Prevention of mother-to-child-transmission of HIV in Khayelitsha: a contemporary review of services 20 years later

Florence Malehlabathe Phelanyane

PHLMAL003

Submitted to the University of Cape Town in partial fulfilment of the requirements for the degree of

MASTER OF PUBLIC HEALTH (MPH) in Epidemiology and Biostatistics

School of Public Health & Family Medicine

University of Cape Town

February 2021

Supervisor:

Dr Emma Kalk

Centre for Infectious Disease and Epidemiology & Research

School of Public Health & Family Medicine

University of Cape Town

DECLARATION

I, *Florence Malehlabathe Phelanyane*, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signed by candidate

Signature: ……

Date: 2021-03-01 ……

Background: It's been 20 years since the Western Cape (WC) province of South Africa launched its first Prevention of Mother-To-Child-Transmission of HIV(PMTCT) pilot programme in Khayelitsha. The programme evolved alongside the World Health Organization (WHO) guidelines; in 2013 the recommended guidelines in the province was WHO Option B+(life-long antiretroviral therapy (ART) irrespective of CD4 count, and exclusive breastfeeding for the first 6 months of life). Alongside the explanation of the PMTCT programme, the province gradually implemented patient administrative systems in all fixed public health facilities; these systems all shared a unique patient identifier called the folder number. The digitization of folder number lead to the establishment of the Provincial Health Data Centre (PHDC), an African health information exchange (HIE) developed and hosted in the WC Department of Health.

The HIE also integrated data from disease management information systems (Three Interlinked Electronic Registers (TIER) and the Electronic Tuberculosis Register (ETR)), allowing the ability to track the cohort of pregnant women living with HIV who attend public health services across the Western Cape. Here we report the latest analysis of vertical HIV transmission in the era of WHO Option B+ with the advantage of a maturing consolidated African HIE. The primary aim of the study was to describe coverage of the PMTCT care cascade, including the implementation of maternal viral load monitoring and early infant diagnosis, among HIV positive women who presented antenatal care, or delivered in the absence of antenatal care, at a public health facility in Khayelitsha sub-district in 2017; and to quantify MTCT risk factors and outcomes among this cohort up to 12 months post-partum.

Methods: Patient-level consolidated PHDC data were used to draw an observational cohort consisting of all live-born and linked mother-infant pairs in which the mother was HIV positive, at any point prior to her first antenatal visit up to 12 months post-partum and attended antenatal care, or in the absence of antenatal care delivered in Khayelitsha in 2017. The PHDC provided a single summative record per pregnancy for each woman (linked to her infant after birth) which enabled the assessment of PMTCT uptake from her first antenatal visit through delivery to infant early infant diagnosis (EID) of HIV-PCR testing and PHDC ascertainment of HIV up to the end of the index period (i.e. 12 months post-partum).

Using this cohort of HIV-exposed infants, a protocol was designed (Section A: Protocol) to assess the outcomes of the implementation of WHO Option B+(lifelong ART for all HIV positive pregnant women; and periodic re-testing of HIV negative women) under the latest EID guidelines of routine birth HIV-PCR (within 1 week of birth), and repeat testing at 10 weeks (between 2 and 14 weeks of birth) or a first HIV-test at 10 weeks if the infant had not been tested at birth.

Continuous variables were converted to categorical variables according to pre-set thresholds, all categorical variables were described using proportions, and frequency tables were used for comparison. Timing of ART initiation was categorized as a binary variable which was assigned 1 if the mother started ART before the first antenatal visits, and 0 of she started ART at the first antenatal visit or anytime during the pregnancy. Viral load was categorised according to coverage and suppression status; virologic suppression was defined as having a viral load of 1000 copies/ml or less after 3 months on ART. Analysis was performed in using R studio; descriptive statistics were used to assess coverage along the PMTCT care cascade, and logistic regression was run to quantify *a priori* defined risk factors associated with MTCT.

Results: The study cohort of 2 576 mother-infant pairs (2548 women living with HIV (WLHIV)) presented in the manuscript was a young cohort with a median age of 30 years (interquartile range of 26 – 34), in which most women delivered vaginally (70.5%), and 78.3% attended at least one antenatal visit before delivery.

Most WLHIV (88.3%) presented to their first pregnancy related visit (antenatal care or delivery) already knowing their status, of whom 77.9% were already on ART. 94.5% of women diagnosed prior to birth were initiated on ART prior; 85.0% of these women received a viral load test antenatally, of whom 88.0% were virologically suppressed. Early infant diagnosis coverage was sub-optimal with birth HIV-PCR (within 7 days of birth) coverage of 79.21% among HIV exposed infants (HEI); an even lower proportion (57.9%) of HEI who tested negative at birth had a repeat test around 10-weeks. HIV-PCR ascertained MTCT was 0.8% at 10 weeks, consolidated data from the PHDC suggested an MTCT of 1.8% by the end of the index period (the PHDC HIV episode identified an additional 16 HIV-exposed (HEI) infants with HIV who were not detected by laboratory tests).

PWLHIV who started ART prior to the first antenatal visit had 50% reduced risk of MTCT compared to those who started ART during the pregnancy. Women who were not suppressed antenatally had a 5-fold (aOR = 5.3, 95% CI: 2.5 – 12.3) increased MTCT risk compared to those were suppressed antenatally. Women who did not attend ANC were at highest risk of transmission (aOR=1.6,95%CI: 0.7 – 3.6).

Conclusion: Although women most women present to care already knowing their HIV status, ART initiation and uptake of viral load testing is very low at presentation but improved significantly during pregnancy, evidence of maturing PMCT services. National and Provincial MTCT is likely to be underestimated as it relies solely on PCR results; the uptake of the birth PCR among HIV-exposed infants is still not 100% (where it should be) and the uptake of a repeat tests among infants that tested negative is even lower. PHDC data, which consolidates HIV data from multiple sources, revealed a higher MTCT than HIV-PCR testing alone.

ACKNOWLEDGMENTS

I would like to thank my supervisor and investigator on the B-Positive project, Dr Emma Kalk, for the tremendous guidance and support throughout.

Prof Andrew Boulle, the Principle Investigator on the B-positive project, for coming up with the project and giving me the opportunity to work on it.

The Provincial Health Data Centre team for their continuous hard work on the data, making this kind of analysis possible.

My late father for his love and support throughout my academic career. My mother, brother, sister, and brother in-law for all their encouragement.

Co-authors on the manuscript:

Alexa Heekes, Centre for Infectious Disease & Epidemiology Research, School of Public Health & Family Medicine, University of Cape Town

Mariette Smith, Centre for Infectious Disease & Epidemiology Research, School of Public Health & Family Medicine, University of Cape Town

David Coetzee, Centre for Infectious Disease & Epidemiology Research, School of Public Health & Family Medicine, University of Cape Town

Andrew Boulle, Centre for Infectious Disease & Epidemiology Research, School of Public Health & Family Medicine, University of Cape Town

Jonathan Euvrard, Centre for Infectious Disease & Epidemiology Research, School of Public Health & Family Medicine, University of Cape Town

Nisha Jacob, Centre for Infectious Disease & Epidemiology Research, School of Public Health & Family Medicine, University of Cape Town

Emma Kalk, Centre for Infectious Disease & Epidemiology Research, School of Public Health & Family Medicine, University of Cape Town

TABLE OF CONTENTS

PART B: MANUSCRIPT

PART C: APPENDICES

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

aOR	Adjusted Odds Ratio
ANC	Antenatal Care
ANS	Antenatal Survey
ART	Antiretroviral Therapy
ARV	Antiretroviral
AZT	Zidovudine
CI	Confidence Interval
EID	Early Infant Diagnosis
HIE	Health Information Exchange

HIV	Human Immunodeficiency Virus
IQR	Interquartile Range
MOU	Midwife Obstetric Unit
MTCT	Mother-to-Child Transmission
NHLS	National Health Laboratory Services
OR	Odds Ratio
NVP	Nevirapine
PCR	Polymerase Chain Reaction
PGWC	Provincial Government of the Western Cape
PHDC	Provincial Health Data Centre
PWLHIV	Pregnant Women living with HIV
PMTCT	Prevention of Mother-to-Child Transmission
POC	Point of Care
SA	South Africa
UNAIDS	The Joint United Nations Programme on HIV and AIDS
VL	Viral Load
WC	Western Cape
WHO	World Health Organization
WLHIV	Women living with HIV

PART A. RESEARCH PROTOCOL

1. Synopsis

Title: Prevention of mother-to-child transmission (PMTCT) of HIV in Khayelitsha: a contemporary review of the service 20 years later

Background: The provision of lifelong antiretroviral therapy (ART) to pregnant women living with HIV (WLHIV) (WHO Option B+) has resulted in better outcomes in prevention of mother to child HIV transmission (PMTCT) programmes. The provision of PMTCT in the Western Cape province of South Africa has a rich history of engagement which began in Khayelitsha, the country's pilot site. PMTCT in Khayelitsha was initially documented through paper registers which evolved to off-line electronic medical records, and then later the data were oragnised in the form of networked electronic disease information systems. The establishment of electronic medical records was assisted by digitization of component data systems such as laboratory, pharmacy and public health facility visits along with associated diagnosis and procedure codes. The digitization of these component systems has allowed for the Provincial Health Data Centre (PHDC), a health information exchange (HIE), to integrate these data with existing electronic HIV disease management information systems, allowing the ability to track an entire cohort of HIV-infected pregnant women who attend public health care across the Western Cape. As the oldest PMTCT site in South Africa, Khayelitsha provides the opportunity to review the effect of the expansion and evolution of PMTCT guidelines over time. Since the inception of the first program in 1999, the impact of PMTCT in Khayelitsha has been regularly reviewed. This study will be the latest to investigate vertical HIV transmission in the era of WHO Option B+ and a maturing linked electronic medical records system.

Purpose and Objectives: The purpose of the study is to examine infant HIV outcomes constructed from multiple HIV laboratory tests (polymerase chain reaction, antibody/serology tests, viral load, CD4 count, and genotypic resistance assays) at birth, 10 weeks, and 12 months for all infants born to women with first evidence of pregnancy in a public health facility in Khayelitsha in the 2017 calendar year. Findings will be placed in

context of the type of PMTCT intervention the mother received up to 12 months post-partum, as well as other variables that impact vertical transmission.

Methods: This study is a sub-analysis within the broader B-positive project, a prospective population- level cohort study designed to assess the risks and benefits of early initiation of lifelong ART among pregnant WLHIV (PWLHIV). This study will include all mother-infant pairs in which the mother had her first evidence of pregnancy in a public health facility in Khayelitsha in the 2017 calendar year.

Descriptive statistics will be used to describe current HIV prevalence and access to ART among pregnant women. Logistic regression will be used to quantify the crude and adjusted associations between study risk factors and HIV transmission at 12 months post-partum. Longitudinal analysis will be used to show time to maternal virologic failure (Kaplan-Meier) and analyse risk factors associated with maternal virologic failure (Cox-proportional hazards)

Risks and Benefits: The major potential risk is a breach of patient confidentiality. To mitigate this risk, the PHDC will only release anonymized data for analysis in which all identifiers have been removed, and dates and other data which could lead to re-identification have been perturbed. The study is therefore considered low risk.

There will be no direct benefit for the mother-infant pairs, but they may benefit indirectly. This analysis of linked mother-infant longitudinal data will allow for the measurement of the uptake of PMTCT, as well the timing of vertical HIV transmission. This evaluation is therefore important both locally and internationally as it allows for more detailed assessment of PMTCT outcomes.

PROTOCOL

Prevention of mother-to-child transmission (PMTCT) of HIV in Khayelitsha: a contemporary review of the service 20 years later

1. Background

Substantial progress has been made in the provision of antiretroviral therapy (ART) and prevention of mother-to-child transmission of HIV (PMTCT) across sub-Saharan Africa, South Africa (SA), and particularly the Western Cape province (WC). Over the period of 1990 to 2015, both the overall HIV prevalence and antenatal HIV prevalence in the WC has been lower than the national estimates (1). The 2015 National Antenatal Survey reported the current antental HIV prevalence in SA and the WC to be 30.8% and 18.9% respectively (NDOH,2017). The WC Provincial AIDS Council Annual Progress Report 2015/6 estimated a provincial HIV vertical transmission rate of 1% at 6 weeks (1).

In 2013, while the South African National Department of Health was implementing World Health Organization's (WHO) "Option B":PWLHIV women inititated on ART regardless of CD4 count with cessation of ART upon the cessation of breastfeeding in those women with CD4 >350 cells/µl)(NDOH,2015); the provincial protocol in the WC introduced WHO "Option B+": the the provision of lifelong ART in PWLHIV irrespective of CD4 count, and support for exclusive breast feeding for up 6 months post-partum (1). The implementation of "Option B+" had important implications for both the *provision* of ART to PWLHIV (ART in pregnancy was initiated in maternity clinics as opposed to dedicated ART clinics), and the *increased uptake of exclusive breastfeeding* among mothers on the program. These changes could impact postnatal HIV transmission, infant health, and the monitoring of program effectiveness. This provision and monitoring of ART in maternity facilities (as opposed to dedicated HIV clinics) has resulted in fewer people being lost to care during the antenatal referral process (i.e. from maternity clinic to HIV care) but may have deferred this risk to the postnatal period (2).

The introduction of WHO Option B+ falls in the era of the reduction of pill burden through the use of the universal fixed-dose combination (FDC) ART. FDC for PWLHIV allows for simplified treatment programes which increases uptake of/adherence to PMTCT (3). ART during

pregnancy and breastfeeding is extremely beneficial in terms of improvements in maternal health and the reduction of vertical transmission, however there are still concerns with respect to the adherence to treatment and effectiveness of PMTCT programmes. The investigation of these concerns is made difficult due to: the absence of robust clinical and information systems in many low resource settings, rapdily changing guidelines and service realities, and the complexities which arise from following up sufficient numbers of HIV-exposed children over time in order to exclude both postnatal HIV transmission and potentially harmful side-effects.

1.1 History of PMTCT In Khayelitsha

Khayelitsha is an urban township, located on the Cape Flats 50kms from the Cape Town city centre. It has a long standing history of PMTCT services which dates back to 1999 when Provinical Government of the Western Cape (PGWC) launched the first pilot PMTCT programme in April; *Médecins Sans Frontières* (MSF) added their technical support in September of the same year. The programme provided antenatal voluntary counselling and testing (VCT) in midwife obstetric units (MOUs) and short course zidovudine (AZT) was dispensed from 36 weeks of gestation. Initially antiretrovirals (ARVs) were provided antenatally only and no further HIV services were offered to women (5). Continuinity of care beyond delivery was poor as post-natal services were framgemented. After complex negotiotiations to get the then resistant national government on board, MSF opened more PMTCT and ART centers, and the provision of ART (to pregnant women and other eligibile patients) evolved with the evolving WHO guidelines(5).

The expansion of PMTCT in the province was based on the provision of maternal single-dose nevirapine (sd-NVP) peri-delivery. Khayelitsha, however, continued with the AZT regimen during the expansion period. Thereafter the regimen changed, in all facilities, to include antenatal AZT supplemented by peri-delivery sd-NVP and post-natal infant prophylaxis (5).

In parallel to the evolving PMTCT regimens, guidelines on the eligibility of pregnant women also expanded, with PWLHIV with a CD4 count of 350 cells/µl or less being eligible for life-long ART from 2013. In 2015, all PWLHIV were eligible for ART regardless of CD4 count. Whereas national policy initially prescribed that woman with CD4 counts above 350 cells/µl

should stop ART after the end of breastfeeding or after delivery if not breastfeeding (WHO Option B), the Western Cape elected to continue all women on lifelong ART irrespective of CD4 count (WHO option B+) (5).

1.1.1 Early Infant Diagnosis

Currently, WHO Option B+ is being implemented for all PWLHIV; HIV-negative pregnant women are re-tested at 20 weeks gestation, 32 weeks gestation, in labour/immediatley after delivery, at the 6 weeks (post-partum) Expanded Programe on Immunisation (EPI) visit, and every 3 months while breatsfeeding. HIV-exposed infants(HEI) are to receive a routine HIV-PCR test at birth, and a repeat HIV-PCR test at 10 weeks if the infant's first result is negative or inconclusive; a HIV-PCR test is also indicated at 10 weeks if an infant did not receive one at birth. All subsequent infant testing is closely tied to EPI: repeat testing at around 18 weeks (breastfeeding HEI who received NVP for 12 weeks then stopped), and at 9 and 18 months (all HEI not on ART, irrespective of feeding choice). The use of a viral load test to confirm the infant HIV-PCR test is no longer recommended (16).

1.1.2 Effectiveness of the PMTCT program in Khayelitsha

It has been 20 years since the Western Cape launched its first PMTCT pilot in Khayelitsha. The pilot site offered HIV counselling and testing, AZT at 36 weeks gestation and during labour, formula feeding, and infant HIV testing at 9 months. The programme was extended to 5 sites by 2001; at this time, sd-NVP was available for use in mothers and infants. By early 2003, the programme was rolled out to MOUs as a predominantly nurse driven service. By July of the same year, findings presented at an AIDS conference in Barcelona demonstrated that short-course AZT used in conjunction with sd-NVP administered to both mother and infant, could significantly reduce vertical transmission. In response, the provincial protocol was revised immediately; the new protocol incorporated these changes along with CD4 testing for all HIV-positive pregnant women and PCR testing of their infants (4).

In 2008, Draper and Abdullah reviewed changes made to the Western Cape's PMTCT protocol and its impact on programme outputs and outcomes in the provincial health system. The

review describes: programme indicators before and after changes made to the PMTCT protocol, the introduction of routine CD4 testing into the programme, and the interface of the PMTCT programme with the introduction of the ART program (7).

Uptake of PMTCT rose by 21% among the total women tested in 2004 from 2003. The number of women who tested positive decreased from 12.4% in 2003 to 11.8% in 2004; for both these years the metropole district had the highest portion of women testing positive, in some subdistricts the proportion exceeded 20%. The proportion of sd-NVP uptake did not changes much from 2003 to 2004, it remained at 60%. However, the administration changed from a predominantly take-home dose in 2003 to more women receiving NVP during labour in 2004. The coverage for both AZT and sd-NVP were same for urban and rural districts in the province (7).

The infant testing guidelines up to 2003 had posed a real challenge of considerable loss to follow up. In 2003, the proportion of children tested at 6 weeks old was 8%, of whom 17.5% tested HIV positive. The introduction of PCR testing at 14 weeks in 2004 lead to 80% of infants in the Metropole being offered testing, of which 98% accepted. 7% of these infants tested HIV positive. A less than 10% vertical transmission rate was reported for 8 of the 9 urban sub-districts (7). These results were consistent with a cross-sectional study by Coetzee *et al*., (4) which reported a 77% coverage of the PMTCT guidelines (according to the then protocol) and a vertical transmission rate of 8.8% (95% Confidence Interval: 6.2 – 10.9).

Maternal CD4 counts had very low coverage, there were no data in 2003; in 2004 there were only data from two national central hospitals, Groote Schuur and Tygerberg. The number of CD4 counts done saw a steady monthly increase, and CD4 counts were done on 51% of the patients during the second half of the year. Of these, approximately 19.8% of these were below 200 cells/ul (7). PWLHIV with a CD4 count < 200 cells/ul were considered to be patients at high risk both obstetrically and for vertical transmission. In 2014, the WC PMTCT protocols were changed to include CD4 testing and referral of women with CD4 count < 200 cells/ul or WHO stage 4 for ART. At that time there was very little evidence on the best approach to implement ART services in resource-poor settings. The integration of ART into MOUs/ANC at a primary care level posed many challenges such as laboratory monitoring requirements,

multiple ANC visits, linkage to post-partum ART, as well as the clinical skills to manage both HIV and pregnancy. MSF responded to these challenges by beginning a pilot project to initiate eligible women on ART within 2 Khayelitsha MOUs in December 2004. This streamlined the process of ART initiation, even among late presenters, and decreased loss-to-follow-up during the referral process. The implementation of the integration posed many challenges, it took 6 years to achieve the objective of midwife-managed ART initiation despite the well-managed and effective nurse-driven ART services at adjoining ART clinics. The increase in the national CD4 threshold from 200 to 350 cells/ul (WHO Option A) saw an increase in the proportion of women eligible for ART during pregnancy. MSF partnered with WCGH to implement the nurse-initiated management of ART (NIMART) mentorship programme in Khayelitsha in December 2011, with the first NIMART-trained midwives providing ART at Site B MOU in 2012 (5).

The first national evaluation of the South African PMTCT (SA PMTCT) programme was conducted between June and December 2010, falling within the transition period between the 2008 and 2010 PMTCT guidelines. The second SAPMTCTE was conducted in between August 2011 and March 2012 during the implementation of the 2010 PMTCT guidelines; this was the first SAPMTCTE to evaluate WHO PMTCT Option A. The third SAPMTCTE was conducted between October 2012 and May 2013; it was second national evaluation of WHO PMTCT Option A. The SA PMTCT guidelines changed from WHO PMTCT Option B in April 2013, and to WHO PMTCT Option B+ in January 2015 (20).

All SAPMTCT evaluations were cross-sectional facility-based surveys whose primary objective was to measure MTCT at 6 weeks post-partum, and secondary objective was to estimate coverage of PMTCT interventions and services (e.g. HIV testing, CD4 count testing, infant ARV prophylaxis, and infant feeding counselling) periodically (20).

The 2011 and 2012-13 studies were conducted after WHO PMTCT Option A was adopted in South Africa and therefore provide population-level data on its effectiveness. The evalutions provide estimates of early MTCT using province-wide and nation-wide population-based representative sample of infants between the ages of 4 and 8 weeks. Results from the SAMPTCTEs show HIV testing in pregnancy decreased from 98.8% (2010-2011) to 95% (2012-

2013), this could be due to more women already knowing their status upon presentation. The reported antenatal prevalence for these periods increased from 32.0% to 33.1%. ART uptake among self-reported PWLHIV increased from 33% (2010-2011) to 55.7% (2012-2013), and more mothers were likely to be initated during the index pregnancy (55.7%) than before it (42.2%) or after it (1.9)%. The weighted MTCT risk decreased from from 3.5% (2010-2011) to 2.6% (2012-2013) (20).

The evaluations also provided data on infant feeding and uptake of the PMTCT program and had a few limitations. The province-wide and nation-wide data was taken from facilities using infants who presented for immunisation; it excluded infants who did not come for immunisation or had already died by 6 weeks, and is therefore creating potential under-estimation of antenatal and intrapartum MTCT. Maternal sero-conversion was based on self-reports of HIV-negative status and the presence of HIV antibodies in the infants ELISA test. Maternal self-report could be confounded by fear of stigma that arises from disclosure; confidentiality was assured and discussed to reduce this potential caveat.
PMTCT program indicator coverage was based on maternal recall and it wasn't verified with maternal antenatal or intrapartum records. Representativeness was another limitation; a two-stage cluster random sample was used to sample only primary health care(PHC) units which reported at least 130 immumusation per year and therefore excluded smaller PHC facilities as well as secondary and tertairy facilites in order to focus on PMTCT in PHC. The last limitation was that none of the surveys measured post-natal tranmission (20).

1.2 The use of unique identifiers enables linkage of patient data across health information systems

The establishment of complete coverage of medical records system poses challenges even in well-resourced settings. Historically, population-level HIV data (including PMTCT data) have been reported in South Africa as aggregates derived from paper registers and were not available centrally at the individual patient level. This had posed many challenges in the understanding of HIV-related health data in the context of high patient mobility between various health facilities. The absence of patient-centric data has made the assessment of linkage to care, uptake of ART and ART-adherence, and losses to follow-up very difficult (17).

The Western Cape Government Health (WCGH) Provincial Health Data Centre (PHDC) has adopted the Patient Master Index (PMI) as a pragmatic approach to digitization which ensures that an individual will have the same unique patient health identifier or folder number across all the provincial health services, while not creating excessive infrastructure requirements which could hinder routine health care operations (9). This shared folder number, the PMI, is hosted by the hospital information system (Clinicom: included in all major hospitals) as well as in the Primary Health Care Information System (PHCIS) used in primary care facilities. Sharing of the PMI is facilitated via web-service communication to determine whether or not the patient has an existing folder number; a new folder number is registered in the event that no record exists, otherwise the patient is allocated the same number (9). All captured information (i.e. both new registrations as well as changes to existing information) are written back to the PMI. The PMI is also used in capturing of laboratory (all laboratory results are currently digitized and stored electronically by the National Health Laboratory Services (NHLS) which provides all government sector laboratory assays) and pharmacy (all hospitals and most primary health care facilities have electronic dispensing) data. Specific disease management systems mentioned above (i.e., electronic registers and disease-specific electronic medical record systems) with complete coverage of treatment 'episodes' are available for HIV and TB, and are also linked to the PMI. There is potential for the PMI to be linked to province-wide mortality systems for all deaths and still-births, as well as a province-wide birth registration system (9).

Figure 1: Figure depicting data harmonization which brings patient-level data, from multiple source systems, together in one place using the unique folder number (PMI).

The PHDC has developed the maternity cascade which identified all pregnancies and consolidates relevant data related to each pregnancy in a single continuously updated dataset, which feeds into operational reports (9). Within the PHDC, an 'episode' is a combination of evidences from clinical data (i.e., clinic visits, dispensing data, test results etc.) that can be used to infer health conditions. For example, visits to an HIV clinic, HIV diagnosis codes, receipt of ART, and HIV related laboratory tests (i.e., CD4 or viral load testing etc.) are all used in the construction of an *HIV Episode*. Episodes can be acute and/or chronic and are not limited to infectious diseases. Each episode is a single record which includes: first and last evidence dates, treatment start and end dates, the facilities in which patients attended, the data sources from which the data were extracted, and the list of evidences used in the episode's construction. A person may have more than one episode for the same condition if that conditions ends (e.g., multiple pregnancies with end dates), but can only have one have one chronic episode (i.e., HIV) with one a start date and a last seen date that is updated each time the patient seeks care (9).

An episode can be rolled up into a 'cascade', which is a comprehensive patient-level depiction of episodes, including key dates, attended facilities, evidences, outcomes and co-morbidities relevant to patient management. Cascades can provide a cohort in the absence of registers, and they can be optimized for operational management purposes. Cascades can occur as line listings of individual patients, or they can be easily aggregated by one more parameters such as time-period, age group, demographic area, demographic (i.e., children under 5 or HIV positive pregnant women) (9).

2. Justification

The transition to WHO Option B+ (July 2013) has been remarkably smooth; women are now initiated on ART frequently with very few women refusing testing and treatment. The implementation of the fixed-dose combinations (FDC) has been easier for both staff and women; the adaptation to adherence to counseling lead to shorter sessions which allowed for same-day initiation. The challenge has shifted from initiation to retention on ART to achieve virological suppression.

Previously, population-level PMTCT studies relied on aggregate data, from either the NHLS or district health indicators, that cannot be reliably de-duplicated; and mother-infant pairs could not be linked to each other. The PHDC contains harmonized longitudinal data on each patient who has ever touched a provincial public health care facility, allowing for linkage of the mother-infant pairs as well as the disaggregation of NHLS laboratory tests (i.e., PCR and/or other HIV-related laboratory tests) per individual infant. The linkage of mother-infant pairs allows for a more accurate comparison of exposure (mother HIV positive and/or ART status) and outcome (infant HIV status). The linkage of exposure and outcome allows for a more accurate timeframe of when transmission occurred.

PHDC longitudinal data also allows us to look at HIV diagnosis in infants not restricted by the availability of pregnancy data, thus allowing the *quantification of HIV infections outside of the PMTCT cascade*. This study offers an edge to comprehensively describe PMTCT implementation in the subdistrict, as well identify the remaining gaps in care.

As the oldest PMTCT site in South Africa, Khayelitsha provides the opportunity to review the effect of the expansion and evolution of PMTCT guidelines over time. Since the inception of the first program in 1999, the impact of PMTCT in Khayelitsha has been regularly reviewed. This study will be the latest to investigate vertical HIV transmission in the era of WHO Option B+ and a maturing linked electronic medical records system.

3. Aims an Objectives

The primary aim is a descriptive analysis of PMTCT uptake and outcomes in the Khayelitsha sub-District of Cape Town in the era of WHO Option B+.

The objectives are to:

- Characterize HIV prevalence and coverage along the PMTCT care cascade among women who attended their first pregnancy visit at a public health facility in the Khayelitsha sub-district in the 2017 calendar year.
- Describe infant HIV PCR testing, and the proportion and timing of MTCT in the 12-months following delivery, among infants born to these women
- To describe associations between maternal risk factors and vertical transmission

4. Methods

The project is a sub-analysis within the B-positive study, a prospective cohort study which considers the risks and benefits of early initiation and lifelong ART among PWLHIV (Appendix C). B-positive uses routinely collected electronic data centralized in the PHDC to determine infant exposures, birth outcomes, and morbidities. This study will use the infrastructure of B-positive and the PHDC to define a cohort of HEI whose mothers attended their first pregnancy visit in Khayelitsha in 2017 and will follow this group longitudinally for 12 months post-partum.

4.1 Study design

A prospective observational cohort analysis of anonymized routine data from Khayelitsha health care facilities defined using the PHDC operational maternity cascade.

4.2 Setting, characteristics of the study population, and sampling

Khayelitsha is township located on the Cape Flats in the Western Cape Province of South Africa. In 2011, the sub-district was home to 319 749 people, of whom 98.6% were black. The 2011 suburb census indicated a 62% unemployment, and 45% of households live in formal dwellings (Statistics SA, 2011). Khayelitsha has 1 district hospital, 2 midwife obstetric units (MOUs), and 25 primary health care facilities. Approximately 8500 women booked into one of these public health facilities for their pregnancy first evidence (either antenatal care or delivery) in 2017.The HIV prevalence among these women was 33%, all of whom were eligible for ART.

Inclusion criteria:

- For the main analysis, the mother-infant pairs in which the mother attended her first pregnancy visit at a public health facility in Khayelitsha during the 2017 calendar year.
    - The mother must be identified as woman living with HIV (WLHIV) at any point prior to or during the index pregnancy, or up to 12 months postpartum.
    - The liveborn infant must have a folder number that can be linked to the mother.

4.3 Research procedures and data collection methods

This analysis will use data from the PHDC Maternity Cascade. The Maternity Cascade is a comprehensive patient-level depiction of pregnancy episodes including key dates (i.e. pregnancy first evidence, pregnancy outcome/birth), evidences used to determine pregnancy (i.e., rhesus test, diagnosis/procedure code indicating pregnancy/delivery, birth register indicating live birth, MOU visit, Momconnect registration), outcomes (i.e., live birth, still birth, miscarriage, early neonatal death, termination of pregnancy), and co-morbidities (e.g., mother HIV first evidence date, mother HIV treatment start date) related to the index pregnancy. Pregnancy data in the maternity cascade dates back as early as 2000 until today, the episodes and cascades are rebuilt daily in the face of new evidences. Only PHWLIV and infants where the mother gave birth in Khayelitsha in 2017 will be used in the generation of HIV-exposed live-born infants. All data will be anonymized before the analysis.

4.3.1 Exposures

Having an HIV-infected mother antenatally or up to 12 months postpartum is the exposure. Both nationally and provincially women are tested for HIV at their first antenatal visit and subsequent visits throughout the pregnancy, at delivery, as well as during the breastfeeding period. Women can present to the antenatal clinic either already knowing their HIV positive status or find out their HIV positive status at the first or subsequent antenatal and postnatal tests. This means that a woman can enter the cohort anytime from her first antenatal visit right through to 12 months post-partum.

4.3.2 Laboratory measurements

The National Health Laboratory Sciences (NHLS) provides a quality controlled validated laboratory service for all government health facilities. NHLS lab data in the Western Cape is stored electronically against the PMI; the PHDC receives these electronic laboratory data daily. Maternal CD4 and viral load tests; along with infant PCR, antibody serology, CD4, and viral load NHLS lab tests were joined to the data from the maternity cascade to generate the cohort.

4.3.3 Linking maternal and infant data

All primary health care (PHC) facilities in the WC, including in Khayelitsha, enter delivery data into the Maternity Module of PHCIS which automatically generates a folder number for the infant. This links the mother-infant pair, the link is recorded in the maternity record as well as in the infant road-to-health book. Clinicom, the hospital information system, records the link in a similar manner. These data are imported to the PHDC daily, the folder numbers (both mother and baby) are run through the PHDC's PMI engine, a matching algorithm which matches individuals from different data sources and updates the PMI if the record exists (i.e. in the case for the mother), and creates a new PMI if it doesn't (i.e., the infant)
(6).

4.3.4 Key Variables

Table 1: Baseline variables

Variable	Description	Detail
Mode of Delivery	Categorical	• Vaginal • Caesarean-section
Maternal Factors		
Age at first evidence	Categorical	• <=15 • 15-24 • 25-34 • >=35
Number of known previous pregnancies	Numerical	• First Pregnancy • Second or subsequent pregnancy
HIV status at index pregnancy (i.e., estimated pregnancy start reverse calculated from delivery date)	Categorical	• Positive prior to index pregnancy • Positive at first evidence • Positive after index pregnancy within 12 months post-partum
ART Experience	Categorical	• Already on ART • Started ART during (between first evidence and birth) • Started ART post-partum up to 12 months • Never started ART
VL Suppression	Continuous	
Infant Factors		
Infant HIV lab evidence test	Categorical	• Birth (<= 1 week) • 10 weeks (2-14 weeks) • 12 months

4.3.5 Outcomes

- Proportion of vertical transmission among HEI from birth up to 12-months post-delivery (per time point).

5. Statistical analysis

- Data will be analyzed through R statistical software (R Core Team (2013)).
- Descriptive statistics will be used to describe baseline characteristics for of the study variables.
    - Continuous variables will be categorized into ranges and they will be described using proportions, and frequency tables will be used to compare proportions.
- Logistic regression will be used to assess risk factors associated with transmission based on the indicated exposures selected *a priori*.
- Time to event/outcome (i.e., HIV transmission) data will be determined using the Kaplan-Meier method.
- Cox-proportional hazard model will be fitted to assess risk factors for maternal virologic failure

6. Ethical considerations

This study is part of the broader B Positive study which has already been approved by the University of Cape Town (UCT) Human Research Ethics Committee (HREC REF: 541/2015); Appendix C). Therefore, an application for an Expedited ethics was requested and granted by the UCT HREC (HREC REF: 817/2019) for the study for the Masters in Public Health mini-dissertation.

6.1 Informed Consent

There is no recruitment process for this study; it uses data collected and processed by the WCGH as part of its service provision. As the study is based on anonymized routine data, we request a waiver of informed consent, in line with the parent study.

6.2 Description of risks and protection against risks

The major potential risk is breaches of patient confidentiality. To mitigate this risk, the data centre will only release anonymized data for analysis in which all identifiers have been removed, and dates and other data which could lead to re-identification have been perturbed.

All anonymized data will be transferred as a password protected file, and sent from the PHDC via UCT filesend, the password and file will not be in the same email. The study is therefore considered low risk.

6.3 Potential benefits

There is no direct benefit on the mother-infant pairs as this a prospective analysis of routinely collected data, but they may benefit indirectly.

This analysis of mother-infant linked longitudinal data will allow the for the measurement of the uptake of PMTCT, as well the timing of vertical HIV transmission. Variables associated with PMTCT uptake and vertical transmission may be ascertained and quantified, allowing for the for the identification of vulnerable mothers and infants who may need additional services and/or support. Findings from this study could be incorporated into PMTCT programmes to increase their effectiveness.

6.4 Reporting and implementation

The results from this study (sub-analysis of *B-positive*) will be submitted to a peer-reviewed publication and presented at appropriate conferences.

7. Stakeholders

- The WCGH – who would be able to use this research, and others like it, as part of their monitoring and evaluation of PMTCT effectiveness for the province as whole.
- The University of Cape Town, School of Public Health, who are in a partnership with the Western Cape Department of Health to facilitate integration and best use of Provincial health data.
- People living with HIV in the Western Cape and accessing government health care, who are the source of the anonymized data; these people stand to benefit from any improvements made to increase the effectiveness of PMTCT.
- The Western Cape and National general populations, who stand to benefit from a

further reduction in MTCT incidence and long-term prevalence of HIV.

- Other researchers who perhaps didn't know that such data exists in the PHDC and they too can apply for access and conduct health research.

8. Conflict of interest

There are no conflicts of interest.

9. Budget

No overhead costs are associated with this project.

10. References

1. Poolman M, van der Walt N, Luwaca B. WESTERN CAPE PROVINCAL AIDS COUNCIL Anual Progress Report 2015/16 [Internet]. 2017 [cited 2017 Jul 12]. Available from: http://sanac.org.za/wp-content/uploads/2017/06/Western-Cape.pdf

2. Myer L, Phillips TK, Zerbe A, Ronan A, Hsiao N-Y, Mellins CA, et al. Optimizing Antiretroviral Therapy (ART) for Maternal and Child Health (MCH). JAIDS J Acquir Immune Defic Syndr [Internet]. 2016 Aug [cited 2019 Jul 28];72:S189–96. Available from: http://insights.ovid.com/crossref?an=00126334-201608011-00014

3. Fowler MG, Qin M, Fiscus SA, Currier JS, Flynn PM, Chipato T, et al. Benefits and Risks of Antiretroviral Therapy for Perinatal HIV Prevention. N Engl J Med [Internet]. 2016 Nov 3 [cited 2019 Apr 15];375(18):1726–37. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1511691

4. Coetzee D, Hilderbrand K, Boulle A, Draper B, Abdullah F, Goemaere E. Effectiveness of the first district-wide programme for the prevention of mother-to-child transmission of HIV in South Africa. Bull World Health Organ [Internet]. 2005 Jul [cited 2018 Aug 9];83(7):489–94. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16175822

5. Stinson K, Giddy J, Cox V, Burton R, Ibeto M, Cragg C, Van Gusten G, Hilderbrand K, Boulle A, Coetzee D, Goemaere E. Reflections on a decade delivery PMTCT in

Khayelitsha, South Africa. *SAfrJHIVMed* 2014;15(1):30-32. DOI:10.7196/SAJHIVMED.1025

6. Heekes A, Tiffin N, Dane P, Mutemaringa T, Smith M, Zinyakatira N, et al. Self-enrolment antenatal health promotion data as an adjunct to maternal clinical information systems in the Western Cape Province of South Africa. BMJ Glob Heal. 2018;3:1–9.

7. Draper, Beverly, & Abdullah, Fareed. (2008). A review of the prevention of mother-to-child transmission programme of the Western Cape provincial government, 2003 - 2004. SAMJ: South African Medical Journal, 98(6), 431-434. Retrieved July 02, 2019, fromhttp://www.scielo.org.za/scielo.php?script=sci_arttext&pid=S0256-95742008000600010&lng=en&tlng=en.

8. Fowler, M. G. *et al.* (2016) 'Benefits and Risks of Antiretroviral Therapy for Perinatal HIV Prevention', *New England Journal of Medicine*. Massachusetts Medical Society, 375(18), pp. 1726–1737. doi: 10.1056/NEJMoa1511691.

9. Boulle A, Heekes A, Tiffin N, Smith M, Mutemaringa T, Zinyakatira N, et al. Data Centre Profile: The Provincial Health Data Centre of the Western Cape Province, South Africa. Int J Popul Data Sci [Internet]. 2019 [cited 2019 Dec 27];4(2). Available from: https://ijpds.org/article/view/1143

10. Kaplan R, Orrell C, Zwane E, Bekker LG, Wood R. Loss to follow-up and mortality among pregnant women referred to a community clinic for antiretroviral treatment. Aids. 2008;22(13):1679-1681

11. Boulle A, Clayden P, Cohen K, et al. Prolonged deferral of antiretroviral therapy in the SAPIT trial: did we need a clinical trial to tell us that this would increase mortality? S Afr Med J. 2010;100(9):566, 568, 570-561.

12. Cornell M, Grimsrud A, Fairall L, et al. Temporal changes in programme outcomes among adult patients initiating antiretroviral therapy across South Africa, 2002-2007. AIDS. 2010;24(14):2263-2270.

13. Boyles TH, Wilkinson LS, Leisegang R, Maartens G. Factors influencing retention in care after starting antiretroviral therapy in a rural South African programme. PLoS One. 2011;6(5):e19201.

14. Stinson K, Boulle A, Coetzee D, Abrams EJ, Myer L. Initiation of highly active antiretroviral therapy among pregnant women in Cape Town, South Africa. Trop Med Int Health. 2010;15(7):825-832.

15. Lallemant, M et al.,(2004) 'Single-dose Perinatal Nevirapine plus Standard Zidovudine to Prevent Mother-to-Child Transmission of HIV-1 in Thailand'. *New England Journal of Medicine.* Massachusetts Medical Society, 351(3),pp. 217 – 228. doi: 10.1056/NEJMoa033500.

16. National Department of Health Republic of South Africa. National Consolidated Guidelines for the Prevention of Mother-to-Child Transmission of HIV (PMTCT) and the Management of HIV in Children, Adolescents and Adults, April 2015. Pretoria: National Department of Health 2015.

17. Tiffin, N. 'Analysis if ART initiation and outcomes at facilities in the Western Cape, comparing facility-specific IeDEA cohort data with collated and individualized routine public health data ' Thesis submitted for Master of Public Health, University of Cape Town, Cape Town South Africa, 2017.

18. National Department of Health Republic of South Africa. The South African Antiretroviral Treatment Guidelines 2013. https://www.westerncape.gov.za/assets/ndoh_pmtct_guidelines.pdf (Accessed 5 June 2019)

19. Statistics South Africa (2011) 'Census 2011'. https://www.statssa.gov.za/publications/P03014/P030142011.pdf (Accessed 27 May 2019)

20. Woldesenbet S, Jackson D, Lombard C, Dinh TH, Puren A, Sherman G, et al. Missed opportunities along the prevention of mother-to-child transmission services cascade in South Africa: Uptake, determinants, and attributable risk (the SAPMTCTE). PLoS One [Internet]. 2015;10(7):1–15. Available from: http://dx.doi.org/10.1371/journal.pone.0132425

PART B: MANUSCRIPT

1. Title Page

Prevention of mother-to-child-transmission of HIV in Khayelitsha: a contemporary review of services 20 years later

Florence Phelanyane[1§],

1. Centre for Infectious Disease and Epidemiology Research, School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa

§ Corresponding author

Florence Phelanyane, Level 5 Norton Rose House, 8 Riebeek Street, Cape Town, 8001

Tel: +27 21 483 6857

florence.phelanyane@uct.ac.za

Key words

HIV, mother-to-child-transmission, prevention of mother-to-child transmission

This manuscript meets the requirements for submission to the Journal of the International AIDS Society

Word count Abstract: 379/350

Word count Text: 3 753/3500

As per mini-dissertation guidelines, potential co-authors for a journal submission are not included in this section but are listed with their affiliation in the Acknowledgements

2. Abstract

Background: The first Prevention of Mother-To-Child-Transmission of HIV (PMTCT) pilot programme in the Western Cape (WC), South Africa, was launched in Khayelitsha in 1999. Since then, PMTCT guidelines have expanded in complexity and scope. In the WC, all public health facilities share a unique patient identifier allowing linkage across electronic health systems through the Provincial Health Data Centre (PHDC), a Health Information Exchange (HIE) developed and hosted within the WC Department of Health. Using this technology, we aimed to describe contemporary PMTCT uptake in Khayelitsha and quantify MTCT risk factors based on routine data.

Methods: Prospective observational cohort analysis of all live-born linked mother-infant pairs in which the HIV positive mother attended antenatal care (ANC) in Khayelitsha in 2017. Descriptive statistics assessed PMTCT coverage along the care cascade, including the implementation of maternal viral load testing and early infant diagnosis (EID). Logistic regression analysis quantified *a priori* defined risk-factors associated with vertical HIV transmission.

Results: Antenatal HIV prevalence in the cohort was 31.3%; MTCT (among live-born linked infants with a PHDC HIV outcome) was 1.8% at 12 months old. 88.3% of women knew of their HIV positive status at the first antenatal visit; 77.9% of whom were already on ART. 94.5% of women diagnosed prior to delivery were initiated on ART prior; 85.0% received a viral load test antenatally and 88.0% were virologically suppressed. EID coverage was sub-optimal with the birth HIV-PCR (within 7 days of birth) present in 79.2% of infants. An even lower proportion (57.9%) of infants who tested negative at birth had a repeat test around 10-weeks. The PHDC HIV episode identified an additional 16 HIV-exposed (HEI) infants with HIV who were not detected by laboratory tests. Women who were not suppressed antenatally had a 5-fold (aOR = 5.3, 95% CI: 2.5 – 12.3) increased MTCT risk compared to those were suppressed antenatally. Women who did not attend ANC were at highest risk of transmission (aOR=1.6,95%CI: 0.7 – 3.6).

Conclusions: Although most women present to care already knowing their HIV status, ART initiation and viral load uptake was sub-optimal at presentation to ANC but improved during pregnancy, evidence of maturing PMCT services. MTCT risk reliant on laboratory HIV-PCR alone underestimated

transmission: HIV data from multiple sources, consolidated in the PHDC suggested higher MTCT than program-reported HIV-PCR testing alone.

3. Introduction

It has been 20 years since the Western Cape Province (WC) of South Africa launched its first Prevention of Mother-To-Child-Transmission of HIV (PMTCT) pilot programme in Khayelitsha, an urban township 50km from the Cape Town city centre (1). The programme, supported by *Médecins sans Frontiers*, provided antenatal voluntary counselling, and testing in midwife obstetric units (MOUs) with short course zidovudine (AZT) from 36 weeks-gestation. Initially antiretrovirals (ARVs) were provided antenatally only; continuity of care beyond delivery was poor, and post-natal services were fragmented (1). The WC PMTCT programme has mirrored the World Health Organization (WHO) guidelines. In 2013 antiretroviral (ART) eligibility was expanded to WHO "Option B+": the provision of lifelong ART to pregnant women irrespective of CD4 count, and support for exclusive breast feeding for up to 6 months post-partum) (2).

Since the inception of the first program in 1999, PMTCT in Khayelitsha has been regularly reviewed (1,3). In the past, many studies looked at single elements of the cascade e.g., maternal testing or maternal prophylaxis. More recently, EID and infant HIV status (which is the outcome of interest) have been investigated. Here we report an updated analysis of the entire PMTCT cascade starting from maternal HIV diagnosis, ART experience, viral load (VL) uptake, as well as vertical HIV transmission in the era of WHO Option B+ with the advantage of longitudinal data consolidated in the Health Information Exchange (HIE). The HIE allows for the linking of mother-infant pairs, thus linking exposure (maternal HIV status, ART experience, and virologic suppression) and outcome (vertical transmission of HIV). The use of a unique patient identifier/folder number in the WC public health sector has allowed for the disaggregation of routine laboratory data (VL, infant HIV-PCR and/or HIV serology) facilitating better ascertainment during the transmission windows i.e., antenatal, intrapartum, and during breastfeeding/postpartum.

The primary aim of this study was to describe the uptake of PMTCT among women living with HIV (WLHIV) who presented for their first antenatal care (ANC) visit or, in the absence of ANC, delivered

in a public health care facility in the Khayelitsha sub-district of Cape Town, WC in 2017; and to quantify MTCT risk factors and outcomes among their infants up to 12 months post-partum.

4. Methods

The routine electronic programme data were in entered in real-time into health care facility/pharmacy/laboratory information systems; these data were consolidated by Provincial Health Data Centre (PHDC), a HIE developed and hosted within the Provincial Government of the WC. A 2017 observational cohort was defined and followed up prospectively until the infants reached 12 months of age.

4.1 Setting and participants

A cohort of (2 549) pregnant WLHIV attending their first electronically captured pregnancy-related visit at any public health care facility in the Khayelitsha sub-district of the WC in 2017 and their HIV-exposed infants (2 576 mother-infant pairs [includes twins]) was defined. Only women to whom a live-born infant who could be linked in the PHDC were included (Figure 1).

WHO Option B+ was the PMTCT policy at the time of the study. Guidelines recommended that all WLHIV should be initiated on ART, and HIV negative women should be offered a HIV test at presentation for ANC and periodically thereafter until the end of breastfeeding (2). Thus, a woman could enter the cohort at any date from her first electronic evidence of pregnancy up to 12 months post-partum. This was defined as the index pregnancy period.

From December 2015, early infant diagnosis (EID) guidelines recommended that all HIV-exposed infants should receive a HIV-PCR test at birth (within 1 week of birth), and a repeat HIV-PCR test at 10 weeks (2 - 14 weeks, inclusive) if the first result was negative or inconclusive; a HIV-PCR was also indicated at 10-weeks old if the infant didn't receive one at birth (2).

4.2 The Provincial Health Data Centre

The PHDC is a HIE leveraged on the use of a unique patient identifier, used as a folder number in all public sector health facilities in the WC (4). This shared folder number is hosted by information systems in all hospitals and primary health care clinics. Key additional data sources include electronic laboratory (National Health Laboratory Services [NHLS]) and pharmacy dispensing services, as well as data from disease information systems designed to assist program management of high priority diseases (i.e., HIV and tuberculosis)(4).

Within the PHDC, an 'episode' encompasses a combination of evidences from clinical data (e.g., clinic visits, dispensing data, laboratory results etc.) that can be used to infer a health condition (4). For example, visits to an HIV clinic, HIV diagnosis codes, receipt of ART, and HIV-related laboratory tests (e.g., CD4, VL etc) are all used in the construction of a *HIV Episode*. Each episode is a single record which includes: first and last evidence dates, treatment start and outcome dates (death, cure, birth), facilities attended, the data sources from which the data were extracted, and the list of evidences used in the episode's construction (4).

An episode can be rolled up into a 'cascade', which is a comprehensive patient-level depiction of episodes, including key dates, facilities attended, and evidences, with the addition of outcomes and co-morbidities relevant to patient management. Cascades can provide a cohort in the absence of registers (4). We used a combination of the maternity cascade (to define pregnancy) and HIV episode (to define HIV exposure) to establish the cohort.

4.3 Linkage and PHDC infant HIV episodes

In the WC all infants are assigned a folder number at birth which is electronically linked to maternal folder number as per the provincial standard operating procedures. The study relied on this linkage. Infant HIV status was ascertained using the PHDC HIV episode which consolidated *all* HIV evidences, including but not limited to laboratory test results (CD4, VL), electronically captured ART start dates, visits to HIV clinics, ART dispensing events, alongside the indicated HIV-PCR and/or HIV-serology tests.

4.4 Analysis

Analysis was performed using R statistical software (v 3.6.2). Continuous variables were categorised according to pre-set thresholds (i.e., low birth weight [birth weight < 2500g], viral suppression [VL <1000 copies/ml after 3 months or more on ART], maternal age in bands of 10 years, and first or subsequent pregnancy). Categorical variables were described using proportions and frequency tables were used for comparison.

Logistic regression analysis was run to estimate associations with vertical transmission. Risk factors (maternal age, number of electronically recorded pregnancies, attendance of antenatal care, timing of ART initiation, and virologic suppression) were selected *a-priori* from the literature. Mother-infant pairs in which the infant had a missing HIV outcome (i.e., HIV status unknown at the end of the index period) as well as pairs in which the mother was diagnosed post-partum were excluded from the final cohort for logistic regression.

4.5 Ethics

This study was approved by the University of Cape Town's Human Research Ethics Committee (HREC 817/2019 and HREC 541/2015) and the Provincial Government of the WC's Department of Health Research. There was no recruitment process as we used data collected and processed by the WC Government Department of Health as part of its service provision. As the study is based on anonymized routine data, the waiver of informed consent was granted in line with the parent study.

5. Results

There were 8298 mother-infant pairs in which the mother had her first electronic evidence of pregnancy at a public sector health facility in the Khayelitsha sub-district in the 2017 calendar year. Among the infants, 3065 (36.9%) were exposed to HIV during the index period. The antenatal HIV prevalence in the entire cohort was 31.3% (Table 1). Among the WLHIV, 483 women were excluded as the pregnancy ended in termination/miscarriage/stillbirth or mother could not be linked to an infant (Figure 1).

The final cohort consisted of 2 576 mother-infant pairs in which the infant's mother had a PHDC HIV episode during the index period. Of 2 576 infants: 41 had a PHDC HIV positive episode (i.e., confirmed

HIV-infected by consolidated evidence), 2 286 infants had evidence of a negative HIV test result (HIV-PCR and/or serology at some point over 12 months), and 249 had no electronic evidence of a HIV test result. Of the infants with no HIV outcome, 53.8% (134) had no post-birth encounter with the provincial health system i.e., no evidence of well-baby or vaccination visits (Figure 1).

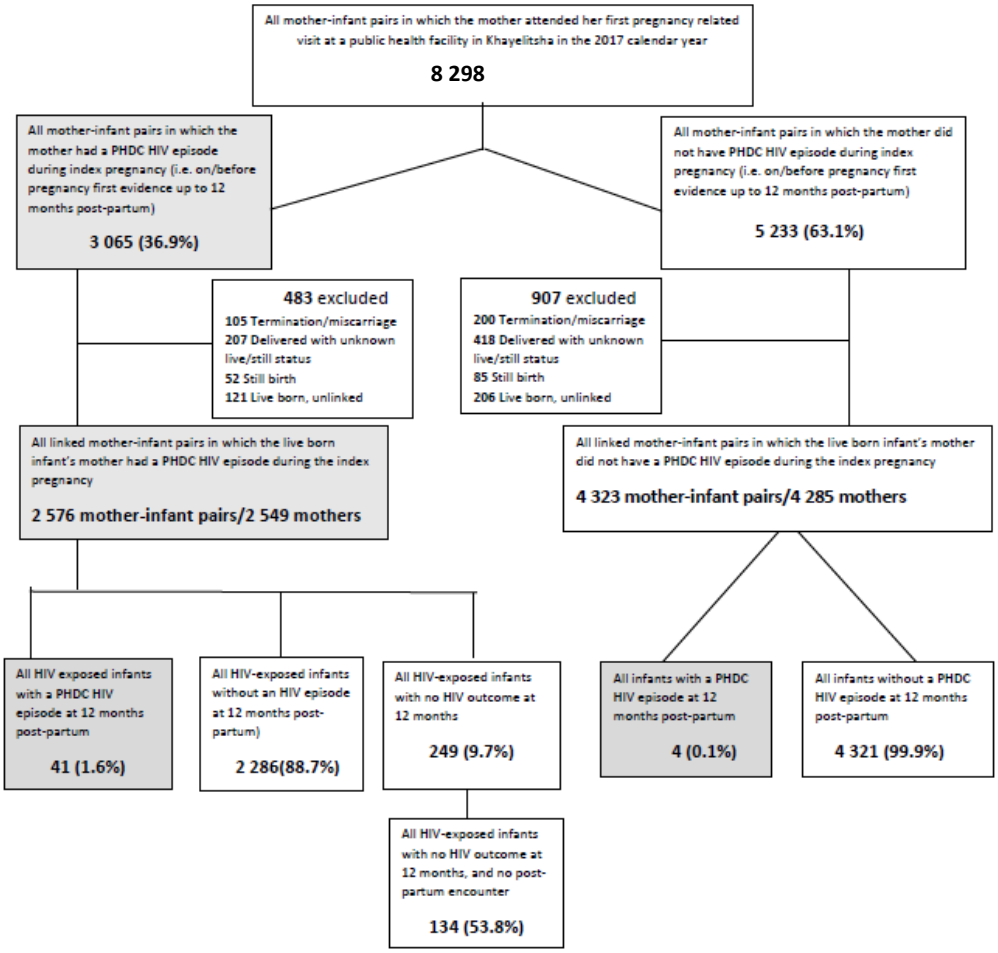

Figure 1: Flow diagram summarizing the cohorts and HIV outcomes

Among the 2 548 mothers, the median maternal age was 30 years (interquartile range (IQR) 26 – 34 years) (Table 1). Most deliveries were vaginal (70.5%). This was the first recorded pregnancy (in the PHDC) in 46.9% of the cohort. Most women had some electronic evidence of ANC (78.3%), defined as having an electronic evidence of ANC at either a hospital or a primary health care MOU at least 7 days before the date of delivery.

Eighty-eight percent (n= 2 251) of WLHIV knew their HIV positive status at presentation to ANC, and 10.1% (n= 257) were diagnosed during the index pregnancy. Seventy-eight percent (n = 1 753) of those who knew their positive HIV status at first ANC visit had started ART prior, and 94.5% (n = 2 369) of the 2 508 WLHIV diagnosed prior to delivery started ART before delivery. Forty-one (n= 21) percent of the 2 251 WLHIV diagnosed prior to first ANC visit received a VL test prior, and virologic suppression was 92% among these women. Of the entire cohort (n= 2 548), 80.6% received a VL test at some point during the index period. Among the 2 508 WLHIV diagnosed prior to delivery, 85.0% (n= 2 131) received a VL test antenatally, of whom 88.0% were virologically suppressed. Seventy-three out of 139 (52.5%) with no digitally recorded ART, who received a VL antenatally, had a VL < 1000 copies/ml.

There was very little electronically documented infant mortality by the end of index period: 0.58% and 0.19% early and late neonatal death, respectively. Most infants (84.4%) had a normal birth weight (Table 1).

Table 1: Baseline characteristics of mother-infant pairs in the final cohort

Variables	n	%	n total
Mother Age (years)			
< 15	1	0.0	2548
15 - 24	461	18.1	2548
25 - 34	1506	59.1	2548
>34	580	22.8	2548
Delivery Method			
Vaginal or Assisted	1797	70.5	2548
Caesarean Section	751	29.5	2548
First Pregnancy			
Yes	1195	46.9	2548
No	1353	53.1	2548
Evidence of antenatal care			
Attended antenatal care	1995	78.3	2548
Did not attend antenatal care	553	21.7	2548

Mother HIV Status			
Positive prior to index pregnancy	2251	88.3	2548
Positive during index pregnancy	257	10.1	2548
Positive after pregnancy outcome within 12 months post-partum	40	1.6	2548
Mother ART Experience			
Positive prior to antenatal care			
Started ART prior to antenatal care	1753	77.9	2251
Positive prior to end of index			
Started ART before pregnancy	1753	68.8	2548
Started ART during pregnancy	566	22.2	2548
Started ART post-partum up to 12 months	69	2.7	2548
No ART during observation period	160	6.3	2548
ART Experience and Viral Load for WLHIV diagnosed before birth			
Positive antenatally, no evidence ART antenatally	139	5.5	2508
No recorded ART, no virologic assessment	60	43.2	139
No recorded ART, viral load < 1000 copies/ml	73	52.5	139
No recorded ART, viral load > 1000 copies/ml	6	4.3	139
Positive antenatally, evidence of ART antenatally	2369	94.5	2508
ART recorded, no virologic assessment antenatally	316	12.6	2508
ART recorded, virologically suppressed antenatally	1806	88.0	2053
ART recorded, virologically not suppressed antenatally	247	12.0	2053
Infant Vital Status			
Early neonatal death	15	0.6	2576
Late neonatal death	5	0.2	2576
Alive at 12 months	2556	99.2	2576
Infant Low Birth Weight (<2500g)			

ELBW (<1000)	13	0.5	2576
VLBW (1000.001 - 15000)	39	1.5	2576
LBW (1500.001 - 2500)	324	12.6	2576
NW (1500.001 - 4 200)	2173	84.4	2576
OW (>4200)	27	1.0	2576
Infant received PCR test during index			
Yes	2543	98.7	2576
No	33	1.3	2576
Infant HIV Status at 12 months			
Positive (entire cohort)	41	1.6	2576
Positive (excluding infants with missing outcomes)	41	1.8	2327
Positive (mother diagnosed prior to antenatal care)	31	1.4	2273
Positive (mother diagnosed antenatally)	6	2.3	263
Positive (mother diagnosed postnatally)	4	10	40
Negative	2286	88.7	2576
Unknown (missing outcome)	249	9.7	2576

*** ELBW = extremely low birth weight, VLBW = very low birth weight, LBW = low birth weight, NW = normal weight, OW = overweight**

5.1 First HIV-PCR at birth

Most (79.3%) of the 2 537 HIV-exposed infants (HEI) received a birth HIV-PCR, of whom 15 (0.7%) were positive (Table 2). Fifty-eight percent (n=1 156) of those who tested negative or indeterminate (n= 1 998) were re-tested at 10 weeks; 2 (0.2%) infants were positive. Of the 42.1% (n = 842) who did not receive their repeat test at 10 weeks, 12.2% received their repeat test beyond 10 weeks of whom 1 (1%) was positive (Table 2).

5.2 First HIV-PCR at 10 weeks

Five hundred and twenty-four (20.7%) infants did not receive an HIV-PCR at birth, 71.2% of whom received their first HIV-PCR at 10 weeks, 4 (1.1%) infants tested positive. 151 infants were missed by EID.

Table 2: EID coverage and outcomes among HEI whose mothers tested positive before birth

	First test at birth	Repeat test at 10 weeks	Repeat test beyond 10w	First test at 10w
Total Eligible	2537	1998	842	524
Total Tested	2013 (79.3%)	1156 (57.9%)	103 (12.2%)	373 (71.2%)
Positive	15 (0.7%)	2 (0.2%)	1 (1.0%)	4 (1.1%)
Negative	1995 (99.1%)	1150 (99.5%)	102 (99.0%)	368 (98.7%)
Indeterminate	3 (0.2%)	4 (0.3%)	0 (0.0%)	1 (0.3%)
Not tested	524 (20.7%)	842 (42.1%)	739 (87.8%)	151 (28.8%)

5.3 Logistic Regression

The final cohort for logistic regression excluded infants with a missing PHDC HIV outcome and those born from mothers who tested HIV positive post-partum. Table 3 shows the results of the univariate and multivariate logistic regression with MTCT outcome (HIV positive/negative) as the dependent variable. Maternal age was not linear, and it seemed to have some effect on transmission; a maternal age category of greater 34 years and a 10-year increase in maternal age both decreased the odds of transmission by 20% in the univariate models (OR = 0.8, 95% CI: (1.0 - 4.0) and (OR = 0.8, 95% CI: 0.4 - 1.4) respectively. However, this effect did not persist in the multivariate models (Table 3).

Women on their second or subsequent pregnancy had 30% higher odds of vertical transmission in both the univariate (OR = 1.3 ,95% CI: 0.7- 2.6) and multivariate (aOR = 1.3, 95% CI: 0.7 – 2.6) models. Those who did not attend any antenatal services but presented for the first time for delivery had double the risk of MTCT in the univariable model (OR = 2.1(95% CI: 1.0 - 4.0), this effect persisted in the multivariable model with reduced size (aOR = 1.6, 95% CI: 0.7 – 3.6). Women who started ART prior to the first electronically captured booking had a 40% decreased risk of vertical transmission (OR = 0.6, 95% CI: 0.3 – 1.3), this decrease in vertical transmission risk increased to 50% (aOR = 0.5, 95% CI: 0.3 – 1.3) after adjustment.

Women who were not virologically suppressed antenatally had more than 5 times higher MTCT risk compared to who were suppressed antenatally in both the univariate (OR = 5.5 ,95% CI: 2.4 – 12.6)

and multivariate (aOR = 5.3, 95% CI: 2.5 – 12.3) models; whereas women with no virologic assessment antenatally had more than 7-fold (OR = 7.2 ,% CI: 3.3 – 15.9) increased MTCT risk in the univariate model , this effect was slightly smaller (6-fold) increase risk after adjustment (aOR= 6.1, 95% CI: 2.7 – 12.3).

Table 3: Logistic regression results showing unadjusted and adjusted odds ratio for maternal MTCT risk factors among HIV exposed infants whose mothers were diagnosed with HIV antenatally

Covariate	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Mother age category (< 25 reference)(years)		
25 - 34	1.0 (0.4 - 2.5)	1.3 (0.6 – 3.4)
>34	0.8 (0.3 - 2.3)	1.1 (0.3 – 3.2)
Mother age per 10 years	0.8 (0.4 - 1.4)	
First pregnancy (No)	1.3 (0.7 - 2.6)	1.3 (0.7 – 2.6)
Delivery method category (Caesarean Section)	0.5 (0.2 - 1.1)	
Attended antenatal care (No)	2.1(1.0 - 4.0)	1.6 (0.7 – 3.6)
VL Suppression (reference = Virologically suppressed antenatally)		
Virologically not suppressed antenatally	5.5 (2.4 – 12.6)	5.3 (2.5 – 12.3)
No virologic assessment antenatally	7.2 (3.3 – 15.9)	6.1 (2.7 – 14.2)
ART started antenatally (No)	0.6 (0.3 – 1.3)	0.5 (0.3 – 1.3)

6. Discussion

We present an updated analysis of the PMTCT programme in Khayelitsha, 20 years after the initiation of short-course AZT was introduced for PMTCT in 1999. At that time, antenatal HIV prevalence was between 16.0% (January 1999 to May 2000) and 20.3% (June to December 2000) and vertical transmission estimated to be 20 - 30% without intervention (5) and 12.5% with the intervention (6). In 2017, WHO Option B+ was the PMTCT policy with EID including birth HIV-PCR for all HIV-exposed infants. While antenatal maternal HIV prevalence had increased (31.3%) since 1999, the ART programme had matured significantly reaching more women with diagnosis (88.3% of WLHIV were aware of their status before first ANC) and treatment (77.9% of whom were on ART). Ninety-five percent of all WLHIV diagnosed before delivery had been initiated on ART prior to delivery. The

expanded EID guidelines were incompletely implemented but HIV vertical transmission (determined using multiple evidences) was reduced to 1.8% at 12 months old.

6.1 HIV antenatal seroprevalence

We found an antenatal HIV prevalence of 31.3%, which was similar to the national prevalence (30.7%) but higher than both the antenatal prevalence for the City of Cape Town Metropolitan district (20.9%) and the antenatal prevalence for the WC province (15.9%) reported in the 2017 National Antenatal Survey (ANS) (7). This difference could be attributed to cohort's demographic and socioeconomic factors; this was a young cohort (77.2% less than 35 years old) in a low-income setting with high rates of unemployment and informal housing, all of which are risk factors for HIV (8). The 2017 ANS reported that nationally 39.2% of PWLHIV were unaware of their HIV-positive status before pregnancy, whereas we reported just less than 12% of PWLHIV not knowing their HIV-positive before their first antenatal visit.

6.2 Access to PMTCT and ART

The Joint United Nations Programme on HIV and AIDS (UNAIDS) has set the 90-90-90 targets toward ending the HIV epidemic where 90% of people living with HIV (PLHIV) know their HIV status, 90% of those with known status receive ART, and 90% of those on ART are virologically suppressed (10).

Knowledge of HIV status (at first presentation for ANC) among our Khayelitsha cohort was 88.3% falling just short of the first 90. Among those women aware of their HIV status before pregnancy only 77.9% had been initiated on ART (second 90); it is uncertain whether these women qualified for ART prior to falling pregnant, had not been offered treatment or elected not to attend for treatment. The proportions may change with the introduction of Test and Treat Guidelines in South Africa in 2018 in which all PLHIV are eligible for ART regardless of clinical or immunological parameters (11,12). The proportion of women on ART at presentation to ANC was slightly lower than the provincial estimate for PWLHIV on ART (81.4%) reported in the 2017 ANS (7). This could be a result of bias in which individuals who chose to participate in the survey may have better ART seeking practices, or the effect of pooled samples where better performing regions increase the overall percentage. However, by delivery 98.4% pregnant WLHIV were aware of their HIV status; similar to the 2017 ANS 98.2% self-reported on ART. Only 41.0% of WLHIV who diagnosed prior to ANC had received a VL test within the previous 12 months, but most (92.0%) were virologically suppressed. The 2017 ANS did not report on

virologic suppression, however we reported a higher coverage and suppression than a point-of-care study on maternal HIV VL testing (around time of delivery) from four obstetric units in Gauteng which reported a 34.0% testing coverage, and 77.5% with VL < 1000 copies/ml (13).

The majority (94.5%) of WLHIV who were diagnosed prior to delivery were initiated on ART before delivery; most (85.0%) received a VL test antenatally, and 88.0% of those with a recorded ART start date were virologically suppressed. This high coverage antenatally could be due to the long history of PMTCT engagement in Khayelitsha, evidence of the maturity of the HIV programmes in the area (1).

6.3 EID and missed opportunities

In 2015, the South African National PMTCT Guidelines introduced routine HIV-PCR diagnostic testing for all HIV-exposed infants at birth, with repeat testing at 10 weeks to identify peri-partum and early postnatal infections (14). This was implemented in the WC in November 2015 (2). This study showed a relatively good coverage of the birth HIV-PCR (79.3%); but poor uptake of the repeat test around 10 weeks old. The birth HIV-PCR coverage was lower than the provincial estimates reported by National Department of Health guideline review, between April 2016 to March 2017 (87.9%), using laboratory data only (15). This difference could be attributed to de-duplication and disaggregation of HIV-PCR data by the PHDC (compared to aggregated NHLS data) which allowed for better ascertainment of the timing HIV-PCR uptake. Coverage at 10 weeks was relatively good (71.2%) for first time HIV-PCR among infants who were not tested at birth, and overall coverage of the any HIV-PCR by 10-weeks was 92.7%, similar to that reported by Kalk *et al.* in nearby Mitchell's Plain (16) and to the 93% national EID coverage reported by Moyo *et al*., analysis of the 2015 Routine HIV Birth Testing in the South African National Consolidated Guidelines (23).

Ninety-four percent of HIV exposed infants had received their first test by the end of the index period (12 months old) , incomplete coverage (less than 100%) of birth HIV-PCR and subsequent tests will result in underestimation of true MTCT, the outcome by which the success of PMTCT programmes is determined. In the final cohort, MTCT at 12 months post-partum was 1.8% which was similar to the MTCT (1.6%) reported in the 'Closing the gaps study' conducted at Khayelitsha site B community health centre by Ibeto *et al*. in 2014 (9)

The PHDC ascertained an additional 16 HIV positive episodes, using evidence other than HIV-PCR tests, such as VL/CD4 testing, entry into HIV disease registers, issue of triple ART regimens. In other words, dependence on laboratory evidence only, underestimated the rate of MTCT.

6.4 Risk Factors

Women who did not attend ANC had increased odds of HIV transmission when compared to women who attended ANC. The integration of ART services into ANC was associated with significant increases in the proportion of women who were initiated ART before delivery (19,20); PWLHIV who did not attend ANC were therefore at higher risk of not being initiated on ART antenatally and thus had increased risk of transmission. PWLHIV who do not attend ANC may be less likely to initiate ART or to have VL testing.

Consistent with the literature (17), virologic suppression had the biggest impact on MTCT. Compared to PWLHIV who were suppressed antenatally, PWLHIV who were not suppressed antenatally and PWLHIV with no virologic assessment antenatally had a 5 and 6-fold increase of MTCT risk, respectively.

6.5 Strengths and Limitations

One of the study's strengths was that it was a facility-based study using electronic medical records (centralized in the PHDC) which removes the necessity of primary data collection. Health care facilities in Khayelitsha have an extensive history of engagement in the provision of PMTCT services resulting in a great number of staff acclimatizing to the provision HIV care. This, along with migration into and out the region makes the sub-district an ideal place for detecting differences that can possibly be extrapolated to other populations. The use of the electronic medical record allowed for the high ascertainment of infant outcomes as previous observational studies reported high attrition rates.

Previous assessments of the PMTCT programme often relied solely on laboratory data (15,18); these studies reported difficulties in linking infants with maternal exposures, and in the de-duplication of results. Within the PHDC, we were able use additional data sources to identify infants with HIV (4). The cohort had the advantage over previous studies in that maternal exposures (such as the timing of

HIV diagnosis and ART initiation, as well as maternal VL test outcomes (and changes)) can be linked to the to her infant's outcome, and thus demonstrate the real-world implementation of WHO Option B+.

The study's major limitation was that we were limited to electronically captured data by the various source information systems. We therefore had no control over quality of data entered and couldn't account for missing data (i.e., missing electronic lab tests and/or electronic drug dispensing events, missing or incorrect linkage of mother-infant pairs), however missingness was very low.

We also had a lack of information with regards to women who 'drop out' of the Western Cape population (53% of those infants lost to follow-up had no evidence of post-birth encounters with the health system on the PHDC). HIV positive infants, particularly those who haven't been initiated on ART, have relatively high mortality and are more likely to migrate out of the province (21). The PHDC only consolidates data from the public sector; approximately 25% of the population are members of private sector medical schemes (22), therefore these results are only representative of PWLHIV who access the public sector health facilities.

7. Conclusion

In this study we comprehensively assessed the implementation and outcomes of the Western Cape PMTCT guidelines in Khayelitsha including coverage along the PMTCT care cascade and ascertainment of numerous evidences of vertical transmission. Although most women presented to care already knowing their HIV status, ART initiation and uptake of VL testing before pregnancy remained less than 90%. However, almost all women were initiated on ART and most who received a VL test were virologically suppressed before birth. National and Provincial MTCT is likely to be under-estimated as it relies solely on PCR results; the uptake of the birth PCR among HIV-exposed infants is not optimal and the uptake of a repeat tests among infants that tested negative is poor. The PHDC HIV episode (which consolidates HIV data from various data sources, facilitated by the folder number) suggested higher MTCT proportion than PCR testing alone, although transmission at 12 months is lower than previously assessed.

8. References

1. Stinson K, Giddy J, Cox V, Burton R, Ibeto M, Cragg C, et al. Reflections on a decade of delivering PMTCT in Khayelitsha, South Africa. South Afr J HIV Med. 2014;15(1):30–2.

2. Poolman M, van der Walt N, Luwaca B. WESTERN CAPE PROVINCAL AIDS COUNCIL Annual Progress Report 2015/16 [Internet]. 2017 [cited 2017 Jul 12]. Available from: http://sanac.org.za/wp-content/uploads/2017/06/Western-Cape.pdf

3. Coetzee D, Hilderbrand K, Boulle A, Draper B, Abdullah F, Goemaere E. Effectiveness of the first district-wide programme for the pre- vention of mother-to-child transmission of HIV in South Africa. Bull World Health Organ. 2005;83(7):489–94.

4 Boulle A, Heekes A, Tiffin N, Smith M, Mutemaringa T, Zinyakatira N, et al. Data Centre Profile: The Provincial Health Data Centre of the Western Cape Province, South Africa. Int J Popul Data Sci [Internet]. 2019 [cited 2019 Dec 27];4(2). Available from: https://ijpds.org/article/view/1143

5. Abdullah MF, Young T, Bitalo L, Coetzee N, Myers JE. Public health lessons from a pilot programme to reduce mother-to-child transmission of HIV-1 in Khayelitsha. S Afr Med J [Internet]. 2001 Jul [cited 2020 Jan 8];91(7):579–83. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11544974

6. Khayelitsha 2001 - 2011: 10 years of primary care HIV and TB programmes | Garone | Southern African Journal of HIV Medicine [Internet]. [cited 2020 Jan 8]. Available from: https://sajhivmed.org.za/index.php/hivmed/article/view/170/286

7. Woldesenbet, S.A., Kufa, T., Lombard, C., Manda, S., Ayalew, K., Cheyip, M., and Puren, A. (2019). The 2017 National Antenatal Sentinel HIV Survey, South Africa, National Department of Health.

8. Shisana O. Rehle T., Simbayi I., C, Zuma K., Jooste S., Jungi N., Labadarios D., Onoya D., et al (2014). South African National HIV Prevalence Incidence and Behaviour Survey 2012, Cape Town, HSRC Press

9. Ibeto M, Giddy J, Cox V. Closing the gaps: Steps towards elimination of mother-to-child transmission of HIV. South Afr J HIV Med [Internet]. 2014 Sep 8 [cited 2018 Aug 11];15(3):108–9. Available from: https://sajhivmed.org.za/index.php/hivmed/article/view/11

10. UNAIDS. 90-90-90; An ambitious treatment target to help end the AIDS epidemic. 2014;

Available from; http;//www.unaids.org/sites/default/files/media_asset/90-90-90_en.pdf.

11. South African National Department of Helath (2019). Guideline for the Prevention of Mother to Child Transmission of Communicable Infections

12. Republic of South Africa National Department of Health (2019) . 2019 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy, Adolescents, Children, Infants and Neonates.

13. Moyo F, Mazanderani AH, Murray T, Technau K-G, Carmona S, Kufa T, et al. Characterizing viral load burden among HIV-infected women around the time of delivery. JAIDS J Acquir Immune Defic Syndr [Internet]. 2020 Jan [cited 2020 Jan 16];1. Available from: http://journals.lww.com/10.1097/QAI.0000000000002267

14. National Department of Health Republic of South Africa. National Consolidated Guidelines for the Prevention of Mother-to-Child Transmission of HIV (PMTCT) and the Management of HIV in Children, Adolescents and Adults, April 2015. Pretoria; National Department of Health 2015.

15. Goga A, Chirinda W, Ngandu NK, Ngoma K, Bhardwaj S, Feucht U, et al. Closing the gaps to eliminate mother-to-child transmission of HIV (MTCT) in South Africa: Understanding MTCT case rates, factors that hinder the monitoring and attainment of targets, and potential game changers. South African Med J. 2018 Mar 2;108(3a):17.

16. Kalk E, Kroon M, Boulle A, Osler M, Euvrard J, Stinson K, et al. Neonatal and infant diagnostic HIV-PCR uptake and associations during three sequential policy periods in Cape Town, South Africa: a longitudinal analysis. 2018 [cited 2020 Jan 16]; Available from: http://onlinelibrary.wiley.com/doi/10.1002/jia2.25212/full

17. Myer L, Phillips TK, Hsiao N-Y, Zerbe A, Petro G, Bekker L-G, et al. Plasma viraemia in HIV-positive pregnant women entering antenatal care in South Africa. 2015 [cited 2020 Jan 10]; Available from: http://dx.doi.org/10.7448/IAS.18.1.20045

18. Sherman GG, Mazanderani AH, Barron P, Bhardwaj S, Niit R, Okobi M, et al. Toward elimination of mother–to–child transmission of HIV in South Africa: how best to monitor early infant infections within the Prevention of Mother–to–Child Transmission Program. J Glob Health [Internet]. 2017;7(1). Available from: http://jogh.org/documents/issue201701/jogh-07-010701.pdf

19. Stinson K, Jennings K, Myer L (2013) Integration of Antiretroviral Therapy Services into Antenatal Care Increases Treatment Initiation during Pregnancy:A Cohort Study. PLoS ONE

8(5): e63328. doi:10.1371/journal.pone.0063328

20. Myer L, Phillips T, Manuelli V, McIntyre J, Bekker LG, Abrams EJ. Implementation and operational research: Evolution of antiretroviral therapy services for HIV-infected pregnant women in Cape Town, South Africa. J Acquir Immune Defic Syndr. 2015;69(2):e57–65.

21. Anglewicz P, VanLandingham M, Manda-Taylor L, Kohler HP. Migration and HIV infection in Malawi. AIDS 2016; 30:2099-2105.

22. Statistics South Africa. General Household Survey 2017. Pretoria; 2018. Available: http://www.statssa.gov.za/publications/P0318/P03182017.pdf. Accessed 15 March 2020

23. Moyo, Faith MSc[*,†]; Haeri Mazanderani, Ahmad MBChB[*,‡]; Barron, Peter BCom, FFCH (SA)[§]; Bhardwaj, Sanjana MBBS, MD, MPH[¶]; Goga, Ameena Ebrahim MBChB, DTMH, DCH, MScMCH, MSc Epidemiology, FC(Paeds), PhD[‖,**]; Pillay, Yogan PhD[††]; Sherman, Gayle G. MBBCh, MMed (Haem), PhD[*,†,‡‡]Introduction of Routine HIV Birth Testing in the South African National Consolidated Guidelines, The Pediatric Infectious Disease Journal: June 2018 - Volume 37 - Issue 6 - p 559-563 doi: 10.1097/INF.0000000000001840

PART C: APPENDICES

B positive: A population-based evaluation of expanded (anti-retroviral therapy) ART access in pregnancy (short title: 'B positive')

1. Background and project outline

Globally there has been a move to provide universal HIV treatment for HIV-infected pregnant women, irrespective of CD4 count ('Option B+'). There are many anticipated benefits for maternal, child and population level outcomes. Uncertainty remains however as to the feasibility of achieving these benefits with the added service burden of expanded treatment, and in the unique context of pregnancy, child birth and early child rearing where there are already data to suggest that mothers and people starting antiretroviral therapy (ART) at higher CD4 counts are less likely to remain in care. There are also ongoing questions as to the long-term safety of ART exposure in pregnancy for mothers and their children, apart from HIV transmission.

South Africa, and the Western Cape in particular, were early adopters of this global guidance, and together with the availability of strong routine information systems, the Western Cape is one of the few settings in which population level data on the benefits and risks of the intervention can be collected and analysed at scale. The Province in partnership with the Centre for Infectious Disease Epidemiology and Research (CIDER) successfully competed for an award to address these questions in linked population-wide (based on routine data) and sentinel (based on a new prospective cohort) studies. The current proposal is for the province-wide study, as well as the planning phase for the sentinel studies.

2. Purpose and objectives:

The primary aim of the study is to comprehensively monitor the effectiveness, impact and risks of the Option B+ prevention of mother-to-child transmission (PMTCT) of HIV strategy (policy of universal initiation of lifelong ART for HIV-infected pregnant women) at a population level in the entire Western Cape Province based on province-wide surveillance through harmonization of existing data systems for HIV/AIDS, antiretroviral treatment (ART) and maternal and child health.

Objectives of the study are as follows:

1: Describe the care cascade and ART and PMTCT program effectiveness for all pregnant women initiating ART including associations with

(a) patient level factors such as pregnancy, CD4 count, viral load, feeding choice, treatment knowledge, mental health, life circumstances and support environment.

(b) health service delivery models and characteristics as they pertain to all services and services for pregnant women in particular.

2: Determine event rates for adverse pregnancy outcomes including serious adverse events in mothers, major congenital anomalies, stillbirths and preterm and low birth weight deliveries, and their associations with ART exposure during conception and pregnancy, based on novel surveillance systems.

3: Describe health effects of ART exposure during conception, pregnancy and breastfeeding and of feeding choice on children beyond the perinatal period.

4: Model the population-level impacts of expanded ART access for pregnant women, based on real world parameterization of provincial and national HIV models, on onward HIV transmission and on HIV treatment programs in general.

3. Implementation and methods

The core enabling work will primarily be conducted by the Provincial Department of Health (PDoH) augmented by personnel employed through this project who will be seconded to the PDoH data centre. The Principal Investigator of the study is also the provincial lead for the data centre. The study will be based on linkage and curation of various data linked on the unique patient number (Clinicom number) in use in the Province, including: disease registers (TIER.Net, EKAPA, Prehmis), laboratory, pharmacy, clerical (Clinicom, PHCIS), maternity (Clinicom, PHCIS), mortality (PPIP, vital registration), and other routine provincial data sources already being housed by the PDoH. Related to each objective:

1: Describe the care cascade and ART and PMTCT program effectiveness.

This is a cohort study following all patients in the Province already on ART and newly initiating ART, including all HIV-infected pregnant women.

Key variables include exposures at baseline (age, sex, ART status (new or duration on ART), pregnancy and gestation at ART initiation if not already on ART, baseline and time-updated CD4 count and viral load, initial and current ART regimen, facility, location of ART (maternity setting or dedicated clinic), and adherence as reflected by visit attendance or pharmacy refill data).

Outcomes will be date of last health service contact (for retention and vital status), vital status, regimen changes, virologic suppression and failure, pregnancy status (as an outcome as well for non-pregnant women on ART), and infant HIV testing outcomes.

2: Determine event rates for adverse pregnancy outcomes including serious adverse.

This is a clinical audit and surveillance exercise working backwards from pregnancy outcomes, which enables retrospective cohort analyses, case-control studies and case-cohort designs on the population of all deliveries in the province. The starting point will be adverse pregnancy outcomes from existing clinical audit (PPIP) and mortality surveillance. The putative study population will be enumerated through a comprehensive pregnancy and births database constructed within the data centre from all available sources.

Key outcomes will be prematurity (with low birth weight deliveries as a proxy), stillbirths and neonatal deaths. Congenital anomalies not compatible with life, as recorded in the clinical audit system, will be included as outcomes in analyses. The initial focus in terms of exposures will be on HIV and ART exposure, peri-conception or during subsequent antenatal care, ascertained through record linkage, later augmented by other drug exposures from drug dispensing data systems.

Aim 3: Health effects of ART exposure beyond the perinatal period

The pregnancy and birth database will have HIV and ART exposures continuously updated for all births to enable future association studies with distal and rare outcomes. Any additional studies looking to associate a specific outcome with birth exposures will be separately detailed in an amendment (if the current protocol is still active) or a future protocol.

Aim 4: Model the population-level impacts of expanded ART access for pregnant women

The THEMBISA (Treatment and HIV Elimination through Medical and Behavioural Interventions in South Africa) HIV and demographic model is a deterministic model of HIV in South Africa developed by CIDER. It will be adapted and re-calibrated to estimate the impact of Option B+ on the epidemic and model the program and population impact of future guideline changes based on the refined and re-calibrated model.

4. Description of risks and benefits:

The study is based entirely on consolidation of existing data collected as standard of care and poses no newly introduced risks to patients. A waiver on informed consent is therefore requested. Newly appointed staff seconded into the data environment will be fully inducted into the provincial procedures designed to safeguard patient confidentiality, will sign the same data access agreements as other provincial staff, and will manage data on the enterprise provincial platform in line with the security arrangements in place for all identified patient data. Only anonymised datasets will be extracted for study analyses.

The procedures described here are analogous to those of an individual facility-based cohort applying for permission to analyse data that have been anonymized and extracted from the routine data environment within that facility, as is the case with many of the HIV treatment cohorts in the Western Cape Province and nationally. Data staff in these facilities have access to identified data as part of facilitating service delivery, and this often includes seconded staff from health system strengthening projects. Researchers however only ever work with anonymized datasets.

The service environment in the current study is however the provincial department of health central environment. The data staff are similarly employed to assist with a service delivery function, only it is at the head office rather than an individual facility, and researchers will similarly only gain access to anonymized data.

There are anticipated benefits to the design and quality improvements of programs to provide HIV care for pregnant women, which should accrue locally as well as in similar contexts.

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.08.21
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	28/8/2020

Note: Please note that incomplete submissions will not be reviewed.
Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)			
HREC REF Number	541/2015	Current Ethics Approval was granted until	30/08/2020
Protocol title	B positive: a population-based evaluation of expanded (anti-retroviral therapy) ART access in pregnancy		
Protocol number (if applicable)	2.0		
Are there any sub-studies linked to this study?		x Yes ☐ No	
If yes, could you please provide the HREC Ref's for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.		HREC REF: 749/2015 (separate FHS016 enclosed)	
Principal Investigator	Professor Andrew Boulle		

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Department / Office Internal Mail Address	Centre for Infectious Disease Epidemiology & Research, School of Public Health & Family Medicine, 5th floor Falmouth Building, UCT FFHS, Anzio Road

1.1 Does this protocol receive US Federal funding?	x Yes	☐ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval? **Note:** Any annual approvals for **Full Committee** review MUST be submitted on the monthly HREC submission dates. (Please send electronic copy for full committee review to hrec-enquiries@uct.ac.za)	☐ Yes	x No
If yes in 1.2 please complete section 1.3 below for invoicing purposes		
1.3 Annual Approval for **full committee** review	- R 3450 (inclusive of vat)	
For invoicing purposes, please provide:		
Sponsor's name		
Contact person		
Address		
Telephone number		
Email Address		

2. List of documentation for approval

N/A

3. Protocol status (tick ✓)

x	Open to enrolment
☐	Closed to enrolment (tick ✓)
☐	Research-related activities are ongoing
☐	Research-related activities are complete, long-term follow-up only
☐	Research-related activities are complete, data analysis only
☐	Main study is complete but sub-study research-related activities are ongoing
☐	Study is closed → Please submit a Study Closure Form (FHS010)

4. Enrolment

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Number of participants enrolled to date	N/A
Number of participants enrolled, since last HREC Progress report (continuing review)	
Additional number of participants still required	

5. Refusals

Total number of refusals (participants invited to join the study, but refused to take part)	

6. Cumulative summary of participants

Total number of participants who provided consent	
Number of participants determined to be ineligible (i.e. after screening)	
Number of participants currently active on the study	
Number of participants completed study (without events leading to withdrawal)	
Number of participants withdrawn at participants' request (i.e. changed their mind)	
Number of participants withdrawn by PI due to toxicity or adverse events	
Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)	
Number of participants lost to follow-up. Please comment below on reasons for loss of follow-up	
Number of participants no longer taking part for reasons not listed above. Please provide reasons below:	

7. Progress of study

Please provide a brief summary of the research to date including the overall progress and the progress since the last annual report as well as any relevant comments/issues you would like to report to the HREC:
See attached sheet.

8. Protocol violations and exceptions (tick ✓ all that apply)

☐	No prior violations or exceptions have occurred since the original approval

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

☐	Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved
☐	Unreported minor violations that have occurred since the last review, as well as significant deviations not yet reported, are attached for review

9. Amendments (tick ✓ all that apply)

☐	No prior amendments have been made since the original approval
x	Prior amendments have been reported since the last review and have already been approved
☐	New protocol changes/ amendments are requested as part of this continuing review (See note below)

Note: If new protocol changes are being requested in this review, please complete an amendment form (FHS006).
Specific changes in the amended protocol and consent/assent forms must be **bolded**, *italicised* or tracked and all changes must include a rationale.

10. Adverse events

10.1 Please provide below or attach a narrative summary of serious adverse events and/ or unanticipated problems since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC). Please comment on whether causality to any study procedure or intervention could be established.
N/A

10.2 Have participants received appropriate treatment/ follow-up/ referral when indicated (e.g. in the case of abnormal or incidental clinical findings, distress or anxiety)?		
☐ Yes	☐ No	x Not applicable
If yes, please describe:		

11. Summary of Monitoring and Audit Activities (tick ✓)

11.1 Was this study monitored or audited by an external agency (e.g. SAHPRA, FDA)?		
☐ Yes	x No	☐ Not applicable

11.2 Did a Data and Safety Monitoring Board publish a report?		
☐ Yes	☐ No	x Not applicable

11.3 If yes, please identify the agency and attach a summary of the findings.					
Agency Name		Report attached	☐ Yes	☐ No	☐ Not applicable
		DSMB report attached	☐ Yes	☐ No	☐ Not applicable

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

11.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team?	
☐ Yes	x No
If yes, please explain:	

12. Level of risk (tick ✓)

12.1 In light of your experience of this research, please indicate whether the level of risk to participants has:	
☐	Increased
☐	Decreased
x	Shown no change
If there has been a change, please explain:	

12.2 Please provide a narrative summary of recent relevant literature that may have a bearing on the level of risk.

13. Statement of conflict of interest

Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ✓)	
☐ Yes	x No
If yes, please explain and if necessary, attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form FHS013):	

14. Signature

My signature certifies that the above is complete and correct.			
Signature of PI		Date	29 July 2020

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Western Cape Government
Health

STRATEGY & HEALTH SUPPORT
Health.Research@westerncape.gov.za
tel: +27 21 483 6857: fax: +27 21 483 9895
5th Floor, Norton Rose House,, 8 Riebeek Street, Cape Town, 8001
www.capegateway.gov.za)

REFERENCE: WC_2016RP6_286
ENQUIRIES: Ms Charlene Roderick

University of Cape Town

Anzio Road

Observatory

Cape Town

7925

For attention: Dr Andile Nofemela, Prof Landon Myer, Dr Emma Kalk, Prof Andrew Boulle, Dr Mary-Ann Davies, Dr Ushma Mehta, Dr Gregory Petro

Re: **B positive: A population based evaluation of expanded ART (antiretroviral therapy) access in pregnancy.**

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research.

Please contact following people to assist you with any further enquiries in accessing the following sites:

Gugulethu CHC	**Lunga Makamba**	**021 637 1280**

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.
2. Researchers, in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final feedback (**annexure 9**) within six months of

completion of research. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).

3. In the event where the research project goes beyond the *estimated completion* date which was submitted, researchers are expected to complete and submit a progress report (**Annexure 8**) to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).

4. The reference number above should be quoted in all future correspondence.

Yours sincerely

AT HAWKRIDGE.

DR A HAWKRIDGE

DIRECTOR: HEALTH IMPACT ASSESSMENT

DATE: 7/9/2016.

CC: **P OLCKERS** **DIRECTOR: KLIPFONTEIN/MITCHELLS PLAIN**

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

20 January 2020

HREC REF:817/2019

Prof A Boulle
School of Public Health & Family Medicine
Room: 5.45 Building
Falmouth Building

Dear Prof Boulle

PROJECT TITLE: PREVENTION OF MOTHER-TO-CHILD TRANSMISSION (PMTCT) OF HIV IN KHAYELITSHA; A CONTEMPORARY REVIEW OF THE SERVICES 20 YEARS LATER (SUB-STUDY 541/2015) (MASTER'S DEGREE - MS F PHELANYANE)

Thank you for submitting your study to the Faculty Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 January 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Ms Florence Phelanyane will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) **This serves as notification of annual approval, including any documentation described below.**			
☑ Approved	Annual progress report	Approved until/next renewal date	30.01.22
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	15/2/21

Note: Please note that incomplete submissions will not be reviewed.
Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	2021-01-24		
HREC REF Number	817/2019	Current Ethics Approval was granted until	2021-01-30
Protocol title	Prevention of mother-to-child transmission (PMTCT) of HIV in Khayelitsha: a contemporary review of the services 20 years later		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes ☒ No		
If yes, could you please provide the HREC Ref's for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Dr Emma Kalk		

Department / Office Internal Mail Address	

1.1 Does this protocol receive US Federal funding?	☐ Yes	☒ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval? **Note:** Any annual approvals for **Full Committee** review MUST be submitted on the monthly HREC submission dates. (Please send electronic copy for full committee review to hrec-enquiries@uct.ac.za)	☐ Yes	☐ No
If yes in 1.2 please complete section 1.3 below for invoicing purposes		
1.3 Annual Approval for **full committee** review	- R 3450 (inclusive of vat)	
For invoicing purposes, please provide:		
Sponsor's name		
Contact person		
Address		
Telephone number		
Email Address		

2. List of documentation for approval

3. Protocol status (tick ✓)

☐	Open to enrolment
☐	Closed to enrolment (tick ✓)
☐	Research-related activities are ongoing
☐	Research-related activities are complete, long-term follow-up only
☒	Research-related activities are complete, data analysis only
☐	Main study is complete but sub-study research-related activities are ongoing
☐	Study is closed → Please submit a Study Closure Form (FHS010)

4. Enrolment

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Number of participants enrolled to date	8298
Number of participants enrolled, since last HREC Progress report (continuing review)	
Additional number of participants still required	

5. Refusals

Total number of refusals (participants invited to join the study, but refused to take part)	

6. Cumulative summary of participants

Total number of participants who provided consent	
Number of participants determined to be ineligible (i.e. after screening)	
Number of participants currently active on the study	
Number of participants completed study (without events leading to withdrawal)	
Number of participants withdrawn at participants' request (i.e. changed their mind)	
Number of participants withdrawn by PI due to toxicity or adverse events	
Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)	
Number of participants lost to follow-up. Please comment below on reasons for loss of follow-up.	
Number of participants no longer taking part for reasons not listed above. Please provide reasons below:	

7. Progress of study

Please provide a brief summary of the research to date including the overall progress and the progress since the last annual report as well as any relevant comments/issues you would like to report to the HREC:
Summary of anonymized cohort; analysis on-going. Submission for MPH and publication pending

8. Protocol violations and exceptions (tick ✓ all that apply)

☐	No prior violations or exceptions have occurred since the original approval

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

☐	Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved
☐	Unreported minor violations that have occurred since the last review, as well as significant deviations not yet reported, are attached for review

9. Amendments (tick ✓ all that apply)

☒	No prior amendments have been made since the original approval
☐	Prior amendments have been reported since the last review and have already been approved
☐	New protocol changes/ amendments are requested as part of this continuing review (See note below)

Note: If new protocol changes are being requested in this review, please complete an amendment form (FHS006).
Specific changes in the amended protocol and consent/assent forms must be **bolded**, *italicised* or tracked and all changes must include a rationale.

10. Adverse events

10.1 Please provide below or attach a narrative summary of serious adverse events and/ or unanticipated problems since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC). Please comment on whether causality to any study procedure or intervention could be established.
N/A

10.2 Have participants received appropriate treatment/ follow-up/ referral when indicated (e.g. in the case of abnormal or incidental clinical findings, distress or anxiety)?		
☐ Yes	☐ No	☐ Not applicable
If yes, please describe:		

11. Summary of Monitoring and Audit Activities (tick ✓)

11.1 Was this study monitored or audited by an external agency (e.g. SAHPRA, FDA)?		
☐ Yes	☐ No	☒ Not applicable

11.2 Did a Data and Safety Monitoring Board publish a report?		
☐ Yes	☐ No	☒ Not applicable

11.3 If yes, please identify the agency and attach a summary of the findings.					
Agency Name		Report attached	☐ Yes	☐ No	☐ Not applicable
		DSMB report attached	☐ Yes	☐ No	☐ Not applicable

11.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team?	
☐ Yes	☐ No
If yes, please explain:	

12. Level of risk (tick ✓)

12.1 In light of your experience of this research, please indicate whether the level of risk to participants has:	
☐	Increased
☐	Decreased
☒	Shown no change
If there has been a change, please explain:	

12.2 Please provide a narrative summary of recent relevant literature that may have a bearing on the level of risk.

13. Statement of conflict of interest

Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ✓)	
☐ Yes	☒ No
If yes, please explain and if necessary, attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form FHS013):	

14. Signature

My signature certifies that the above is complete and correct.			
Signature of PI	Emma Kalla	Date	28 Jan 2021

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY Open Access

Sections

1. SUBMISSION

Please carefully read through the Instructions for Authors and prepare your manuscript according to the guidelines, including structuring it manuscript based on the chosen article category. Manuscripts that do not follow the instructions may be returned to the authors for corrections.

Authors should kindly note that submission implies that the content has not been published or submitted for publication elsewhere except as a brief abstract in the proceedings of a scientific meeting or symposium.

Once the submission materials have been prepared in accordance with the Author Guidelines, manuscripts should be submitted online at https://mc.manuscriptcentral.com/jias. The submission system will prompt authors to use an ORCID iD (a unique author identifier) to help distinguish their work from that of other researchers. Click here to find out more.

You will be asked to suggest potential peer reviewers for your manuscript: they should be experts in the field and be able to provide an objective assessment of the manuscript. Any suggested peer reviewers should not have published with any of the authors of the manuscript within the past five years, should not be current collaborators, and should not be members of the same institution. Suggested reviewers will be considered alongside potential reviewers identified by the Editorial team.

Click here for more details on how to use ScholarOne.

2. AIMS AND SCOPE

The *JIAS* welcomes submissions on HIV-related topics from across all scientific disciplines, including but not limited to:

- Basic and biomedical sciences
- Behavioural sciences
- Epidemiology
- Clinical sciences
- Health economics and health policy
- Operations research and implementation sciences
- Social sciences and humanities, including political sciences and media

The *JIAS* prioritizes submissions from operational research and implementation science as publication of such material can provide valuable information on various algorithms for monitoring and providing support for comprehensive, yet affordable and sustainable treatment, prevention and care programmes in different contexts.

Submission of HIV research carried out in low- and middle-income countries is strongly encouraged.

3. MANUSCRIPT CATEGORIES AND REQUIREMENTS

The *JIAS* accepts submissions in the following categories:

- **Research**
- **Short report**
- **Review**
- **Debate**
- **Commentary**
- **Letter to the Editor**
- **Viewpoint**

Research - full reports of data from original research studies

Abstract:

Headings: Introduction, Methods, Results, Conclusions

Word limit: 350 words

Main text:

Headings: Introduction, Methods, Results, Discussion, Conclusions

Word limit: 3500 words

Numbers of figures and tables: Unlimited

Additional files: Yes

Download the manuscript template

4. PREPARING THE SUBMISSION

Cover letter

In the cover letter, please explain why your manuscript should be published in the journal. If necessary, address any issues relating to our editorial policies .and declare any competing interests (see **Editorial Policies and Ethical Considerations**)

Parts of the Manuscript

The manuscript should be submitted as a main text file including figures and appendices and supporting information should be supplied as separate files.

Main Text File

The text file should be presented in the following order:

1. Title page;
2. Keywords;
3. Abstract;
4. Main text;
5. Conflict of Interest Statement;
6. Authorship;
7. Acknowledgments;
8. References;
9. Tables;
10. Figures;

Title page

The title should not contain abbreviations, except commonly used abbreviations such as HIV or AIDS (see **Wiley's best practice SEO tips**).

On the title page, you should mention the title of the manuscript, list all authors' names in full, and list any study groups if applicable. Each authors' affiliation should be numbered in superscript consecutively and listed underneath, including department, institution, city and country.

The corresponding author should be marked with the symbol § in superscript and full contact details should be provided, including a telephone number with country code. Authors who have contributed equally to the work should be marked with the symbol * in superscript. Deceased authors should be marked with the symbol ^ in superscript. The email addresses of all authors should be listed by their initials.

Keywords

Pease provide six keywords. Keywords should be taken from those recommended by the US National Library of Medicine's Medical Subject Headings (MeSH) browser list at **https://www.nlm.nih.gov/mesh/**. Preferably alternate words to those found in the abstract in order to improve search hits for the article in repositories.

Abstract

The Abstract should not exceed 350 words and should be structured according to the headings of the selected article category (see above), excluding the heading “Discussion” for Research articles. Avoid using abbreviations and do not cite references in the Abstract. If you are reporting results from a controlled health care intervention, please include your trial registry, together with your unique identifying number at the end of the Abstract. For randomized controlled trials, follow the **CONSORT extension for abstracts** .

Main Text

Article sections

Introduction

The Introduction section should introduce the topic to readers without specialist knowledge in that area and must clearly outline the current state of knowledge in this field, the motivation and the aim of the study or the article.

Methods

The Methods section should include all information necessary to repeat the study, in particular, the study design, how data was collected and analyzed, clarifying the choice of methods that were

made. If applicable, you should describe the setting of the study, the dates the study were conducted, and the sample or participants, as well as necessary power calculations and materials, including statistical packages, used. Interventions and programmes should be described in detail. Generic names for drugs or any molecules should be used.

All studies involving humans or animals require a statement on ethical approval, and for the former, the consent procedure that was followed. Please include the names of the ethics review board(s) that approved the study. If the research study was specific to one sex/gender, the reasons for this should be clearly stated.

Results

This section should include only data and findings from the authors' study. Presentation of statistical results should mention confidence intervals and levels of significance where appropriate. Quotes from qualitative study participants of less than three lines should be quoted in the text using quotation marks. For quotes longer than three lines, place the quote in a separate, indented paragraph and introduce it with a colon. No quotation marks are needed in this case. Details of the participant can be added in round brackets following the quote, but should not contain identifiable information to ensure confidentiality. Clarifications within the quotation should be placed in square brackets.

Submitting authors are strongly encouraged to include data disaggregated by sex (and, whenever possible, by race) and provide a comprehensive analysis of gender and racial differences. The authors should include the number and percentage of men, women and, if appropriate, transgender persons who participated in the research study. Anatomical and physiological differences between men and women (height, weight, body fat-to-muscle ratios, cell counts, hormonal cycles, etc.), as well as social and cultural variables (socio-economic, education, access to care, etc.), should be taken into consideration in the presentation of data and/or analysis of the results.

Discussion

In the Discussion section, you should discuss your main findings and place these within the context of the current body of knowledge in the field. Limitations of the study, for example, selection bias, can also be discussed, and should address how these influence the results and conclusions. If statistically significant differences were found between men and women or between different racial or cultural groups in the effects of the studied intervention, the implications, if any, for clinical

and/or public health should be adequately discussed.

Conclusions

In your Conclusions section, state your key messages from the study and explain their importance and relevance, as well as implications. Future studies and recommendations can be included in this section. The conclusions drawn must be strictly based on the data provided.

Conflict of Interest Statement

Authors will be asked to provide a conflict of interest statement during the submission process. For details on what to include in this section, see the 'Conflict of Interest' section in the **Editorial Policies and Ethical Considerations** section below. Submitting authors should ensure they liaise with all co-authors to confirm agreement with the final statement.

Authorship

Please refer to the journal's Authorship policy in the **Editorial Policies and Ethical Considerations** section for details on author listing eligibility. The individual contributions of each author must be specified in the Authors' Contributions section. Please use authors' initials and state that all authors have read and approved the final manuscript. An example of a suitable statement is: "S.W., N.J., D.W. and S.S. performed the research. S.W., N.J., H.H. and T.L. designed the research study. H.H. and S.S. contributed essential reagents or tools. S.W., N.J. and D.W. analysed the data. S.W. and N.J. wrote the paper." Please see the 'Authorship' section in the Editorial Policies and Ethical Considerations section below for what constitutes authorship.

Acknowledgments

Contributions from anyone who does not meet the criteria for authorship should be listed, with permission from the contributor, in an Acknowledgments section. Financial and material support should also be mentioned. Thanks to anonymous reviewers are not appropriate.

References

All external sources of information should be referenced within the text, the tables and figures, using consecutive numbering in square brackets, e.g. [1], [3-5], [3,4]. The references should be up to date and adequately reflect the current state of knowledge in the field. Citation bias, for example, by country or point of view must be avoided. Numbers of references are unlimited for all article categories and should be formatted in standard Vancouver style; **see Sample references from ICMJE** . Unpublished observations, personal communications and manuscripts currently under consideration should be cited in the text in round brackets and not in the reference list.

Tables

They should be supplied as editable files, not pasted as images. Tables should be inserted into the text. They should have the header: "Table 1. Title of table". All tables should be cited in the text in consecutive order. The tables should not contain colour or shading, and no vertical, visible lines. If tables are copied or adapted from another source, permission must be sought by the authors prior to publication and these should be clearly cited as such. If a table spans more than one page, authors may want to consider uploading the table as an additional file instead. Tables should be self-contained and complement, not duplicate, information contained in the text. A legend can be provided underneath the title, listing any abbreviations or meanings of symbols used. If several tables are included, please ensure that symbols are used consistently. Legends should be concise but comprehensive – the table, legend, and footnotes must be understandable without reference to the text. All abbreviations must be defined in footnotes. Footnote symbols: †, ‡, §, ¶, should be used (in that order) and *, **, *** should be reserved for P-values. Statistical measures such as SD or SEM should be identified in the headings.

Figures

Figures should be cropped as closely as possible and have the header: "Figure 1. Title of figure". All figures need to be cited in the text in consecutive order.

Although authors are encouraged to send the highest-quality figures possible, for peer-review purposes, a wide variety of formats, sizes, and resolutions are accepted. **Click here** for the basic figure requirements for figures submitted with manuscripts for initial peer review, as well as the more detailed post-acceptance figure requirements.

Figure legends should be concise but comprehensive – the figure and its legend must be understandable without reference to the text. Include definitions of any symbols used and define/explain all abbreviations and units of measurement. If several figures are included, please ensure that symbols are used consistently.

Additional Files

Appendices

Appendices will be published after the references. For submission, they should be supplied as separate files but referred to in the text.

Supporting Information

Supporting information is information that is not essential to the article, but provides greater depth and background. It is hosted online and appears without editing or typesetting. It may include tables, figures, videos, datasets, etc. **Click here** for Wiley's FAQs on supporting information.

Note : if data, scripts, or other artefacts used to generate the analyses presented in the paper are available via a publicly available data repository, authors should include a reference to the location of the material within their paper.

General Style Points

The following points provide general advice on formatting and style:

• **Abbreviations:** In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Initially, use the word in full, followed by the abbreviation in parentheses. Thereafter use the abbreviation only.

• **Acronyms:** Acronyms should be used sparingly, and not in headings or in the Abstract. Only commonly known acronyms may be used, and they should be spelt out at first use followed by the abbreviation in brackets. SI units should be used, with litre and molar being permitted.

• **Units of measurement:** Measurements should be given in SI or SI-derived units. Visit the Bureau International des Poids et Mesures (BIPM) website **here** for more information about SI units.

• **Numbers:** Numbers under 10 are spelt out, except for: measurements with a unit (8mmol/l); age (6 weeks old), or lists with other numbers (11 dogs, 9 cats, 4 gerbils).

• **Trade Names:** Chemical substances should be referred to by the generic name only. Trade names should not be used. Drugs should be referred to by their generic names. If proprietary drugs have been used in the study, refer to these by their generic name, mentioning the proprietary name and the name and location of the manufacturer in parentheses.

• **Footnotes:** Footnotes are not allowed in the text, the information shall be included directly into the text, where it fits best, and if these are references, to include in the reference section at the end.

• **Language**: All submissions must be in UK English (International) and UN-accepted terminology should be followed. No capitalization should be used except for grammatically correct use, official names and titles, and abbreviations.

• **General recommendation:** Use line spacing of 1.5 and an easily readable font, for example, Times New Roman, size 12. Your manuscript should contain line numbers to facilitate editors' and reviewers' comments

Wiley Author Resources

Manuscript Preparation Tips: Wiley has a range of resources for authors preparing manuscripts for submission available **here** . In particular, authors may benefit from referring to Wiley's best practice tips on **Writing for Search Engine Optimization** .

Editing, Translation, and Formatting Support: **Wiley Editing Services** can greatly improve the chances of a manuscript being accepted. Offering expert help in English language editing,

translation, manuscript formatting, and figure preparation, Wiley Editing Services ensures that the manuscript is ready for submission.

. **Find more information here**.

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES

FORM D18 - DECLARATION/WORD COUNT FORM -- MASTER'S DEGREE CANDIDATES

Title:	Ms	***Student No:***	PHLMAL003
Name, Surname:	Florence Malehlabathe Phelanyane		
Tel No's:	0826349262		
Email add:	Florence.phelanyane@uct.ac.za		
Dissertation Title:	Prevention of mother-to-child-transmission (PMTCT) of HIV in Khayelitsha: a contemporary review of the service 20 years later		

Supervisor	Dr Emma Kalk	**Word count**	3533	**No. of pages**	79

1. IMPORTANT NOTES:

1.1 Candidates for graduation in June and December may expect to receive notification of the outcome of the examination of the dissertation not later than 1st week in June and last week in November, respectively, provided the dissertation was submitted by the due date. Where a dissertation has been submitted well in advance of the due date, earlier notification will be given, if possible. However, the University does not undertake to reach a decision by any specific date.

1.2 Candidates who are required to revise and re-submit for re-examination are required to register during the revision phase. Fees will be calculated according to the date of the notification of the "revise and re-submit" result and the date of re-submission. [Faculty will advise Fees by sending copy of R&R result to Fees.]

1.3 Candidates are asked to note that the University will not permit degree/diploma qualifiers to graduate if they have any outstanding fees, fines, interest or dues**. The final date for payment of outstanding amounts is 30 April in the** case **of qualifiers for June graduation and 31 October in the case of qualifiers for December graduation.**

1.4 Please note that should your examination process run into the following year, you will have to re-register in order to be considered for graduation.

2 DECLARATIONS:

2.1 I am presenting this dissertation in FULL/PARTIAL fulfilment of the requirements for my degree.

2.2 I know the meaning of plagiarism and declare that all of the work in the dissertation, save for that which is properly acknowledged, is my own.

2.3 I hereby grant the University of Cape Town free licence to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever of the above dissertation.

Signature		***Date:***	2021-03-12

3 FUNDING AND FEES:

Candidates submitting have a choice in regard to fees and funding options:

3.1 To claim a fee rebate* and discontinue funding through the PGFO, if applicable (the student remains registered until graduation or the start of the next academic year (see University Rule G5.2). *(Only applicable in second or subsequent year in which the dissertation is being completed - Fee Rule 8)

3.2 To remain registered and engaged in the department while **writing up a paper for publication**, with full student rights and full access to facilities, full liability for fees for the year and continued eligibility for funding already awarded for that academic year. Access will extend only until such time as you graduate. Should you need access beyond this, you will need to arrange for 3rd party access within your department.

Please indicate your preference

I wish to claim the rebate and discontinue funding (if applicable) and physical and library access**	
I wish to continue fee liability, funding eligibility (if applicable) and access to all facilities	

Please note: If you are in the first year of registration for the dissertation or dissertation component of your programme you are not eligible for a rebate

****Students asking for a fee rebate acknowledge**

a) the implications of the fee rebate on their access to facilities and eligibility for funding, and

b) that if they were to stay on in the department and receive payment through the payroll, such payment is taxable.

Signature		***Date:***	2021-03-12

FOR COMPLETION BY FACULTY OFFICE

I acknowledge receipt of the uploaded copy (on PeopleSoft) of the Master's dissertation of the above candidate submitted for examination:

Signature		***Date:***	
Abstract submitted	Yes		No

cc **Fees**
IAPO
PGFO
Student Housing