body mass index