A longitudinal analysis of the completeness of maternal HIV testing, including repeat testing, during pregnancy, and the predictors thereof, in Mitchell's Plain, Cape Town

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DECLARATION

I, Shani de Beer, 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.

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DISSERTATION ABSTRACT:

HIV testing during pregnancy is the gateway to the HIV-related services that are part of the prevention of mother-to-child transmission (PMTCT) cascade. The virtual elimination of vertical HIV transmission cannot be achieved without universal antenatal care (ANC) HIV testing. Furthermore, women are at an increased risk of HIV infection and subsequent mother-to-child transmission (MTCT) during pregnancy. Emphasis has thus been placed on repeat testing during pregnancy among women who have a HIV-negative result at their first ANC test. Very little has been published on the current uptake and adherence to antenatal and repeat HIV testing in sub-Saharan Africa (SSA) countries.

In line with the World Health Organization Guidelines, the *Western Cape Prevention of Mother-to-Child Transmission of HIV (PMTCT) Clinical Guidelines* in 2014 recommended a repeat HIV test between 32 - 34 weeks gestation and again at delivery in addition to testing at "booking" (< 20 weeks gestation), meaning that there were three "testing windows" during which pregnant women not previously diagnosed as HIV-infected should undergo testing. Between 2013 and 2016 the Closing the Gaps study established an electronic PMTCT register (e-register) that consolidated routine care data from a primary healthcare facility and its secondary and tertiary referral sites in Cape Town, South Africa. This provided a single longitudinal record, from antenatal care to delivery, for each pregnant woman which enabled the longitudinal assessment of maternal HIV testing uptake and treatment. Utilizing these data, we conducted a retrospective sub-analysis investigating the implementation of PMTCT HIV testing guidelines (until delivery), in Cape Town, for the period 1 July 2014 – 31 December 2016. The main objectives of the study were to assess the coverage and timing of initial HIV testing during pregnancy, the completion of HIV testing at "booking" and within the recommended testing windows (including delivery), HIV prevalence and incidence at the recommended testing windows, and the predictors of missed testing opportunities.

The research protocol (Part A) was designed to describe the proposed significance, objectives and methodology of the study.

The literature review (Part B) critically evaluated available literature on: antenatal and repeat HIV testing proportions, HIV positivity, the feasibility and acceptability of repeat

testing, and the predictors of testing completeness within different SSA countries, for the period 2010 – June 2018. Its aim was to inform this study. The need for post-Option B+ implementation, longitudinal studies that analyze antenatal and repeat HIV testing coverage and implementation within SSA was identified.

In Part C I present the methods, results and interpretation thereof for the analysis of individual-level, longitudinal, maternal HIV-testing patient data from the Closing the Gaps study e-register as a manuscript to be submitted for publication.

Among 8558 women who delivered at either the primary care facility or its referral sites, 7213 were not diagnosed HIV-positive prior to their first visit and thus eligible for testing in pregnancy. Among these women, 91% received ≥1 HIV test and 85% "booked" >5 days before delivery with 98% testing completeness at "booking". Only 49% of women eligible for testing "booked" ≤22 weeks gestation. Among women that "booked" ≤22 weeks gestation who weren't diagnosed HIV-positive before delivery and delivered >5 days after the start of the third trimester, 10% received tests in all three recommended windows. Thirty-one percent of women that had not been diagnosed HIV-positive before delivery had an uncertain (i.e. last tested ≥3 months before delivery) or unknown (i.e. never tested) HIV status after delivery. Out of the women that had a known HIV status at delivery, 21% were HIV-positive of whom 95% were known HIV-positive before current pregnancy and 4% were diagnosed at "booking". Overall, HIV incidence in those with ≥2 HIV tests during pregnancy/at delivery was estimated to be 0.2% between "booking" and delivery. Women who enrolled after 2014 were less likely to miss ≥1 of the three recommended tests (aOR: 0.70; CI: 0.55 – 0.90) and not test at delivery (aOR: 0.63; CI: 0.55 – 0.71) compared to those who enrolled in 2014.

Conclusion: In our study, HIV testing completion at "booking" was high, but women tended to "book" late during pregnancy resulting in late initial testing and missed opportunities for early HIV diagnosis. Implementation of repeat HIV testing is poor, particularly at delivery. HIV incidence between first negative ANC test and delivery is very low and therefore future studies to assess the most cost–effective number and timing of HIV tests, and feasibility of implementation, should be considered. Overall, maternal HIV testing within the PMTCT programme in Cape Town has matured post 2014 with improved implementation over time.

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LIST OF ABBREVIATIONS

ANC	Antenatal Care
ART	Antiretroviral Therapy
ARV	Antiretrovirals
banc	basic antenatal clinic
CDC	Center for Disease Control and Prevention
CTG	Closing the Gaps
DHIS	District Health Information System
DHS	Demographic and Health Survey
GSH	Groote Schuur Hospital
HBCT	home-based HCT
HCT	HIV counselling and testing
HIV	Human Immunodeficiency Virus
ICU	Intensive Care Unit
MMH	Mowbray Maternity Hospital
MNCH	maternal, newborn, and child health
MOU	Midwife Obstetric Unit
MPMOU	Mitchell's Plain MOU
MPDH	Mitchell's Plain District Hospital
MTCT	mother-to-child transmission
NHLS	National Health Laboratory Services
PGWC	Provincial Government of the Western Cape
PHC	Primary health care
PITC	provider initiated testing and counselling
PMTCT	Prevention of mother-to-child transmission
SA	South Africa
SSA	Sub-Saharan Africa
UCT	University of Cape Town
UCT-HREC	UCT- Human Research Ethics Committee
UNAIDS	The Joint United Nations Programme on HIV and AIDS
VL	Viral Load
WC	Western Cape
WHO	World Health Organization
ZDHS	Zimbabwe Demographic and Health Survey

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PART A: RESEARCH PROTOCOL

SYNOPSIS

Title: A longitudinal analysis of the completeness of maternal HIV testing, including repeat testing, during pregnancy, and the predictors thereof, in Mitchell's Plain, Cape Town.

Background and justification: Despite significant reductions in the mother-to-child transmission (MTCT) of HIV in South Africa (SA) the virtual elimination of vertical transmission (and the validation thereof) remains elusive. This is due to coverage gaps in the prevention of mother-to-child transmission (PMTCT) care continuum of which maternal HIV testing is the entry point. There is evidence that virtual MTCT elimination cannot be reached unless near universal antenatal testing is achieved. Complete maternal HIV testing including repeat testing in late pregnancy/delivery is important as pregnant women are at increased risk for HIV infection and mothers with acute rather than chronic HIV infection are more likely to vertically transmit HIV. Since July 2014 the Western Cape (WC) PMTCT guidelines recommend a minimum of three maternal HIV tests for pregnant women of negative/unknown HIV status: 1) at the first antenatal care (ANC) visit (< 20 weeks); 2) at the third trimester ANC visit; 3) in labour or within a few days post-partum. PMTCT coverage is currently determined using aggregate reporting at each step of the continuum. As a result, there is little individual-level information on the implementation and coverage of maternal HIV testing, including repeat testing, in SA. Aggregate level reporting is likely to overestimate the true maternal HIV testing coverage when taking each individuals uptake of the repeat testing continuum into account.

Objective: Utilizing longitudinal maternal data from the Closing the Gaps (CTG) study, this sub-analysis will examine: the coverage of HIV testing at recommended time points within the PMTCT continuum; HIV prevalence and incidence; and the factors associated with testing incompletion during pregnancy. By doing so we hope to provide direction to the targeting of future interventions for the effective closure of identified gaps.

Methods: This is a descriptive longitudinal retrospective cohort sub-analysis conducted on consolidated maternal HIV test data obtained from the novel integrated PMTCT electronic register (e-register) implemented during the CTG study. Data was obtained from existing, routinely collected, maternal data sources of Mitchell's Plain Midwife Obstetric Unit (MPMOU) (primary level) and its secondary and tertiary level referral sites: Mitchell's Plain District Hospital (MPDH), Mowbray Maternity Hospital (MMH) and Groote Schuur Hospital (GSH) respectively, within the Klipfontein sub-district of the WC. We will include women that attended antenatal care and/or delivered at either MPMOU or one of its referral sites with a live or still birth pregnancy outcome between July 2014 and December 2016. Both women for whom no pregnancy outcome can be found and those who "booked" (i.e. presented for ANC >5 days before delivery) at basic antenatal clinics will be excluded from the study as full testing data cannot be determined. No patient contact or involvement is required for this study and data will be de-identified prior to analysis.

Testing completion, HIV prevalence and incidence will be described using descriptive statistics. Logistic regression will be used to determine potential predictors of not testing: at all, at "booking", at delivery, and missing one of the three recommended tests.

Ethical considerations: The CTG study received ethical approval from both the University of Cape Town Human Research Ethics Committee (UCT-HREC) (HREC: 145/2013) and the Provincial Government of the Western Cape Department of Health Research (RP063/2013).

Risks and Benefits: The main risk to study participants in this sub-analysis is that of breaching patient confidentiality. Significant precautionary measures will however be in place throughout the study process to protect patient confidentiality, thus rendering the study minimal risk. The inclusion of folder numbers as a data linkage field is necessary for the consolidation and cleaning of episode and test data but will be removed from the dataset prior to analysis.

The proposed study will not directly benefit participants. It will however, provide important insights into the individual level PMTCT HIV testing coverage gaps which could, through targeted interventions, potentially benefit individuals at a local and international level in the future.

Informed Consent: Data collection for the CTG study did not require participant recruitment as it was routinely collected by health services. A waiver of informed consent was therefore granted for the construction of the e-register. No additional participant recruitment is required for this sub-analysis.

Privacy and confidentiality: Once the linkage of episode and maternal HIV test data is complete participant identifiers will be removed to anonymize the dataset. All data will be password protected and securely stored on the UCT firewall-protected SQL server housed within the CIDER offices. Only authorized NIH Human Subjects Protection trained researchers will have data access. Essential data transfer will be safeguarded by password protected encryption and compression.

Involvement of vulnerable persons: The data to be analyzed in this study is that of pregnant women, a vulnerable population. These women are the group of interest to whom all study findings will be inferred and therefore the inclusion of their data in this study is necessary.

Research related compensation and insurance: The proposed project is a secondary data analysis and there will therefore be no compensation or potential injury to study participants.

PROTOCOL

A longitudinal analysis of the completeness of maternal HIV testing, including repeat testing, during pregnancy, and the predictors thereof, in Mitchell's Plain, Cape Town.

1. Purpose of the study

1.1 Study Aims and Hypotheses

Aim:

To investigate the HIV testing coverage gaps in the prevention of mother-to-child transmission (PMTCT) care continuum, estimate HIV prevalence and incidence, and determine the predictors associated with testing incompletion amongst pregnant women in Mitchell's Plain, Cape Town.

Hypotheses:

I. Testing completion will be lower at subsequent versus initial antenatal care visits (booking), among women not diagnosed as HIV-positive.

II. Testing completion among pregnant women with an unknown/negative HIV status who present for the first time at delivery will be low.

III. The testing completion proportion for each time point as determined by data recorded using a novel electronic register of PMTCT coverage (PMTCT e–register) will be lower than that reported in the literature using aggregate provincial and/or national data.

IV. There are patient-level, facility-level, and calendar time-level characteristics that are predictive of testing incompletion.

1.2 Study objectives

- To describe the proportion of HIV unknown/previously negative women receiving at least one HIV test during pregnancy or delivery.

- To describe the timing of first-time maternal HIV testing among pregnant women of unknown/previously negative HIV status.

- To describe maternal HIV testing completion at "booking" (first antenatal care visit) among HIV unknown/previously negative women who receive antenatal care and at delivery among HIV unknown/previously negative who don't receive antenatal care.

- To describe the PMTCT programme repeat HIV testing completion, among pregnant women who initially presented as HIV-negative, at each recommended testing step of the continuum of care (until delivery) and with respect to each individual's progress through the care continuum.

- To describe the HIV prevalence and incidence among the above-mentioned women at each recommended testing step of the care continuum up until delivery.

- To determine the predictors of missed testing opportunities, among the above-mentioned women, overall and at each testing step of the care continuum (up until delivery).

2. Background and justification

In 2011 South Africa (SA) was listed as 1 of the 22 countries that accounted for 90% of pregnant HIV-positive women globally and was prioritized as part of the Global Plan to eliminate new cases of HIV infection among children by 2015 [1]. SA has since made great progress in achieving the goals of the Global Plan, accomplishing an 84% reduction in the number of new mother-to-child transmission (MTCT) infections and meeting the target of

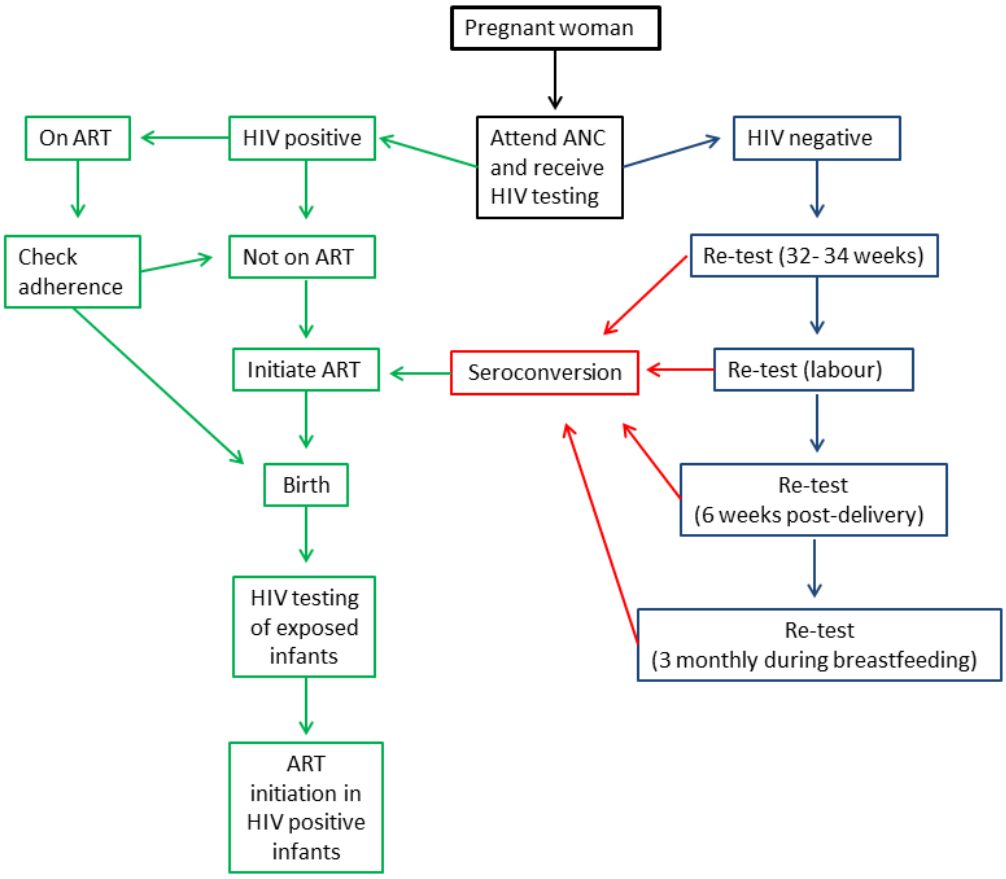

Figure 1. Brief outline of the steps in the prevention of mother-to child-transmission (PMTCT) continuum [7: p.19-27]
ANC= Antenatal care
ART = Antiretroviral therapy

reducing its MTCT rate to 2% [1,2]. Despite the progress made in SA, coverage gaps within the PMTCT care continuum still occur and as a result virtual elimination of MTCT and moreover validation thereof have been elusive [3–6]. Closure of these gaps is essential to ensure the survival of each mother-infant pair.

A recent study conducted by Woldesenbet *et al.* illustrated that in SA 35% of mothers dropped out of the PMTCT continuum at one step or another and furthermore that a third of MTCT was attributable to missed opportunities within the PMTCT care continuum [5]. In order for a PMTCT program to be effective a woman and her infant require not only access to, but also engagement in a continuum of interventions (Figure 1) [7: p.19-27], namely: Antenatal services and HIV testing throughout pregnancy and at birth; the initiation of antiretroviral therapy (ART) if HIV-positive and uptake of the corresponding PMTCT

counselling; safe childbirth practices as well as appropriate infant feeding; and postnatal services including mother and infant HIV testing and the initiation of ART if necessary [2,7]. As the point of entry to the HIV services offered to women in the PMTCT care continuum, antenatal HIV testing is a critical step in the pathway to the elimination of MTCT [8]. Early testing and diagnosis of undiagnosed HIV-positive pregnant women provides them with immediate access to lifelong triple ART which, if adhered to, will offer protection against MTCT during current and subsequent pregnancies [9].

There is evidence that maternal HIV testing, alongside maternal and infant ART initiation, is accountable for the majority of the gaps in the PMTCT continuum. Moreover, virtual MTCT elimination cannot be reached unless near universal testing is achieved [5,10,11]. A 2012 study by Stinson *et al* using cord blood surveillance illustrated that even in a well-resourced setting incomplete antenatal testing contributed 46% toward missed PMTCT opportunities (Figure 2, bar 3) [10: p.202]. Of those mothers identified as HIV-positive via cord blood, 16% had not been tested for HIV during pregnancy (Figure 2, bar 2) [10: p.202].

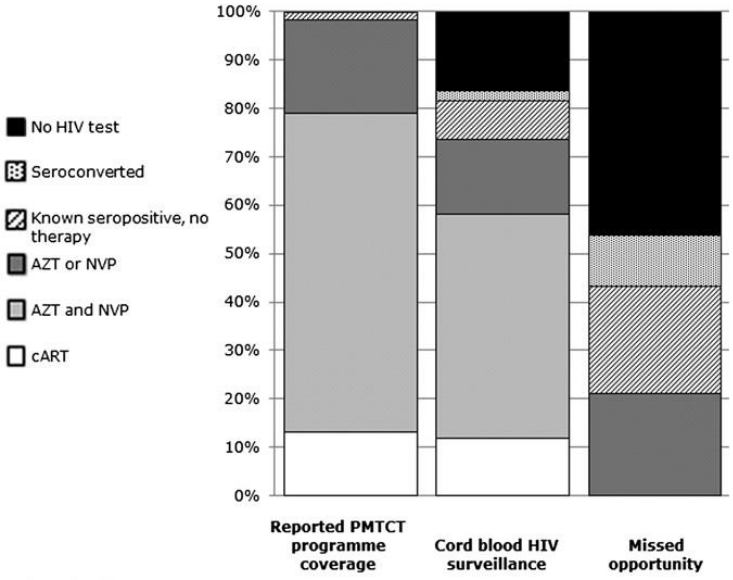

Figure 2. Missed opportunities within the PMTCT continuum in the Western Cape. Adapted from Stinson *et al [10: p.202].*

Since the implementation of immediate lifelong triple ART for all HIV-positive pregnant women (Option B+) in 2015 the majority of South African, previously undiagnosed, HIV-positive pregnant women are initiated on ART at their first antenatal care (ANC) visit, if identified [12]. This is likely to result in a greater proportion of MTCT arising from pregnant women who test HIV-negative at their first ANC visit and then seroconvert during pregnancy or postpartum [13]. This is substantiated by evidence that pregnant women are at increased risk for HIV infection and that, in addition, the risk of MTCT is elevated among women with acute rather than chronic HIV infection [14–19]. This highlights the importance of complete

repeat HIV testing during pregnancy in identifying women who seroconvert subsequent to their first ANC test, enabling them to initiate ART as soon as possible thereafter, thereby limiting MTCT. This will furthermore ensure that HIV exposed infants are identified, followed closely, and tested and initiated on ART early if infected [16,20]. HIV testing early-on in pregnancy is necessary to deem women eligible for HIV retesting in the third trimester of pregnancy or at delivery. This is particularly important for those at risk of seroconversion [21].

Recognizing the importance of repeat testing during pregnancy, the July 2014 *Western Cape Prevention of Mother-to-Child Transmission of HIV (PMTCT) Clinical Guidelines Update* recommended an HIV test at delivery/immediately post-partum for women of negative/unknown HIV status, in addition to the already suggested tests at the first (<20 weeks gestation) and 32-34 weeks gestation ANC visits [22]. This recommendation was also included in the national consolidated guidelines in April 2015 [7]. There is however little information on the implementation and uptake of HIV repeat testing among pregnant women at the individual level. This largely results from aggregate coverage reporting of each step of the PMTCT care continuum separately, rather than tracking individual women longitudinally through pregnancy and post-partum.

Up until now the data that are used to determine service coverage in SA are routinely collected, collated and summarized in paper format at the facility level and then sent monthly to the sub-district level for electronic capture before being imported into the District Health Information System (DHIS) [23]. There are however concerns about the quality of recorded PMTCT data, mainly due to the inaccuracy and incompleteness of its reporting [23,24]. Moreover, the PMTCT care continuum is implemented sequentially throughout pregnancy and involves multiple service providers, ultimately resulting in the collection of data across facilities and at different steps throughout the continuum [10,23]. This approach accounts for aggregate reporting of PMTCT coverage with no linkage across the different platforms and consequently no tracking of an individual pregnant woman's progress through the care continuum [25]. It may therefore appear as though there is sufficient HIV testing coverage at an aggregate level whereas this is likely to be an overestimate of the true coverage when taking each individuals uptake of the repeat testing continuum into account.

In 2014 the Closing the Gaps (CTG) study (Appendix 2) implemented the integration of a PMTCT electronic register (e-register) within the existing service platform at Mitchell's Plain Midwife Obstetric Unit (MPMOU) as well as its referral sites as part of an active PMTCT surveillance system. Its aim was to merge data recorded at different steps of the PMTCT continuum so as to be able to holistically compare the coverage and effectiveness of the PMTCT programme before and after implementing the system. The e-register provided a longitudinal PMTCT record for each women delivering at MPMOU or its referral sites, allowing individual-level assessment of HIV testing from the first ANC visit through to delivery.

Antenatal HIV testing early on in one's pregnancy is essential to the elimination of MTCT [8]. Furthermore, with perinatal seroconversion prominently contributing to vertical MTCT great emphasis has been placed on the importance of repeat HIV testing throughout the pregnancy period [6,13,16,22]. There has however been limited assessment of the antenatal HIV testing coverage specifics and implementation of repeat testing in SA. Utilizing the availability of longitudinal maternal data from the CTG study this sub analysis will investigate: the coverage of maternal HIV testing, including repeat testing, within the PMTCT continuum; HIV prevalence and incidence; and the factors associated with testing incompletion during pregnancy amongst women that attended antenatal care and/or delivered at either MPMOU or one of its referral sites in the Western Cape (WC). By doing so we hope to provide insight into where future interventions should be targeted in order to effectively close identified gaps.

3. Methodology

3.1 Study design

A descriptive longitudinal retrospective cohort study will be conducted, for the period 1 July 2014 – 31 December 2016, on secondary maternal HIV test data obtained from the novel integrated PMTCT e-register implemented during the primary CTG study (Appendix 2). There will be no direct contact with research participants in this study.

The PMTCT e-register was established as one of three linked monitoring and surveillance interventions in the primary NIH-funded CTG study. The e-register, specific for MPMOU and its referral sites, consists of consolidated routinely collected data elements from antenatal HIV testing registers, labour ward HIV PMTCT registers and delivery registers as well as HIV-associated laboratory and ART data.

3.2 Study setting

Data to be analyzed in this study was obtained in the CTG study from the existing data sources of MPMOU and its secondary and tertiary referral sites: Mitchell's Plain District Hospital (MPDH), Mowbray Maternity Hospital (MMH) and Groote Schuur Hospital (GSH) respectively, within the Klipfontein sub-district of the WC, SA. MPMOU is a primary health care facility providing both antenatal care services, including HIV testing, counselling and treatment, and uncomplicated vaginal delivery services which are administered by midwives. MMH and MPDH are secondary level facilities with operating theatres and neonatal intensive care unit (ICU) facilities respectively. GSH is a tertiary care facility with adult and neonatal ICU facilities. Referral from MPMOU to a secondary of tertiary care facility occurs antenatally or peri-partum if a pregnancy is considered to be high risk or requires advanced care. This could be due to: the presence of specific risk factors, certain medical conditions or having a poor obstetric history.

MPMOU forms part of the Mitchell's Plain Community Health Centre which serves an estimated 1.2 million people which are predominantly "Coloured". Furthermore approximately 24% of community members are unemployed with as many 16% of individuals having not completed grade 7 [26].

3.3 Study population

3.3.1 Study participants

Data from the CTG database of pregnant women that attended antenatal care and/or delivered at either MPMOU or one of its referral sites (after referral from MPMOU), during the period 1 July 2014 – 31 December 2016, will be considered for inclusion in the study.

The CTG study automatically enrolled all pregnant women upon their first antenatal visit at MPMOU or alternatively upon presentation for delivery if they had not received antenatal care. Enrollments occurred from 1 February 2014 – 30 June 2016. Individuals were followed to delivery up until the end of 2016. In July 2014 the *Western Cape Prevention of Mother-to-Child Transmission of HIV (PMTCT) Clinical Guidelines* were updated to recommend an HIV test at delivery [22]. For the purposes of this study and maintaining a single policy period with regards to HIV testing of pregnant women, only women that enrolled from 1 July 2014 will be considered for inclusion.

3.3.2 Eligibility criteria

Women will be eligible for inclusion in the study analysis if they: delivered at MPMOU or one of its referral sites, MMH, MPDH or GSH between 1 July 2014 and December 2016 with a live or still birth pregnancy outcome. Women who attended for delivery at MPMOU or one of its referral sites through a basic antenatal clinic (banc) as well as those for whom no pregnancy outcome can be found (after cross checking with clinical records) will be excluded from the study since we do not have access to complete longitudinal HIV testing data for these individuals Without a documented pregnancy outcome and visit data we do not know if the pregnancy was sustained or if participants transferred to other (unobserved) facilities and at what point they did so. Keeping them in the dataset could result in the underestimation of repeat testing completion. That said, it is acknowledged that the testing outcomes for the subset of women without recorded pregnancy outcomes may be systematically different from those for

whom outcomes are recorded and excluding them from the study could introduce selection bias and a slight overestimation of testing completeness.

3.3.3 Sample size

At the time of primary data collection there were approximately 7000 pregnant women presenting at the MPMOU yearly of which 30% present through bancs. When excluding pregnant women that present through bancs it is anticipated that during the two year enrollment period under analysis in this study (1 July 2014 – 30 June 2016) approximately 9800 pregnant women would have attended antenatal care and/or delivered at MPMOU or one of its referral sites.

3.4 Research procedures and data collection methods

This study will use data collected as part of the CTG study. Data for the CTG study were collected prospectively up until December 2016. Point of care rapid HIV tests i.e. antibody assays were performed by community care workers as part of routine ANC services and by nurses in the labour ward of MPMOU and the labour/post-natal ward of the hospitals. Data elements from antenatal HIV testing registers, labour ward HIV PMTCT registers and delivery registers as well as HIV-associated laboratory and ART data were digitized and consolidated to form the PMTCT e-register. Data linkage fields included WC unique patient identifiers ("folder numbers"), birth dates and delivery dates. Study enrollments were stopped from 1 July 2016.

Maternal PMTCT episode and visit test data for the period 1 July 2014 – 31 December 2016 will be extracted from the database of the CTG cohort for the purposes of this study (see Table 1 for variables of interest). No patient contact or involvement is required for this study and data will be de-identified prior to analysis.

3.5 Data management

Data extracted from the password-protected CTG database will be secured as an encrypted and password protected electronic file and stored within the UCT firewall-protected SQL server. In addition, the dataset and study information will be backed up on a password protected hard drive. Data cleaning will include: filtering the dataset according to the studies inclusion/exclusion criteria; identifying and deleting across-all-variable duplicates; and following up of logic violations and missing observations/outcomes with original clinical records. All data queries, responses and edits will be recorded.

Maternal episode data will be merged with maternal visit test data using folder number identifiers resulting in a database of initially HIV unknown/negative pregnant women with their corresponding HIV testing data throughout their pregnancy as well as women who were known HIV-positive at the time of enrollment. Once merging is complete each participant will be allocated a unique study identifier and all prior identifiers will be removed from the dataset.

3.6 List and definition of variables

A list of the variables to form part of data analysis, and their respective classifications and definitions, is shown in Table 1.

Table 1. Variable list

Variable	Classification	Definition
Age	Continuous: numerical (years)	Mother's age at time of enrollment.
Enrollment facility	Categorical: nominal (MPMOU/ MPDH/MMH/GSH)	Facility at which participant first visited for antenatal test or delivery.
Year of enrollment	Categorical: ordinal (2014/2015/2016)	Year in which participant enrolled.
Delivery facility	Categorical: nominal (MPMOU/ MPDH/MMH/GSH)	Facility at which participant delivered.
Mode of delivery	Categorical: nominal (vaginal/assisted/caesarian)	Mode by which baby was delivered.
Birth outcome	Categorical: binary (alive/stillborn)	Birth outcome of infant.
Premature birth	Categorical: binary (yes/no)	Birth <37 weeks gestation.*
Antenatal care	Categorical: binary (yes/no)	Whether or not participant presented for antenatal testing before delivery.
Gestational age at first test	Continuous: numerical (weeks)	A measure of the foetal age when the participant received her first HIV test.
Time from "booking" to delivery	Continuous: numerical (weeks)	Number of weeks before delivery at which participant "booked".
Number of tests	Discrete: numerical (1, 2, 3…)	Number of HIV tests received by participant from "booking" up until delivery/immediately post-partum.
Time of HIV diagnosis	Categorical: nominal (at enrollment, after enrollment, never)	The point at which participant was diagnosed HIV+ from enrollment until delivery.
Seroconversion †	Categorical: binary (yes/no)	Whether or not participant seroconverted between enrollment and delivery.
Gravidity	Discrete: numerical (1, 2, 3…)	The number of pregnancies a participant has had in lifetime.
Second pregnancy	Categorical: binary (yes/no)	Whether or not participant had a second pregnancy during the study period.
Parity	Discrete: numerical (1, 2, 3…)	The number of live births participant has had in lifetime.

*Gestational ages as documented in the delivery registers.

† Seroconversion – The transition from a negative HIV antibody test result to a positive HIV antibody test result due to the production of a detectable quantity of HIV antibodies by an individual [21].

MPMOU: Mitchell's Plain Midwife Obstetric Unit; MPDH: Mitchell's Plain District Hospital; MMH: Mowbray Maternity Hospital; GSH: Groote Schuur Hospital

Outcome variables

1. **Missed maternal HIV testing**

   No HIV testing (i) at all or (ii) during one or more of the recommended testing windows (at "booking" (< 20 weeks); 32 -34 weeks; date of delivery ± 5 days), and delivered at MPMOU or one of its referral facilities.

2. **HIV diagnoses**

   Diagnosis as HIV-positive, either on date of enrollment or at any subsequent testing visits.

The study period for each woman will commence at initial antenatal "booking" and will end 5 days after delivery, allowing leeway time for delivery testing. Among "un-booked" women the study will commence on date of delivery. Women with an unknown pregnancy outcome will be excluded.

3.7 Data Analysis

Data analysis for this study will be carried-out using Stata version 13.0 (Stata Corporation, College Station, Texas, USA).

Descriptive statistics will be conducted using means and confidence intervals (CI) for normally distributed continuous variables, medians and interquartile-ranges (IQR) for non-normally distributed continuous variables, and proportions for categorical variables.

Overall testing completion as well as testing completion within each recommended testing window will be examined using frequency tables to describe the proportion of missed tests among eligible participants at each time point.

Frequency tables will also be used to describe HIV prevalence and incidence at each time point.

Differences will be assessed using the two-sample t-test (normally distributed data) or the Wilcoxon rank-sum (non-normally distributed data) for numerical data and the $\chi 2$ or Fishers Exact test for categorical data. Significance will be determined at a level of 0.05.

As testing outcomes are binary (tested/not tested) multiple logistic regression models will be used to determine potential predictors of not testing: at all, at "booking", at delivery, and missing one of the three recommended tests.

Multivariable models will incorporate covariates (age at enrolment, gravidity, & year of enrolment) that are decided on *a priori* based on them being known or suspected risk factors for the outcome of interest. Other variables will be sequentially added to the model based on univariable analysis significance and retained if they are either significantly associated with the outcome of interest ($p<0.05$) or alter the odds ratios of other variables in the multivariable model by ≥10%. Model outputs will be presented as odds ratios with 95% confidence intervals (CI).

4. Ethical considerations

4.1 Ethical Approval

Ethics approval for the larger CTG study has already been received from both the University of Cape Town Human Research Ethics Committee (UCT-HREC) (HREC: 145/2013; Appendix 3) and the Provincial Government of the Western Cape (PGWC) Department of Health Research (RP063/2013; Appendix 3).

Ethical approval for this proposed CTG sub-analysis study will be sought from the UCT-HREC. The study will be conducted in accordance with the protocol, the Declaration of Helsinki and the local rules and ethical regulations of South Africa.

4.2 Risks and benefits

This study is considered to be minimal risk. The sub-study is a secondary analysis of existing CTG data. The only risk to study participants is breaching of patient confidentiality. However, significant precautions will be taken throughout the study process to protect patient confidentiality. Identifiable data linkage fields included in the data set are: Folder numbers, birth dates and delivery dates. The inclusion of folder numbers is essential for the merging of episode and visit test data, but these will be removed from the dataset once the merge is complete. All analysis will be done on anonymized data.

There will be no direct benefits to participants of this study; however, the proposed study could potentially benefit participants during future pregnancies. The study will still provide insight into the individual level PMTCT HIV testing coverage gaps among pregnant HIV women thereby enabling targeted future interventions for the closure of these gaps. Furthermore, knowledge of risk factors found to be associated with testing incompletion will assist with the antenatal identification of women who, although HIV-negative, may require additional support throughout the PMTCT continuum.

4.3 Informed Consent

The larger CTG study was granted a waiver of informed consent for the construction of the e-register as all data had already collected routinely by health services. No participant recruitment was required. A single trained data clerk, who had completed the online NIH Protection of Human Subjects training, was responsible for entering data onto the current provincial medical records platform. The primary dataset was thus collected in an ethical manner.

No additional participant recruitment is required for this sub-analysis.

4.4 Privacy and confidentiality

All the necessary steps will be taken to ensure the confidentiality of study participants. The dataset will be anonymized by removing participant identifiers once the merge of episode and visit test data is complete and allocating unique identification numbers to participants. The dataset to be analyzed will be password protected and securely stored on the UCT firewall-protected SQL server housed within the CIDER offices. In addition, the dataset will be backed up on a password encrypted hard drive. Any data transfer will be secured by password protected encryption and compression with the password being communicated telephonically or in person. The dataset will only be accessible to authorized researchers.

4.5 Involvement of vulnerable persons

This study involves the analysis of data on pregnant women and therefore a vulnerable population. The inclusion of data from this study group is however essential as they are the group of interest to whom all study findings will be inferred. Nonetheless, measures are in place to protect these participants.

4.6 Research related compensation and insurance

As this project does not involve participant recruitment there will be no compensation or potential injury to study participants.

5. Dissemination of Findings

The research findings obtained from the proposed study will be submitted in partial fulfilment of the requirements for the Master of Public Health (Epidemiology and Biostatistics) degree at the University of Cape Town. Furthermore, the findings will be submitted to an appropriate peer review journal for publication. A report or presentation of the findings will be offered to all interested stakeholders.

6. Logistics

6.1 Timetable

Timetable for proposed study: 2018 - 2019				
	November	December	January	February
Departmental and ethical approval	X			
Clean, check and merge datasets	X	X		
Data analysis		X		
Writing of manuscript		X	X	
Submission of dissertation			X	
Dissemination of findings				X

6.2 Budget

Data for the proposed study has already been collected therefore no further costs will be incurred.

7. Appendices

7.1 Appendix 1

Supplementary methods

7.2 Appendix 3

Closing the Gaps in PMTCT Programme Coverage, Early Infant Diagnosis and Treatment (CTG)

7.3 Appendix 4

- UCT-HREC (HREC: 145/2013)

- PGWC Health Research approval (RP063/2013)

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SECTION B: LITERATURE REVIEW

1. Background

In 2011, 21 sub-Saharan Africa (SSA) countries including South Africa, ranked globally as having the highest number of HIV-positive pregnant women, were prioritized as part of the Global Plan aimed to keep mothers alive and eliminate incident HIV infections among children by 2015 – the "Global Plan" [1].

Shortly after the launch of the Global Plan, the World Health Organization (WHO) introduced the option of the initiation of immediate lifelong triple ART for all HIV-positive pregnant women (Option B+) in 2012 [2]. By 2015, Option B+ was being offered by all the Global Plan countries except Nigeria [3]. Consequently, great progress has been made in reducing mother-to-child transmission (MTCT) in the 21 priority countries [1,3]. However, challenges remain in achieving the virtual elimination of MTCT [1,4,5].

HIV testing of pregnant women is an essential step in the prevention of mother-to-child transmission (PMTCT) [6]. It is the point of entry to the care and treatment necessary to optimize the prevention of transmission. Without universal HIV testing during pregnancy, virtual MTCT elimination cannot be achieved [7,8]. In addition, evidence suggests that women are at an increased risk of HIV infection during pregnancy and furthermore, acute rather than chronic HIV infection leads to an increased risk of MTCT [9–14]. This has placed emphasis on the importance not only of a single HIV test at first antenatal visit, but also of repeat HIV testing throughout pregnancy, particularly testing during late pregnancy and/or at delivery [11,14,15]. Owing to the success of Option B+ at initiating ART in women identified as HIV-infected either prior to or at their first antenatal visit, MTCT may now be more likely to occur in pregnant women who test HIV-negative at their first antenatal care (ANC) visit and seroconvert thereafter (antenatally or postnatally) [14]. The WHO recommends that pregnant women from areas with a generalized HIV epidemic receive HIV retesting in the third trimester, and at delivery, or directly thereafter [6,16].

This literature review aims to inform the proposed study: *A longitudinal analysis of the completeness of maternal HIV testing, including repeat testing, during pregnancy, and the predictors thereof, in Mitchell's Plain, Cape Town,* by critically evaluating the available evidence on antenatal and repeat/late pregnancy HIV testing in SSA countries since the 2010 amendment of the WHO guidelines to recommend repeat antenatal HIV testing in areas with generalized HIV epidemic settings.

2. Objectives

The main objective of the review is to appraise all published quantitative studies that report on antenatal, repeat or late pregnancy HIV testing coverage within SSA countries, for the period 2010 – June 2018.

The specific objectives of the review are to:

- Describe the antenatal and repeat/late pregnancy HIV testing coverage within different SSA countries and to report on the HIV prevalence and/or incidence at respective testing time-points.
- Describe the feasibility and acceptability of repeat/late pregnancy testing within different SSA countries.
- Describe identified predictors of testing completeness within different SSA countries.
- Identify areas of antenatal and repeat/late pregnancy testing that require further research.

3. Search Methods

PubMed and Google scholar were searched for sources relevant to this literature review. Search terms included HIV, PMTCT, antenatal/repeat testing and SSA countries (see Box 1 for variations) with the search being restricted to English publications. The references of included studies were searched for additional relevant sources.

Publications were considered for inclusion if they were either systematic reviews, experimental or observational studies conducted during the period 2010 – present (June 2018). 2010 was selected as the starting point as this is when the WHO amended their recommendations to include repeat antenatal HIV testing [16]. Reports were only included if the study 1) was conducted in a SSA country and 2) included antenatal or repeat/late pregnancy HIV testing coverage as an outcome of interest. Tables 1 and 2 summarize the included studies.

To contextualize the review of included studies I also drew on other studies around HIV testing coverage that may not have met the inclusion criteria for this review.

HIV: "HIV"[Mesh]) OR HIV, Human Immune Deficiency Virus, Human immunodeficiency virus

PMTCT: Mother-to-Child Transmission of HIV, Prevention of Mother- to- Child Transmission of HIV, Vertical Transmission, Vertical Transmission of HIV

Antenatal/repeat testing: repeat HIV testing, delivery testing, delivery HIV testing, testing during late pregnancy, maternal testing, maternal HIV testing, antenatal testing, antenatal HIV testing, testing during labour, retesting

Sub-Saharan Africa: sub-Sahara* Africa*, Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Democratic Republic of Congo, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria, Principe, Rwanda, Sao Tome, Senegal, Seychelles, Sierra Leone, Somalia, South Sudan, South Africa, Swaziland, Tanzania, Togo, Uganda, Zambia, Zimbabwe

Box 1. Search strategy – term variations

4. Summary of the literature

4.1 Antenatal HIV testing

As the point of entry to the HIV services offered to women as part of PMTCT, antenatal HIV testing is a critical step in the pathway to the elimination of MTCT [17].

In 2012 the WHO introduced Option B+ which recommended immediate initiation of lifelong triple ART for HIV-positive pregnant women irrespective of their CD4 count [2]. The

rationale for Option B+ is that through a high detection rate of HIV-positive pregnant women there would be optimal effective treatment coverage therefore offering not only protection against MTCT amongst these women during pregnancy, delivery, breastfeeding and any other subsequent pregnancies during their lifetime, but also a positive impact on the mothers' health [18]. The introduction of Option B+ has significantly reduced MTCT globally, however its success relies heavily on antenatal HIV testing for the detection of HIV-positive mothers [1,3,16,19].

The benefits of antenatal HIV testing are not limited to women who are HIV-positive. Testing and counselling early during pregnancy can provide HIV-negative women with the necessary guidance towards the prevention of HIV acquisition [20]. This is particularly important as pregnant women are at increased risk of HIV infection and, if infected during pregnancy, of transmitting virus to their infants [9–14]. In addition, women who present early for HIV testing and who are HIV-negative are eligible for a second testing opportunity later in pregnancy, in the third trimester of pregnancy or at delivery [16]. This enables the early detection and treatment initiation of women who have seroconverted during pregnancy.

Current WHO recommendations are that provider initiated testing and counselling (PITC) for HIV should form a routine component of ANC services in high HIV prevalence settings [20]. Furthermore PITC should be offered to pregnant women at their first ANC visit which should ideally be in the first trimester, before 12 weeks gestation [21]. It should however be noted that it is not common for pregnant women to present <12 weeks gestation in SSA [22]. There has also been an observed increase in antenatal HIV testing outside of health care facilities through community outreach programmes such as home-based testing [16].

In this literature search 13 studies reporting on antenatal HIV testing coverage among pregnant women in SSA countries, published post 2010, were identified. Of these studies 10 [23–32] were conducted in the period from 2010 onwards while the remaining 3 studies [33–35] included data that was either collected before and after 2010 or during a period that included 2010. All 13 studies were included in this review. The studies were conducted in: Zimbabwe [26,33], Ethiopia [27,29], Nigeria [25,28,30], Congo [25], Mozambique [25], Uganda [25], Ghana [31], Malawi [23,35], Kenya [34] and Tanzania [24,32]. Study types

included: 6 cross-sectional [24,25,27–29,33], 2 quasi-experimental [30,35], 1 prospective cohort [32], 3 retrospective cohort [23,26,34] and 1 retrospective programme-data review [31]. Study sample sizes ranged from 1579 – 2 215 090 pregnant women.

Antenatal HIV testing proportions and HIV prevalence

In this review thirteen studies in 10 different SSA countries reported on antenatal HIV testing proportions which ranged from 46% in Congo [25] to 99.96% in Nigeria [28].

4.1.1 HIV testing in routine care settings

Although The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimated that in 2013 globally only 46% of pregnant women tested for HIV, non-implementation studies (i.e. studies of routine care programmes) across SSA have shown testing proportions ranging from 46% – 85% [23,25,36]. In Zimbabwe a cross-sectional study utilizing data from the 2010/2011 Zimbabwe Demographic and Health Survey (ZDHS) found 60% of pregnant women received antenatal HIV testing, an improvement from the 29% observed in the 2005/2006 ZDHS [33]. More recently Dzangare *et al.* showed, using routine care data, that following the implementation of Option B+ the HIV testing proportion, among women in two rural districts in Zimbabwe who registered or presented in ANC, labour or while breastfeeding, was 81%, with HIV prevalence of 7% in those tested. Unfortunately the proportion of women testing in ANC was not distinguished from those presenting at other timepoints, but 76% of women presented to ANC and the proportion tested amongst the 20% of women presenting in labour was low [26], suggesting ANC testing coverage >81%. In Ghana, a large data review on 2 215 090 ANC attendees countrywide revealed that the HIV testing proportion decreased annually from 83% in 2011 to 75% in 2013, with 487 725 (22%) ANC attendees missing testing opportunities during the 2011 -2013 period. HIV prevalence amongst women receiving ANC ranged between 0.3% - 3% across regions and years, but overall a decline over time was noted [31]. Studies in North-West and North Ethiopia

respectively found 81% and 67% ANC HIV testing proportions among pregnant women in their studies [27,29]. Studies conducted on 2011 - 2013 national survey data reported HIV testing proportions of 76% in Tanzania [24], 82% in Uganda [25], 69% in Mozambique [25], 46% in Congo [25], and 54% in Nigeria [25].

Even though relatively high antenatal HIV testing proportions (>80%) have been observed in several SSA countries since 2010, this remains below the minimal 90% that would be required to ensure that 90% of HIV-positive women have access to ART [7]. Given that antenatal HIV testing is the entry point to the PMTCT programme and that the failure of ANC HIV positivity detection is estimated to account for up to 54% of MTCT in resource-limited settings, it is concerning that testing proportions below 70% were recorded in 5 of the above countries [37]. It should however be noted that the studies in which lowest antenatal testing coverages were observed were based on Demographic and Health Survey (DHS) data from respective countries [25,33]. Study eligibility required women to have been pregnant within 5 years preceding the surveys and the surveys rely on self-report, which could have led to recall/reporting bias, limiting the accuracy of study results. Furthermore, data for these studies were collected between 2010 and 2013 and may therefore not be truly representative of the current coverage of HIV testing in the respective countries [25,33]. On the other hand studies on women attending health care facilities do not account for pregnant women a) attending the private sector and b) who do not attend ANC and/or deliver at home [26,27,29,31]. The HIV testing completion observed in one region of a country is also not necessarily generalizable to the country as a whole. This was demonstrated by the studies in North-West and North Ethiopia by Abtew *et al.* and Alemu *et al.* respectively finding different ANC HIV testing proportions (81% and 67%) [27,29].

Studies conducted after Option B+ implementation showed that although the uptake of antenatal HIV testing was high and there were overall improvements in the PMTCT continuum, challenges with HIV testing remained [23,26,32,35]. In Malawi, Kim *et al.* and Tenthani *et al.* observed antenatal testing proportions of 88% and 86% respectively in different regions post Option B+ implementation [23,35]. HIV prevalence among newly tested women was 7% in the study by Kim *et al.* [35]. Both studies used historical control groups to evaluate the impact of Option B+ on HIV testing proportions. Kim *et al.* observed a significant drop in testing proportions while a small, but non-significant increase was seen

by Tenthani *et al.* [23,35]. It is thought that the unexpected results, i.e. the drop in testing proportions and failure to reach 90% testing completion, seen post the introduction of Option B+ are reflective of challenges at the facility level - in particular a shortage of test kits during the study interval [23,35]. A study in Tanzania found that implementing Option B+ through an integrated service delivery One Stop Clinic resulted in a remarkable 94% HIV testing proportion with 3% of women testing positive. They however reported that 20% of women arrived in labour with an unknown HIV status which is concerning as either they are not attending ANC or there are testing gaps at other facilities [32]. While the above studies are mostly reassuring as they indicate high maternal HIV testing coverage following implementation of Option B+, which suggests promise for the success of B+ in PMTCT [5,16], the large proportion of women presenting in labour with an unknown HIV status means that ANC testing proportions overestimate the true proportion of all pregnant women tested. This introduces the importance of non-traditional setting antenatal HIV testing i.e. testing settings that would not normally form part of conventional routine care e.g. testing outside of healthcare facilities [16].

4.1.2 HIV testing in non-traditional settings

There is evidence that the implementation and/or integration of antenatal HIV testing into non-traditional testing settings provides an opportunity to identify and test pregnant women who don't attend ANC [28,30,32,34]. Akinyele *et al.* investigated the integration of opt-out HIV testing into maternal, newborn, and child health (MNCH) weeks in Nigeria. They found that 99.96% of women attending these weeks accepted testing of whom 31% had not attended ANC. Among those who hadn't attended ANC, 62% had never been tested for HIV. The HIV prevalence among all women being tested was 2%, and among those never previously tested was 5% [28]. Using a quasi-experimental design Chiboza *et al.* evaluated the integration of traditional birth attendants in primary health care (PHC) centers (the "TAP-In" model) in Nigeria. After implementation of TAP-In the intervention group contributed three times the number of pregnant women receiving HIV counselling and testing (HCT) compared to the control group [30]. However, this study did not report proportions of women tested and so comparison of the control and intervention groups is

not possible. In Kenya in a home-based HCT (HBCT) programme, 97% of pregnant women accepted testing of whom 41% had not attended ANC. The overall HIV prevalence among tested women was 7%, but interestingly it was 9% among non-ANC attenders compared to 5% among ANC attenders. A substantial 241(3.3%) women were newly diagnosed as HIV-positive [34]. As mentioned above, Gamell *et al.* reported 94% ANC testing coverage at a One Stop clinic in Tanzania integrating all maternal and pediatric services. In this study 3% of women were newly diagnosed as HIV-positive [32].

The above studies illustrate the potential for closing the access-related gaps in antenatal testing using non-traditional testing settings. Importantly the HIV testing proportions reported were well over 90% and a large proportion of women who hadn't attended ANC were identified which enabled them access to the PMTCT programme. The observation that women who don't attend ANC are more likely to test positive compared to those that do attend ANC highlights the importance of targeting these women through non-traditional interventions to tackle the elimination of MTCT [28,34]. Further investigations need to be conducted to determine the cost effectiveness of these interventions [28].

In summary, the literature indicates that there is a wide range of antenatal HIV testing coverage proportions across SSA, but proportions are mostly below the minimal 90% required to ensure that 90% of HIV-positive women have access to ART [7,24–27,29,31,33]. The uptake of testing post Option B+ implementation was high (>80%) despite facility-level challenges [23,26,32,35]. This is a promising start to the optimization of the effectiveness of Option B+. There are however a large proportion of women who do not attend ANC, some of whom present in labour with unknown HIV status and others that deliver at home [28,31,32,34]. Furthermore, women who don't attend ANC are more likely to be HIV-positive [34,38]. The integration of antenatal HIV testing into non-traditional testing settings/programmes such as MNCH weeks, TAP-In and HBCT has shown to be effective in accessing women who don't attend ANC, thereby increasing antenatal HIV testing among pregnant women [28,30,32,34]. The HIV prevalence among women testing emphasizes the importance of antenatal testing in eliminating MTCT [26,34,35].

4.2 Repeat or late pregnancy HIV testing

There are numerous reasons for the importance of repeat/late pregnancy HIV testing. Women are at an increased risk of seroconverting during pregnancy and those who do seroconvert are more likely to transmit infection [9–11,14]. Moreover, HIV is most commonly diagnosed using a rapid antibody test which fails to accurately diagnose HIV during the so-called "window period" [39]. Given that it can take up to 3 months to produce detectable antibody levels women should have the opportunity to test again later in pregnancy or at delivery [40]. Furthermore, in many resource limited settings pregnant women present to healthcare facilities for the first time during labour with an unknown HIV status [41–43]. Testing during labour enables HIV-positive mothers with previously unknown HIV status and their exposed infants to receive the necessary HIV care to reduce the risk of transmission and prioritize early infant diagnosis [42,44]. Infections only diagnosed late in pregnancy or during labour could also be as a result of incorrect antenatal test results [42]. Considering the importance of repeat/late pregnancy testing, labour room HIV testing was recommended by the Center for Disease Control and Prevention (CDC) in 2004 and was followed by the WHO 2010 recommendation that pregnant women from settings with generalized HIV epidemics receive HIV retesting in either the third trimester, at delivery, or directly thereafter [16,19].

For the 21 SSA countries tasked with the Global Plan of keeping mothers alive and eliminating incident HIV infections among children, reducing MTCT by laying a stable repeat/late pregnancy testing foundation has been essential. In this literature search 7 studies, published from 2010 onwards, that reported on repeat/late pregnancy testing coverage were identified. Of these, only 3 studies were conducted from 2010 onwards [45–47]. Given the limited availability of studies fulfilling the set selection criteria the other 4 studies were included in this review as 3 of them [41,42,48] had been conducted after the CDC recommended HIV testing in labour in 2004 and the remaining one [49], did not report on the study period but was published in 2014. Among these studies, 4 [41,42,45,48] were implementation studies in the sense that repeat/late pregnancy HIV testing was offered as part of the study protocol while the other 3 studies were conducted in settings where repeat testing had already been implemented in routine care [46,47,49]. The studies were

conducted in: Swaziland [42], Nigeria [41,48], Togo [45], Zambia [47,49] and Kenya [46]. Sample sizes in these studies ranged from 104 – 2444 pregnant women.

Repeat or late pregnancy HIV testing proportions and HIV positivity.

Repeat/late pregnancy HIV testing implementation studies around SSA report that high coverage of HIV testing is feasible when offered to women in labour in countries were retesting is not routinely offered [41,45,48]. A cross sectional study conducted in a South-West Nigerian hospital reported that 87% of pregnant women presenting for the first time during labour accepted HIV testing. The HIV prevalence amongst these women was 7%, higher than the national estimated HIV prevalence of 5% around that time [41,50]. In Togo, 92% of pregnant women admitted to hospital during pregnancy were receptive of being HIV tested. Seventy percent of individuals testing in labour had previously tested during ANC and were therefore repeat tested. HIV prevalence among women testing in labour was 9% compared to Togo's estimated national HIV prevalence of 3% at the end of 2009 [45,51]. Onakewhor *et al.* found that in a Southern Nigerian hospital 96% of women who tested HIV-negative at an antenatal visit 12 weeks prior to delivery were tested again during labour with 0.3% of women seroconverting in this period [48].

In contrast to the high acceptance of in-labour HIV testing in the study setting in those countries where repeat testing is not routinely offered, there is evidence that repeat testing coverage is poor in those programmes where repeat testing has already been implemented as part of routine care [47,49]. In Zambia, Hemelaar *et al.* examined repeat HIV testing coverage among women who delivered at a rural district hospital [47]. After delivery 47% of all women had an updated HIV status: 8% were HIV-positive and 39% had tested HIV-negative recently (< 3 months). Out of those with an updated HIV-negative status 63% (25% of all women) had been retested during pregnancy/delivery. Moreover, 53% of women missed opportunities for repeat testing by leaving hospital after delivery with an unclear HIV status either because they were last tested HIV-negative more than three months before delivery or because they never tested during pregnancy and delivery. Among those who were HIV-positive almost half (48%) were newly diagnosed at their initial test in pregnancy

(2 in first trimester, 9 in second trimester, 1 at delivery). No seroconversions were reported [47]. Another Zambian study conducted in a postnatal clinic in Lusaka reported that only 36% of women had been retested antenatally [49]. The low repeat testing coverage may be partly due to the hesitation of health facility staff to counsel and test patients as well as a lack of awareness of the need for repeat testing on the part of pregnant women [42,47,49]. In line with this, a quasi-experimental intervention study conducted in Swaziland found that a targeted one-day training programme for midwife-nurses significantly increased the uptake of repeat testing by women at delivery [42]. At intervention sites 45% of previously tested HIV-negative women and 96% of women with unknown status were tested in comparison to 14% and 65% coverage at control sites. Amongst those testing with unknown HIV status the HIV prevalence was 35% and 45% at the intervention and control sites respectively. The seroconversion rate among those whom enrolled with a HIV-negative status was 4% across all sites [42]. These results emphasize the importance in health workers a) understanding the increased risk of seroconversion during pregnancy and b) having sufficient training to optimally implement the available PMTCT guidelines such as repeat testing.

Four of the above studies were conducted in single hospitals which were referral centers [41,45,47,48]. Many women referred to these labour wards were “unbooked” and presented as emergency cases. Onakewhor *et al.* limited their study to women who had tested negative at “booking”, but both Bello *et al.* and Ekouevi *et al.* had a large proportion of “unbooked” women in their studies [41,45,48]. This is a study limitation as the individuals included are representative of a very specific population of women who have not accessed ANC and the observed results may therefore not be generalizable to the entire population of pregnant women within the respective countries. Another limit to the generalizability of the observed study results is that in the three above mentioned countries the estimated percentage of births attended by skilled personnel, inside and outside health facilities, ranges from 43% – 63% [52], hence HIV testing coverage at delivery for all births may be considerably lower. Although the aforementioned studies [41,42,45,47–49] provide insight to the acceptability and feasibility of repeat or labour HIV testing, very little information is provided on the uptake and adherence of pregnant women to HIV repeat testing in countries where it has already been implemented into the PMTCT guidelines.

The PMTCT care continuum is implemented sequentially throughout pregnancy and may involve multiple service providers, ultimately resulting in the collection of data across facilities and at different steps throughout the continuum [8,53]. This approach accounts for aggregate reporting of PMTCT coverage with no linkage across the different platforms and consequently no tracking of an individual pregnant woman's progress through the care continuum [54]. Reporting on aggregate level data is likely to result in an overestimation of the true coverage (e.g. proportion of women ever HIV tested during pregnancy or proportion of women tested in third trimester) compared to when taking individual level uptake and adherence into account (e.g. proportion of women undergoing all recommended HIV tests). The utilization of longitudinal maternal PMTCT data enables a more accurate estimation of repeat testing coverage [55]. To date only one study has been conducted using longitudinal antenatal data. In 2017 Rogers *et al.* reported a significant increase in HIV retesting among pregnant women in Kenya, from less than 1% in 2011 to almost 45% in 2013, since the implementation of retesting guidelines in 2012 [46]. The study was conducted in a large hospital in rural South-West Kenya and made use of abstracted data from paper ANC registers. Among study participants, the HIV prevalence at delivery was 26%, higher than the already substantial 15% recorded for that area of Kenya [56]. Seven percent of individuals were newly diagnosed HIV-positive with seroconversion from the first to repeat test being 2% among initially HIV-negative women. Despite the improved repeat HIV testing a large proportion (58%) of women had missed opportunities for repeat testing [46].

Overall, the literature suggests that in SSA repeat or late pregnancy HIV testing is feasible and well accepted among pregnant women attending referral hospitals in settings where repeat testing has not yet been adopted by PMTCT guidelines [41,45,48]. Settings that have included repeat HIV testing in guidelines have experienced an increase in provider initiated repeat testing, however major gaps remain [46,47]. Targeted training of healthcare professionals can improve the uptake of repeat testing [42]. It is concerning that in most of these settings there is a large proportion (9% - 34%) of women who present in labour with an unknown HIV status and as a result many individuals are first diagnosed with HIV at delivery [41,42,45]. Furthermore, there are instances where individuals are ineligible for retesting late in pregnancy as their first antenatal visit was less than 3 months before

delivery [47]. These missed opportunities in HIV testing delay essential timely HIV treatment for pregnant women who were unknowingly HIV-positive or who seroconverted, their infants and their partners [26].

4.3 Predictors of HIV testing completeness

Complete HIV testing is the first step to a successful PMTCT programme and ultimately the virtual elimination of MTCT [16,19]. Targeted interventions and their successful implementation are required to close identified gaps in the testing continuum. The identification of predictors of testing completeness will go a long way in directing intervention planning.

4.3.1 Antenatal or early pregnancy HIV testing

A variety of individual as well as health system predictors of receiving an antenatal HIV test have been identified [23–29,33,34,57]. The individual level variables commonly associated with antenatal HIV testing across studies included: age, education, socio-economic status, number of ANC visits, parity, and HIV/MTCT knowledge.

Socio-demographic factors observed to be associated with antenatal HIV testing included higher education [24,25,29,33,34], higher socio-economic status [24,25,33,34], lower parity [26,29,33] and being unmarried [34]. Women of younger age were most commonly reported to be more likely to test antenatally compared to older women [25,28,29,33], although two studies found that that testing likelihood increased with maternal age [23,24].

Other individual-level factors associated with greater likelihood of antenatal HIV testing included: attending more than one ANC visit [23], “booking” at health facilities before labour [26], lack of perception of HIV/AIDS stigmatization [25,27,29,33], knowledge of MTCT and PMTCT [25,29], and receiving ANC counselling on HIV testing [24].

Evidence shows that community and health system related factors also effect the uptake of ANC HIV testing [25,58]. Gunn *et al.* found that women who didn't experience difficulty accessing healthcare facilities were more likely to test antenatally than those that struggled to access facilities. Furthermore they saw that being attended to by a skilled ANC provider was significantly associated with being tested for HIV [25]. Some studies identified urban residence to predict antenatal testing [25,29], however one study found rural residence to be a predictor [27]. This was thought to be context-specific and linked to understanding and education among the rural women [27]. Lack of HIV/AIDS stigmatization at the community-level was also positively associated with ANC HIV testing [33].

4.3.2 Repeat or late pregnancy HIV testing

Multiple individual-level factors have been shown to be associated with repeat or late pregnancy HIV testing [41,44,45,48,49,59,60]. There however appears to be very little coherence between studies with regards to reported predictors. For example, some studies have found that those of younger maternal age were more likely to accept repeat/labour HIV testing [44,59,60] whereas, Onakwhore *et al.* reported that maternal age ≥25 years was significantly associated with repeat testing (OR: 5.0; P<0.02 (no CI provided)) [48]. The study conducted by Onakwhore *et al.* differed from the other three studies in that the study population was specifically women of known HIV-negative status. Furthermore their <25-year age group of women comprised only 10% of study participants and may therefore not have been representative of this age category in the general population.

Another characteristic with conflicting results on association with repeat/late pregnancy HIV testing is education level. Onakwhore *et al.* reported that secondary and post-secondary education were significantly associated with retesting acceptance (OR: 622.4; P<0.001 (no CI provided)) [48]. This result may not be generalizable as only 4% of their study population had an education lower than secondary level. Bello *et al.* on the other hand found that those with a higher level of education were less likely to accept HIV testing in labour (OR: 0.3; CI: 0.1 – 0.7) [41]. These conflicting results may be due to the different study populations and outcomes of interest. Onakwhore *et al.* were studying repeat testing

among known HIV-negative women who had received ANC, whereas Bello *et al.* were studying labour testing among women who presented for delivery without prior ANC. Although not investigated in the study it is likely that presenting "unbooked" may itself be related to having a lower education status. These individuals may then genuinely be more interested in knowing their HIV status compared to the higher educated individuals who are likely to have specific reasons for not wanting to be tested. Also to note, in addition to only studying "unbooked" individuals Bello *et al.* had a relatively small sample of women (104) and may therefore not be representative of the general population of pregnant women in Nigeria [41].

Parity has also been shown to influence acceptance of repeat and labour HIV testing. Women in Nigeria with parity ≥1 were more likely to accept HIV retesting (OR: 17.2; P<0.001 (no CI provided)) [48]. Among pregnant women in Zambia awareness of repeat testing (OR: 3.9; CI: 2.2 – 6.9); attending ≥5 ANC visits (OR: 3.11; CI: 1.8 – 5.3) and "booking" for delivery in the first trimester (OR: 2.4; CI: 1.3 – 4.3) all significantly increased the likelihood of repeat testing [49].

Only a single study reported on the predictors of repeat HIV testing in settings were repeat testing guidelines had been implemented as part of routine care. In Kenya, Rogers *et al.* observed that among women who received ANC early enough and returned to the clinic, deeming them eligible for retesting, the year of pregnancy was significantly associated with retesting relative to 2011 (2012 = OR: 22.2, CI: 3.0 – 163.0; 2013 = OR: 63.4, CI: 8.8 – 456.0). This confirmed that HIV retesting proportions improved subsequent to the guideline updates in 2012. Although not associated with retesting, married women and those of older age were more likely to a) attend ANC at an earlier gestation and b) return for follow-up visits [46]. Targeting those that don't fall within these categories could possibly increase the number of individuals eligible for repeat testing.

In all, the literature has highlighted the various potential predictors of HIV testing completeness, more specifically related to acceptance of retesting, amongst pregnant women in SSA. Unfortunately, due to the limited literature available, factors associated with repeat/late pregnancy HIV testing varied in different contexts with some of them being contradictory and maybe context-specific. Further research is also required to establish the

factors associated with better testing completeness in settings that have implemented repeat HIV testing guidelines.

5 Areas for further research

5.1 Antenatal HIV testing

This review highlights that, despite the acknowledged importance of antenatal HIV testing, a range of different antenatal testing proportions, from as low as 46%, have been observed across SSA. The data collection periods for the studies considered in this review were primarily between 2010 and 2015 and it is therefore unclear how well the results of these studies represent the current proportions of HIV testing amongst SSA countries. Furthermore, the common use of self-report to determine HIV testing proportion means that study results may not reflect true testing proportions due to potential reporting bias. In addition, when assessing ANC HIV testing coverage studies generally didn't consider the large proportion of women that do not attend ANC. Considering that by 2015 Option B+ was offered by all Global Plan countries except for Nigeria, only a handful of studies have reported on antenatal HIV testing rates post Option B+ implementation. Good quality, post Option B+ implementation studies that incorporate routine data from both ANC services and non-traditional testing settings are needed to better understand the current uptake of antenatal HIV testing in SSA as well the predictors thereof. Implementation studies are then required to assess the effectiveness of testing interventions targeted at those with low HIV testing uptake.

5.2 Repeat or late pregnancy HIV testing

This review shows that in general very little research has been conducted on the coverage of repeat or late pregnancy HIV testing within SSA. Many of the studies identified were implementation studies in settings where repeat HIV testing had not yet been introduced

into testing guidelines. Although this provides insight into the acceptability and feasibility of repeat or late pregnancy testing, it provides no information on the uptake and adherence of routine repeat HIV testing within SSA. Furthermore, the majority of studies reviewed were cross-sectional studies conducted in hospitals of which several were referral centers. Women are generally referred to hospitals if their pregnancy is considered to be high risk or requires advanced care. The results of these studies will therefore be very specific to a particular group of women.

The PMTCT care continuum, including repeat HIV testing, is implemented sequentially throughout pregnancy and may involve multiple service providers, ultimately resulting in the collection of data across facilities and at different steps throughout the continuum [8,53]. As a result, the analysis of longitudinal maternal PMTCT data from linked primary, secondary and tertiary care facilities would enable a more accurate estimation of repeat testing coverage. Only a single study that made use of longitudinal antenatal data was identified. In SSA countries that have implemented repeat HIV testing, there is therefore a great need for good quality longitudinal cohort studies that analyze both the completeness of repeat testing and HIV incidence at every step of the testing continuum.

Due to the few studies available on repeat/late pregnancy HIV testing and their lack of comparability due to differing contexts there was little coherence amongst predictors of repeat testing uptake. The identification of these factors in future studies is important in directing targeted intervention studies to improve repeat HIV testing coverage in SSA.

Table 1. Summary of studies including antenatal HIV testing as an outcome of interest.

In-text citation	Author, (year)	Study period	Setting	Design (sample size)	Population	Testing proportion (antenatal)	HIV prevalence among women tested	Predictors of testing
[27]	Abtew, (2015)	2014	North-West **Ethiopia**. 1 hospital, 1 health centre (developing urban).	Cross-sectional (386)	15 – 49-year-old pregnant women attending the health facilities.	81%	Not reported	• Living in rural areas • Berta ethnic group • Merchants, students and employed • Favorable attitude towards PITC • No HIV/AIDs stigmatization
[28]	Akinleye, (2017)	2014	**Nigeria**. 13 Local Government Areas in Benue State (high HIV prevalence).	Cross-sectional (50,271)	Pregnant women residing in Benue State receiving any MNCH service during the week.	100%* (in MNCH week)	2%	• Gestational age (3rd trimester)
[29]	Alemu, (2017)	2012 - 2013	Northern **Ethiopia**. 4 PHC centers. Low income settings.	Cross-sectional (416)	Pregnant women attending their first ANC visit.	67%	Not reported	• Younger age (16 -24 years) • Higher education • From urban areas • Higher monthly expenditure • Nulliparous • Knowledge of MTCT & PMTCT • Favorable attitude towards HIV/ AIDS
[30]	Chizoba, (2017)	2015	Ebonyi **Nigeria**. 20 PHCs in intervention and control groups.	Quasi-experimental (not specified)	Pregnant women attending PHC centers in Ebonyi.	Not reported	Not reported	Not reported
[31]	Dako-Gyeke, (2016)	2011 - 2013	**Ghana** (nationwide).	Retrospective programme data review (2,215,090)	Pregnant women registered at antenatal clinics around the country.	Overall: 78% 2011: 83% 2012: 76% 2013: 75%	≤ 3%† Region and year dependent	Not reported

In-text citation	Author, (year)	Study period	Setting	Design (sample size)	Population	Testing proportion (antenatal)	HIV prevalence among women tested	Predictors of testing
[26]	Dzangare, (2016)	2014	**Zimbabwe**. 34 MCH facilities in rural Chikomba and Gutu districts.	Retrospective cohort (2598)	Women who registered/ presented: in ANC, labour, or MCH while breastfeeding.	81%	7%	• Attending hospitals vs health centers • Low parity • 1st ANC visit ≤ 28 weeks • "booking"
[32]	Gamell, (2017)	2014 – 2015	South-West **Tanzania** (rural). Saint Francis Referral Hospital (SFRH).	Prospective cohort (1579)	Pregnant women attending the Ifakara One Stop Clinic at SFRH.	94%	3%	Not reported
[33]	Gazimbi, (2018)	2005/6 & 2010/11	**Zimbabwe** (nationwide).	Secondary analysis on DHS. Cross-sectional (8471)	Women who had given birth within 5 years preceding the survey.	56% (2010/11)	Not reported	• Year of pregnancy • Age (younger) • Marital status • Higher education • Low Parity • Higher Wealth • Media • Access to health care • Lack of HIV/AIDs stigma • Community awareness • Community stigma
[25]	Gunn, (2016)	Congo, Mozambique & Uganda: 2011 – 2012 Nigeria: 2013	Nationwide: **Congo**, **Mozambique**, **Uganda** & **Nigeria.**	Secondary analysis on DHS. Cross-sectional (not specified)	Women who received ANC during their last pregnancy – within 5 years preceding the survey.	Overall: 61% Uganda: 82% Mozambique: 69% Nigeria: 54% Congo: 46%.	Not reported	Individual level: • Age (younger) • Higher education • Urban residence • Higher wealth index • No HIV stigma • HIV knowledge Health system level: • Facility access • Services from skilled attendant

In-text citation	Author, (year)	Study period	Setting	Design (sample size)	Population	Testing proportion (antenatal)	HIV prevalence among women tested	Predictors of testing
[35]	Kim, (2015)	2009 – 2011; 2011 – 2013	Lilongwe **Malawi**. Urban health centers.	Pre/post B+ quasi-experimental study (13,926 (pre); 14,532 (post))	Pregnant women enrolled in the Tingathe programme antenatally.	Pre-Option B+: 99% During Option B+: 88%	Pre-Option B+: 10% During Option B+: 7%	Not reported
[34]	Ndedge, (2016)	2008 – 2012	Western **Kenya**.	Retrospective cohort study on HBCT (7396)	Women aged 13-50 years.	97% for HBCT (among pregnant women)	Overall: 7% ANC attenders: 5% Non-ANC attenders: 9%	• Having not attended ANC • Higher education • Younger age • Unmarried • Higher income
[24]	Semali, (2014)	2011 - 2012	**Tanzania** (nationwide).	Secondary analysis on THMIS. Cross-sectional (3555)	Women who had given birth 2 years preceding the survey.	76%	Not reported	• Age (35+) • Higher wealth • Higher education • Info on testing during ANC
[23]	Tenthani, (2015)	2010 – 2014	Southern & Central **Malawi**. Sites with EMR ART system in 2011.	Retrospective cohort study (individual-level data: 100,515) (aggregated data: 194,345)	Pregnant women who attended ANC.	Overall: 85% Pre-Option B+: 82% During Option B+: 86%	Not reported	• Being older (20+ years) • Registering in 2010 • >1 antenatal visit

* Actual proportion is 99.96%, but has been rounded up to 100%.

†Denominator is all women receiving ANC.

ANC: antenatal care; MCH: maternal and child health services; PHC: primary health care; PITC: provider-initiated testing and counselling; MTCT: mother-to-child transmission; PMTCT: prevention of mother-to-child transmission; MNCH: maternal, newborn and child health; DHS: demographic health survey; HBCT: home-based counselling and testing; THMIS: Tanzania HIV/AIDS and Malaria Indicator Survey; EMR: electronic medical records

Table 2. Summary of studies including repeat/late pregnancy HIV testing as an outcome of interest.

In-text citation	Author, (year)	Study period	Setting	Design (sample size)	Population	Testing proportion (antenatal/repeat)	HIV prevalence & incidence among women tested	Predictors of testing
[41]	Bello, (2011)	2005 – 2006	South-West **Nigeria**. Labour ward, University College Hospital.	Cross-sectional study (104)	Unregistered pregnant women presenting for delivery.	At labour: 87% of unregistered individuals.	Prevalence at labour: 7%	• Being less educated
[45]	Ekouevi, (2012)	2010	**Togo**. Teaching hospital, obstetrics unit.	Cross-sectional study (508)	Pregnant women admitted to the hospital for delivery.	Antenatal: 71% At labour: 92% of which 70% were retests.	Prevalence at labour: 9%	• Not reported
[47]	Heemelaar, (2015)	2012	**Zambia.** SFH, a rural district hospital in Katete.	Prospective, implementation cross-sectional study (322)	Women delivering at the SFH.	Antenatal: 94% Repeat (antenatally/delivery): 25%	Prevalence at labour: 8%†	• Not reported
[42]	Kieffer, (2011)	2008 - 2009	**Swaziland**. 4 hospitals (2 urban, 2 rural), 2 rural health centers.	Quasi-experimental study (2444)	Pregnant women presenting for delivery.	Antenatal: 91% Repeat (delivery): Intervention site: 45% Control site: 14% At labour (1st test): Intervention site: 96% Control site: 65%	Prevalence among women "unbooked" at delivery: Intervention site: 35% Control site: 45% Incidence: 4%	• Not reported
[49]	Mtaja, (2014)	Not reported	**Zambia.** Postnatal clinic at Chilenje Health Centre in Lusaka.	Cross-sectional study (404)	Postnatal mothers attending their 6th week visit.	Antenatal: 100% Repeat (antenatally): 36%	Not reported	• Booking in 1st trimester • 5 or more ANC visits • Awareness of repeat testing
[48]	Onakewhor, (2013)	2009	**Nigeria.** Hospital obstetrics unit.	Prospective cohort study (415)	Antenatal women testing negative at "booking" (≥ 12 weeks before labour).	At labour: 96%	Incidence at labour: 0.25%	• Maternal age ≥25 years • Secondary & post-secondary education • Parity ≥1

In-text citation	Author, (year)	Study period	Setting	Design (sample size)	Population	Testing proportion (antenatal/repeat)	HIV prevalence & incidence among women tested	Predictors of testing
[46]	Rogers, (2017)	2011 - 2014	**Kenya.** Government hospital, rural southwestern area with highest HIV prevalence.	Longitudinal cohort study (2145; 1375 eligible for retest)	Women attending the hospital antenatal clinic from 2011 to 2014.	First ANC visit: 78% 1st test + 12 weeks: 27% of those eligible	Prevalence at labour: 26%† Incidence: 2%	• Marital status. • Year of pregnancy.

†Denominator is all study participants.
ANC: antenatal care; SFH: Saint Francis Hospital

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PART C: JOURNAL MANUSCRIPT

A longitudinal analysis of the completeness of maternal HIV testing, including repeat testing in Cape Town, South Africa

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Note: This manuscript meets the requirements set out in the instructions to authors of the *Journal of the International AIDS Society* (Appendix 5). In keeping with the mini-dissertation guidelines, co-authors and their affiliations have been listed in the acknowledgments section.

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1. Abstract

Introduction: The virtual elimination of mother-to-child transmission (MTCT) of HIV cannot be achieved without complete maternal HIV testing. In 2014, the Western Cape Province (South Africa) prevention of mother-to-child transmission (PMTCT) guidelines recommended a repeat maternal HIV test between 32 - 34 weeks gestation and at delivery in addition to testing at "booking", the first antenatal visit (<20 weeks gestation). There is limited literature on the uptake of and adherence to maternal HIV testing programmes in sub-Saharan Africa.

Methods: Between 2013 and 2016 we established an electronic PMTCT register (e-register) that consolidated routine data from a primary healthcare facility and its secondary and tertiary referral sites in Cape Town, South Africa. This provided a single longitudinal record, from antenatal care to delivery, for each pregnant woman. Utilizing these data, we conducted a retrospective sub-analysis investigating the completeness (until delivery) of maternal HIV testing according to the PMTCT maternal HIV testing guidelines in Cape Town, and predictors of complete testing, from 1 July 2014 – 31 December 2016.

Results: Among 8558 enrolled women, 7213 were not diagnosed HIV-positive prior to their first visit and thus eligible for HIV testing in pregnancy. Among these women, 91% received ≥1 HIV test. Among 85% who "booked" (i.e. presented for antenatal care) >5 days before delivery, testing completeness at "booking" was 98%. Among women eligible to receive tests at all 3 recommended timepoints, only 10% were HIV tested according to the guidelines. Delivery HIV testing completion among all women not yet diagnosed HIV-positive was 23%. HIV prevalence at delivery was 21% and HIV incidence between "booking" and delivery in those with ≥2 HIV tests was 0.2%. Women who enrolled after 2014 were less likely to miss ≥1 of the three recommended tests (aOR: 0.70; CI: 0.55 – 0.90) and not test at delivery (aOR: 0.63; CI: 0.55 – 0.71) compared to those that enrolled in 2014.

Conclusion: Maternal HIV testing within the PMTCT programme in Cape Town has matured post 2014 with improved implementation over time; however, there are still major implementation gaps, particularly at delivery.

2. Introduction

The implementation of policies recommending immediate lifelong triple antiretroviral therapy (ART) initiation for all HIV-positive pregnant women (Option B+) has been shown to be effective in reducing mother-to-child transmission (MTCT) of HIV worldwide [1,2]. Women's access to these and other HIV-related services in the prevention of MTCT (PMTCT) continuum relies on complete universal antenatal care (ANC) HIV testing, which is essential for the virtual elimination of MTCT of HIV [3,4]. It is estimated that failure to detect maternal HIV infection during ANC is responsible for up to 54% of MTCT in resource-limited settings [5].

The World Health Organization (WHO) recommends that provider-initiated HIV testing and counselling, forming part of ANC services, be offered to pregnant women at their first ANC visit recommended at ≤ 12 weeks gestation [6,7]. Not only will this enable the timely diagnoses of undiagnosed pregnant women living with HIV, it will also provide HIV-negative women with guidance counselling and services to assist with the prevention of HIV acquisition and the opportunity to retest later during the pregnancy [8]. In 2010, WHO recommended that women in areas with generalized HIV epidemics are repeat tested for HIV in either the third trimester, at delivery, or directly thereafter [9]. In 2014, in the Western Cape (WC) Province, South Africa (SA), the *Western Cape Prevention of Mother-to-Child Transmission of HIV (PMTCT) Clinical Guidelines* recommended a repeat test between 32 - 34 weeks gestation and again at delivery, subsequent to testing at first ANC visit (referred to as the "booking" visit) recommended at < 20 weeks gestation [10]. Retesting is important as women are more likely to acquire HIV infection during pregnancy, and, if acutely infected, MTCT risk is increased [11–15]. In addition, the rapid antibody tests may not accurately diagnose HIV during the window period (up to 3 months post acquisition) [13]. In settings such as SA where >80% of deliveries occur in facilities [16], HIV testing at delivery provides a particular opportunity to test women with an unknown HIV status who do not attend ANC – referred to as "unbooked" [17,18].

Across sub-Saharan Africa (SSA) antenatal HIV testing proportions range from 46% - 99%, but are mostly below the minimum 90% required to enable 90% of HIV-positive pregnant

women access to ART [4,19–22]. However, most of these studies were conducted before 2015 with very few reporting on post Option B+ policy implementation testing completion. Furthermore, these studies often use self-report to determine HIV testing completion which could skew results due to reporting bias. In order to better understand the current (i.e. post-Option B+) implementation and uptake of antenatal HIV testing in SSA studies utilizing recent routine data from ANC services is required. Additionally, since repeat HIV testing is implemented sequentially throughout pregnancy, potentially involving multiple service providers, longitudinal maternal data is needed to accurately estimate repeat testing coverage. However very few studies have collected such data and thus reports on coverage of repeat/delivery HIV testing in SSA are lacking [23].

Utilizing prospectively collected, individual-level, longitudinal patient data from a primary health care facility and its referral sites (secondary and tertiary) we aimed to investigate the implementation of and adherence to "booking" and repeat maternal HIV testing PMTCT guidelines (up until delivery) in Cape Town, SA. We assessed the coverage and timing of initial HIV testing during pregnancy, repeat HIV testing in the recommended testing windows (including delivery), HIV prevalence and incidence among those tested, and the predictors of missed testing opportunities.

3. Methods

3.1 Study design

This study was a retrospective sub-analysis carried out on antenatal maternal HIV testing data that were prospectively collected for the Closing the Gaps (CTG) study which has been described previously [24]. Briefly, the CTG study established an integrated electronic PMTCT register (e-register) that consolidated routine data from a primary care antenatal and delivery facility, Mitchells Plain Midwife Obstetric Unit (MPMOU), and its referral sites: Mitchell's Plain District Hospital (MPDH), Mowbray Maternity Hospital (MMH) and Groote Schuur Hospital (GSH), within the urban Klipfontein sub-district of the WC, SA.

3.2 Study setting

At the time of the study MPMOU, a primary care facility that served approximately 1.2 million people, provided ANC and midwife-administered uncomplicated vaginal delivery services [25]. The 2015 WC antenatal HIV prevalence was reported to be 19% [26].

High risk pregnancies or those requiring advanced care were referred from MPMOU to a secondary or tertiary care facility during the antenatal or peri-partum period. MPDH and MMH (secondary level) are equipped with operating theatres and neonatal intensive care unit (ICU) facilities respectively while GSH (tertiary level) has both adult and neonatal ICU facilities.

3.3 Study participants

In the CTG study pregnant women, irrespective of HIV status, were automatically enrolled at their first ANC visit ("booking") at MPMOU, or alternatively upon presentation for delivery if they had not received ANC. Point-of-care rapid HIV tests (i.e. antibody assays for HIV-1 and HIV-2), were performed by community care workers as part of routine ANC services and by nurses in the labour ward of MPMOU and the labour/post-natal ward of the hospitals. The HIV status of women who presented as "known" HIV-positive at their first visit was confirmed from clinical records or HIV retesting if they were not on ART.

In July 2014 the WC PMTCT guidelines were updated with respect to repeat HIV testing [10]. We therefore included women enrolling in the CTG study from 1 July 2014 onwards i.e. who were included in this policy period. We included data from the CTG e-register for all women who delivered at MPMOU or one of its referral sites between 1 July 2014 – 31 December 2016 with a live or still birth pregnancy outcome. We excluded data from women who a) presented for delivery having "booked" at a community basic antenatal clinic (banc) since we did not have access to complete longitudinal HIV testing data for these individuals or b) for whom no pregnancy outcome could be found as we could not exclude pregnancy loss in which case PMTCT testing guidelines would no longer be applicable. Furthermore, in the absence of a documented pregnancy outcome and visit data it is unknown whether

participants transferred out to other facilities and at what point during pregnancy they would have done so. Retaining these individuals in the dataset could potentially have biased study results to underestimate repeat testing completion.

3.4 Procedures and measurements

A single longitudinal record, including HIV testing history from first antenatal visit (if attended) through to delivery, for each mother was extracted from the CTG e-register. We categorized women as having "booked" for delivery if they presented to a health facility >5 days before delivery. We considered women to have tested: at "booking" if they presented before delivery and tested at their first visit; within the first time period (20 weeks gestation) if an HIV test occurred before 22 weeks gestation; during the third trimester if they had an HIV test between 28 weeks gestation and 5 days before delivery; and at delivery if they had an HIV test within ±5 days of delivery. We deemed women eligible for an initial test if on their first visit, whether antenatally or at delivery, they did not have a known HIV-positive status; and eligible for retesting if they had not had a prior positive antenatal HIV test. Tests were considered to be retests if women underwent an HIV test within a recommended time period following a prior HIV-negative test.

We calculated testing completion at "booking" among all women who "booked" before delivery (Figure 1). Testing completion during each recommended window was calculated only among women eligible to be tested in that window as follows: first window – "booked" with an unknown/negative HIV status before 22 weeks gestation; third trimester - "booked" before/during the third trimester, not previously diagnosed HIV-positive and not delivered before 28 weeks plus 5 days gestation; delivery - all eligible irrespective of gestational age at delivery, "booking" status or testing history, if not previously diagnosed HIV-positive. We reported testing outcomes as proportions as the study was based on routine data and we did not have outcome time for all women.

We coded women as having "missed testing opportunities" if they a) did not test at all or b) failed to test during ≥1 of the recommended time periods. Individuals diagnosed HIV-positive during the study period were coded as "diagnosed at enrolment" if they tested HIV-

positive at their initial "booking" test, or alternatively as "seroconverts" if they tested HIV-positive after a previous negative antenatal HIV test. We coded women as having an "uncertain HIV status at delivery" if they tested at least once during ANC but did not test within 3 months before delivery or at delivery, and having an "unknown HIV status at delivery" if they never tested during the current pregnancy.

For women with two pregnancies within the study period, we included the pregnancy for which most data were available. Women who delivered <37 weeks gestation were coded as having a premature delivery.

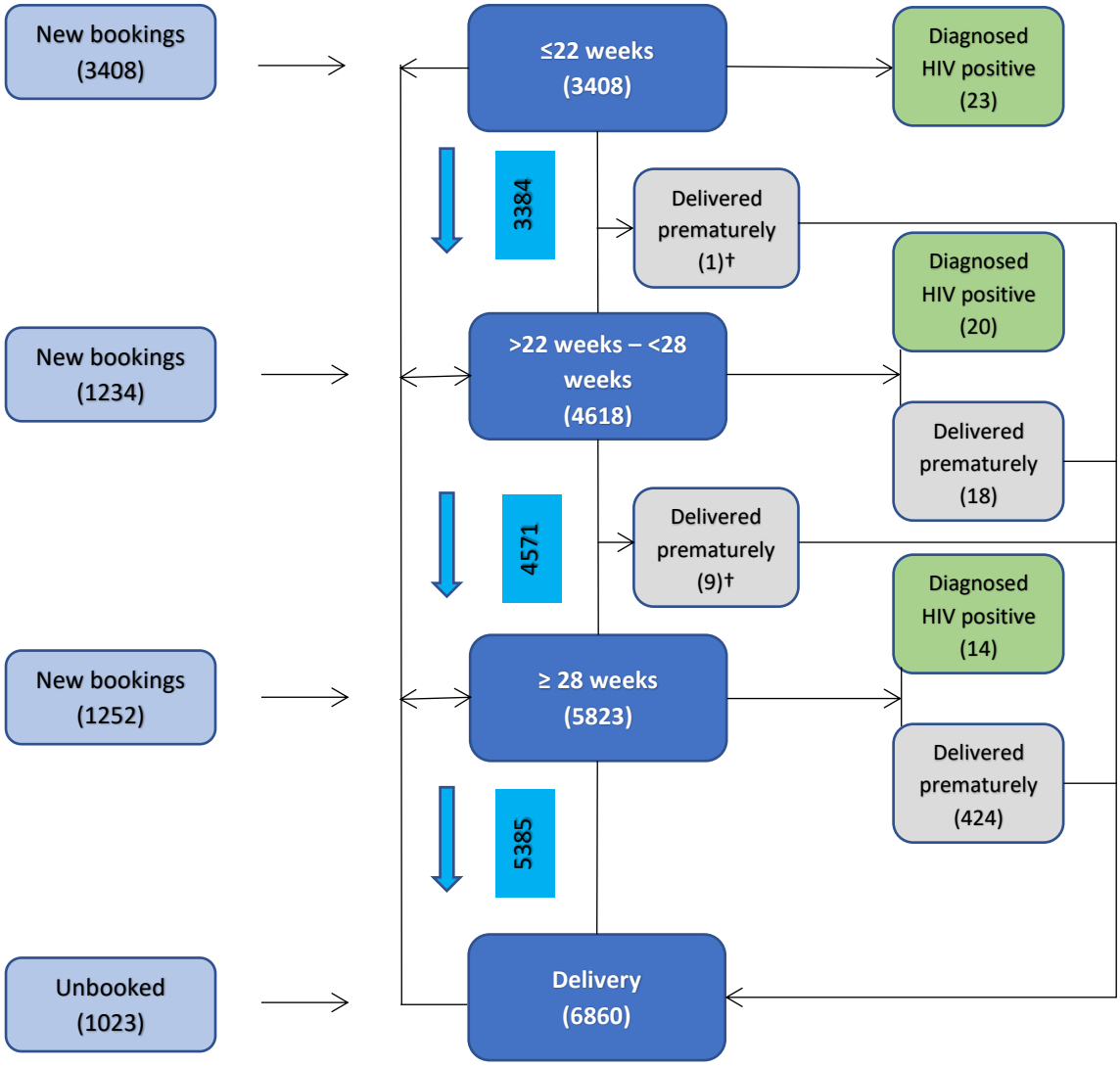

Figure 1. Flow chart illustrating the number of women eligible to be HIV tested within each testing window. Only women for whom gestational age was available were included (n=6860).

†Women that delivered within the first five days of the subsequent period and therefore would not be eligible for testing in that period

3.5 Data analysis

Data analysis was carried-out using Stata version 13.0 (Stata Corporation, College Station, Texas, USA). We summarized normally and non-normally distributed continuous variables using means and confidence intervals (CI) or medians and interquartile-ranges (IQR) respectively. Categorical variables were described and compared using proportions and frequency tables or graphical displays. Differences were assessed using the two-sample t-test (normal distribution) or the Wilcoxon rank-sum test (non-normal distribution) for numerical data and the $\chi 2$ or Fishers Exact test for categorical data. We used logistic regression to assess predictors of not testing: at all, at "booking", at delivery and not receiving the 3 recommended tests. Multivariable models included several variables (age at enrolment, gravidity, & year of enrolment) *a priori* as being possible risk factors for the outcome of interest. Other variables were included in the models by sequentially adding them based on univariable analysis significance. Those that were either significantly associated with the outcome of interest after adjustment for other variables ($p<0.05$) or that altered the odds ratios (ORs) for other variables in the model by ≥10% were retained.

3.6 Missing data

Data were missing for gestational age, gravidity, delivery facility and premature delivery variables. We retained individuals in the dataset for whom data were missing. When assessing testing completion we only included individuals for whom gestational age data were available. Individuals with missing data were excluded for logistic regression using listwise deletion.

3.7 Ethics

The University of Cape Town Human Research Ethics Committee and the Provincial Government of the Western Cape Department of Health Research approved the study.

The CTG study was granted a waiver of informed consent for the e-register as all data had already been collected routinely by health services. No participant recruitment was required and data was deidentified prior to analysis.

4. Results

4.1 Participant characteristics

Between July 2014 and December 2016, 8558 women delivered at MPMOU or one of its referral sites with a live or still birth pregnancy outcome (Table 1). Within the study period, 153 women had two pregnancies of which only one pregnancy was analysed.

HIV-negative/uncertain vs. HIV-positive women were more likely to attend ANC (%: 93 vs. 81; p<0.001) and presented earlier for their first ANC visit (median [IQR] gestation: 21 [15-29] vs. 24 [18-35] weeks; p<0.001) (Table 1). At delivery, HIV status was confirmed in 75% of the cohort of whom 21% were positive. Among HIV-positive women, 95% were known positive (confirmed from clinical records or retested if not on ART) at first ANC visit, 4% were newly diagnosed at their first test in the current pregnancy and 0.7% seroconverted during pregnancy after initially testing HIV-negative. Of the women who tested HIV-negative antenatally, 22% had an uncertain HIV status at delivery (not tested within 3 months of delivery/at delivery). Among all women, 8% did not test during pregnancy/delivery at all. In total, 31% of all women who had not been diagnosed HIV-positive before delivery had an unconfirmed HIV status (i.e. either uncertain or not tested at all during ANC) after delivery.

Table 1. Characteristics of 8558 participants stratified by HIV status post-delivery. Characteristics at first visit (baseline) and delivery are reported.†

Variable	HIV-negative/ uncertain‡ n = 6557 (77%)	HIV-positive n = 1345 (16%)	P-value §	Never tested n = 656 (8%)
Baseline characteristics				
Age (years): n (%)				
13 - <16	76 (1)	3 (0.2)		6 (1)
16 - <21	1074 (16)	75 (6)		111 (17)
21 - <31	3789 (58)	771 (57)	<0.001	415 (63)
31 - <41	1506 (23)	481 (36)		116 (18)
41 - <47	103 (2)	15 (1)		8 (1)
Median (IQR)	26 (22-31)	29 (25-33)	<0.001	26 (22-30)
Gravidity: n (%)				
1	2019 (31)	236 (17)		171 (26)
2	1922 (29)	475 (35)		188 (29)
3	1312 (20)	373 (28)	<0.001	121 (18)
≥4	1197 (18)	226 (17)		167 (26)
Missing	107 (2)	35 (3)		9 (1)
Enrolment year: n (%)				
2014	2365 (36)	497 (37)	0.54	313 (48)
2015/2016	4192 (64)	848 (63)		343 (52)
Antenatal care: n (%)				
Yes	6080 (93)	1096 (81)	<0.001	63 (10)
No	477 (7)	249 (19)		593 (90)
Gestational age at first visit (weeks): n (%)				
≤12	926 (14)	97 (7)		4 (0.6)
>12 - 20	1930 (29)	331 (25)		16 (2)
>20 - 28	1748 (27)	362 (27)	<0.001	17 (3)
>28 - 36	992 (15)	202 (15)		43 (7)
≥37	628 (10)	281 (21)		546 (83)
Missing	333 (5)	72 (5)		30 (5)
Median (IQR)	21 (15-29)	24 (18-35)	<0.001	40 (40–40)
Delivery characteristics				
Delivery facility: n (%)				
MPMOU	2648 (40)	551 (41)		422 (64)
MPDH	2264 (35)	485 (36)		160 (24)
MMH	1164 (18)	231 (17)	0.09	63 (10)
GSH	460 (7)	78 (6)		11 (2)
Missing	21 (0.3)	0 (0)		0 (0)
Premature deliveries: n (%)				
Yes	607 (9)	110 (8)		48 (7)
No	5617 (86)	1166 (87)	0.46	7361 (88)
Missing	333 (5)	69 (5)		30 (5)
Birth outcome: n (%)				
Alive	6468 (99)	1320 (98)	0.17	643 (98)
Stillborn	89 (1)	25 (2)		13 (2)
HIV status at delivery: n (%)				
Known HIV-positive before enrolment	-	1277 (95)		-
Diagnosed HIV-positive at first visit	-	59 (4)		-
Seroconverts	-	9 (0.7)	-	-
HIV-negative	5092 (78)	-		-
Previously HIV-negative‡	1465 (22)	-		-
Not tested	-	-		656 (100)

†Values are rounded to the nearest whole number and proportions do not always add up to 100%/variable.

‡ Individuals that were last tested during antenatal care ≥ 3 months before delivery and therefore have an uncertain HIV status at delivery.

§ P-values are reporting the significance of the difference between HIV-negative/uncertain & HIV-positive.

n: number of participants; IQR: Interquartile range; MPMOU: Mitchells Plain Midwife Obstetric Unit; MMH: Mowbray Maternity Hospital; MPDH: Mitchells Plain District Hospital; GSH: Groote Schuur Hospital

4.2 HIV testing characteristics

Of all women eligible for testing (n=7281), i.e. not been diagnosed HIV-positive before the current pregnancy, 91% received ≥1 HIV test.

Among 7222 women eligible for >1 HIV test i.e. having not been diagnosed HIV-positive at booking, 44% had 2 tests throughout pregnancy (including delivery) and 9% had ≥3 tests (Figure 2). When stratifying the number of HIV tests received by "booking" status, among 1070 "unbooked" women, 55% did not test at all compared to 1% of 6152 "booked" women (p<0.001). Fifty-four percent of HIV-negative/uncertain women had their first HIV test by 22 weeks compared to 40% of newly diagnosed HIV-positive individuals (p=0.02) (Table 2).

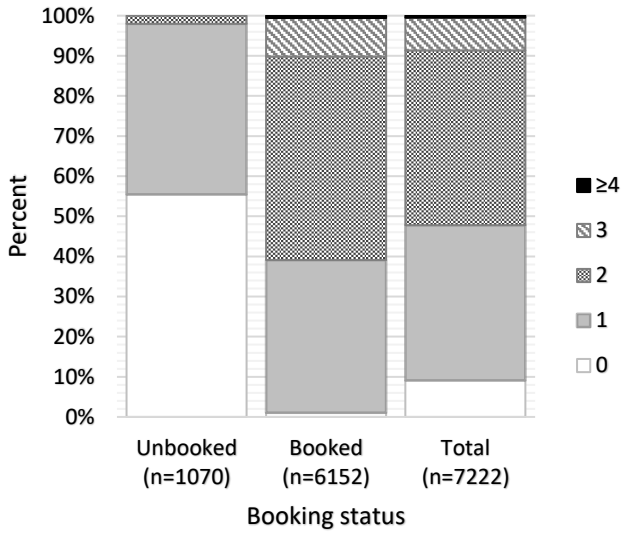

Figure 2. Number of HIV tests received, stratified by "booking" status, among those that were not known HIV-positive or diagnosed HIV-positive at their first test (n=7222).

Table 2. Gestational age at first HIV test, stratified by HIV status at delivery, for participants that were HIV-negative/unknown at enrolment (n =6291†).

Gestational age at first test (weeks): n (%)	HIV-negative/uncertain n = 6224	HIV-positive n = 67	p-value	Total
≤12	917 (15)	4 (6)		921 (15)
>12 - 22	2414 (39)	23 (34)		2437 (39)
>22 - 28	1235 (20)	22 (33)	0.05	1257 (20)
>28 - 36	1002 (16)	10 (15)		1012 (16)
≥37	656 (11)	8 (12)		664 (11)
Median (IQR)	21 (15-29)	23 (16-29)	0.09	21 (15–29)

†Only individuals that tested ≥1 and for whom gestational age was available were included.

4.3 HIV testing completeness by gestational age and HIV incidence

Among all women HIV-negative/unknown at first visit and for whom gestational age data were available (n=6917), 85% “booked” at MPMOU >5 days before delivery with 98% HIV testing completeness at “booking” (Table 3). Among 49% of HIV-negative/unknown women who “booked” at ≤22 weeks gestation, 0.7% (23/3358) were newly diagnosed HIV-positive. Among the 4504 (77%) of women who had previously tested HIV-negative during their current pregnancy, 60% were retested during the 3rd trimester of whom 0.2% (6/2972) seroconverted.

Among “unbooked” women (i.e. did not attend any ANC) (n= 1023), only 45% were tested for HIV at delivery, of whom 1.5% (7/479) were newly diagnosed HIV-positive. Out of those women who had tested earlier in pregnancy, 19% re-tested at delivery, of whom 3 women (0.3%) had seroconverted. The highest delivery HIV testing completion was at the two secondary level facilities (MPDH: 32% and MMH: 21%) (Figure S2). Among women who “booked” in the first window, had gestational age at delivery >28 weeks and 5 days, and were not diagnosed HIV-positive before delivery (hence eligible to have all three recommended tests) (n =3356), 10% received HIV tests in all three windows (Table 4). Out of the 5% of women who were diagnosed HIV-positive during pregnancy/delivery, 64% were diagnosed at their first test before the third trimester while 9% were seroconversions within the third trimester (Figure S3). Amongst the 61% (Figure 2) of “booked” women who had >1 HIV test, 0.2% seroconverted.

Table 3. HIV testing during pregnancy for women for whom gestational age data were available (n=6917).

	Total women†	All women eligible for testing‡		Women untested in current pregnancy					Women previously tested in current pregnancy		
				New visits/bookings		Previously booked					
Testing point/window	**n**	**n (%)**	**% tested**	**n (%)**	**% tested**	**n (%)**	**% tested**	**% positive at first testΔ**	**n (%)**	**% tested**	**% positive at repeat test¥**
Booking§	6917	5894 (85)	98	5894 (100)	98	-	-	0.9	-	-	-
≤22 weeks	6917	3408 (49)	99	3408 (100)	99	-	-	0.7	-	-	-
>22 - < 28 weeks¶	6893	4618 (67)	28	1234 (27)	99	50 (1)	2	1.6	3334 (72)	2	0
28 weeks – <delivery	6828	5823 (85)	68	1252 (22)	97	67 (1)	33	0.7	4504 (77)	60	0.2
Delivery	6860	6860 (100)	23	1023 (15)	45	82 (1)	28	1.5	5755 (84)	19	0.3

n: number of participants

†Total women at each testing window excludes those that were diagnosed HIV-positive during the previous window as well as those that delivered prematurely in the previous window or in the first 5 days of the current window. Women eligible at delivery and booking are regardless of time point.

‡ Eligibility is based on booking status. Women are eligible to test if they booked within the current or previous testing window. At delivery women are eligible regardless of booking status.

§ Booking is reported as a separate testing "window" in addition to testing completeness from longitudinal analysis. Unbooked women excluded.

¶ The >22 - <28 weeks testing window, although not a recommended testing window, was included in this analysis to incorporate individuals who may have tested outside the first recommended window but would still be eligible for retesting in the later windows.

Δ % positivity was calculated as a proportion of those that tested for the first time within that window.

¥ % positivity was calculated as a proportion of those that were receiving a repeat test in that window. The denominator included individuals who booked and had >1 test within the window.

Table 4. Longitudinal HIV testing completion proportions among women with known gestational age who were eligible to receive all three recommended tests.

Testing window	Women eligible: n†	Women tested: n (%)
≤22 weeks	3408	3358 (99)
28 weeks – <delivery	3310	2062 (62)
Delivery	2059	347 (17)
All 3 tests‡	3356	347 (10)

†Eligibility is based on women having strictly tested in previous recommended windows. At the first time point only those who had booked and for whom gestational age data were available were eligible. This number also excludes those that delivered or were diagnosed prior to a specific window. Only those that delivered after the start of the third trimester were considered to be eligible at delivery.

‡All 3 tests includes women that booked in the first window, weren't diagnosed HIV-positive before delivery and delivered >5 days after the start of the third trimester.

4.4 Predictors of maternal HIV testing missed opportunities

Amongst all eligible women, 9% had no HIV tests during pregnancy/delivery (Figure 2). In multivariable analysis late gestational age at "booking" (aOR: 1.10; CI: 1.07 – 1.13, per additional week gestation) and delivering at MPDH (aOR: 1.50; CI: 1.11 – 2.04); or MMH (aOR: 1.98; CI: 1.32 – 2.98); vs. MPMOU were associated with having no HIV test at all (Table 5). "Booking" (aOR: 0.02; CI: 0.01 – 0.04) vs. never "booking" and enrollment in 2015/2016 (aOR: 0.38; CI: 0.30 – 0.49) vs. 2014 were associated with being less likely to miss all testing opportunities.

Among eligible women, 10% received all three of the recommended HIV tests (Table 4). The following factors were associated with being less likely to miss ≥1 of the 3 recommended tests: full-term pregnancy (aOR: 0.60; CI: 0.37 – 0.95) vs. premature delivery; enrollment in 2015/2016 (aOR: 0.70; CI: 0.55 – 0.90) vs. 2014; and delivering at MPDH (aOR: 0.09; CI: 0.06 – 0.14); or MMH (aOR: 0.20; CI: 0.12 – 0.32); vs. MPMOU (Table 5).

Among women eligible for HIV testing at delivery (i.e. all women of negative/unknown HIV status), 23% tested (Table 3). In multivariable analysis "booking" (aOR: 3.96; CI: 2.90 – 5.49) vs. never "booking" was associated with not testing at delivery (Table 5). The following factors were associated with being less likely to miss the delivery test: enrollment in 2015/2016 (aOR: 0.63; CI: 0.55 – 0.71) vs. 2014; having received no ANC testing (aOR: 0.72; CI: 0.55 – 0.94), or having only tested ≤22 weeks (aOR: 0.73; CI: 0.61 – 0.88) vs. having tested in recommended windows one and two; and and delivering at MPDH (aOR: 0.25; CI: 0.21 – 0.29); or MMH (aOR: 0.48; CI: 0.39 – 0.58); vs. MPMOU. Among "unbooked" women, those that enrolled in 2015/2016 vs. 2014 were less likely to miss the delivery HIV testing opportunity (aOR: 0.40; CI: 0.30 – 0.53) (Table S1).

Table 5. Univariable and multivariable factors associated with failure to A. test both antenatally and at delivery, B. receive the three recommended tests, C. test at booking and D. test at delivery.

	A. No maternal HIV testing n = 6886		B. Not receiving three recommended tests† n = 3344		C. Not testing at booking n = 5867		D. No testing at delivery n = 6790	
Variable	**OR (95% CI)**	**aOR (95% CI)**	**OR (95% CI)**	**aOR (95% CI)**	**OR (95% CI)**	**aOR (95% CI)**	**OR (95% CI)**	**aOR (95% CI)**
Age at first visit (years)	0.98 (0.97; 0.99)	0.98 (0.96; 1.01)	1.01 (0.99; 1.03)	1.00 (0.97; 1.02)	1.00 (0.97; 1.03)	0.99 (0.96; 1.03)	1.00 (0.99; 1.01)	1.00 (0.99; 1.02)
Booked: No	**Ref**	**Ref**	*	*	*	*	**Ref**	**Ref**
Yes	0.01 (0.006; 0.01)	0.02 (0.01; 0.04)	*	*	*	*	3.46 (3.01; 3.97)	3.96 (2.90; 5.49)
Gestational age at first visit (weeks)	1.35 (1.32; 1.39)	1.10 (1.07; 1.13)	*	*	1.05 (1.03; 1.07)	1.04 (1.02; 1.07)	0.97 (0.96; 0.97)	0.99 (0.98; 1.01)
Gravidity: 1	**Ref**	**Ref**	**Ref**	**Ref**	**Ref**	**Ref**	**Ref**	**Ref**
2	1.15 (0.93; 1.43)	0.97 (0.69; 1.38)	1.32 (1.01; 1.73)	1.17 (0.87; 1.58)	1.12 (0.71; 1.77)	1.14 (0.70; 1.86)	1.20 (1.03; 1.39)	1.12 (0.94; 1.32)
3	1.09 (0.85; 1.38)	0.73 (0.49; 1.10)	1.40 (1.02; 1.94)	1.18 (0.81; 1.72)	0.78 (0.44; 1.38)	0.80 (0.42; 1.53)	1.09 (0.92; 1.28)	0.97 (0.79; 1.19)
≥4	1.65 (1.32; 2.07)	0.65 (0.42; 1.02)	1.30 (0.92; 1.84)	1.13 (0.73; 1.76)	1.60 (0.98; 2.60)	1.56 (0.81; 3.01)	0.77 (0.66; 0.90)	0.77 (0.61; 0.96)
Premature delivery: Yes	**Ref**	*	**Ref**	**Ref**	*	*	**Ref**	*
No	1.29 (0.95; 1.76)	*	0.61 (0.39; 0.94)	0.60 (0.37; 0.95)	*	*	1.18 (0.98; 1.43)	*
Mode of delivery: Vaginal	**Ref**	*	**Ref**	**Ref**	*	*	**Ref**	*
Assisted	0.48 (0.12; 2.00)	*	0.40 (0.13; 1.20)	*	*	*	0.64 (0.31; 1.35)	*
BBA	3.88 (2.72; 5.52)	*	*	*	*	*	0.34 (0.24; 0.47)	*
Caesarean section	0.43 (0.34; 0.55)	*	0.52 (0.41; 0.65)	*	*	*	0.79 (0.70; 0.90)	*
Outcome: Alive	**Ref**	*	**Ref**	*	*	*	**Ref**	*
Still Born	1.47 (0.82; 2.64)	*	2.08 (0.28; 15.65)	*	*	*	0.58 (0.36; 0.96)	*
Year of enrolment: 2014	**Ref**	**Ref**	**Ref**	**Ref**	**Ref**	**Ref**	**Ref**	**Ref**
2015/2016	0.63 (0.54; 0.74)	0.38 (0.30; 0.49)	0.76 (0.60; 0.96)	0.70 (0.55; 0.90)	0.48 (0.34; 0.69)	0.51 (0.35; 0.72)	0.70 (0.62; 0.79)	0.63 (0.55; 0.71)
Delivery facility: MPMOU	**Ref**	**Ref**	**Ref**	**Ref**	*	*	**Ref**	**Ref**
MPDH	0.44 (0.37; 0.54)	1.50 (1.11; 2.04)	0.10 (0.06; 0.14)	0.09 (0.06; 0.14)	*	*	0.41 (0.36; 0.47)	0.25 (0.21; 0.29)
MMH	0.34 (0.26; 0.44)	1.98 (1.32; 2.98)	0.23 (0.14; 0.37)	0.20 (0.12; 0.32)	*	*	0.74 (0.63; 0.88)	0.48 (0.39; 0.58)
GSH	0.15 (0.08; 0.28)	1.72 (0.69; 4.31)	1.23 (0.43; 3.55)	1.08 (0.37; 3.13)	*	*	1.37 (0.97; 1.93)	0.75 (0.53; 1.08)
Prior ANC testing: Tested ≤22 weeks & 3rd trimester					*	*	**Ref**	**Ref**
No prior ANC testing	*	*	*	*	*	*	0.37 (0.31; 0.43)	0.72 (0.55; 0.94)
Tested ≤22 weeks only	*	*	*	*	*	*	0.77 (0.64; 0.92)	0.73 (0.61; 0.88)
Tested 3rd trimester only	*	*	*	*	*	*	0.87 (0.74; 1.02)	0.84 (0.64; 1.10)

*Not included in the model.

†Only women that booked in the first window, weren't diagnosed HIV-positive before delivery and delivered >5 days after the start of the third trimester were eligible for three tests.

aOR: Adjusted odds ratio; CI: confidence interval; BBA: born before arrival; MPMOU: Mitchells Plain Midwife Obstetric Unit; MMH: Mowbray Maternity Hospital; MPDH: Mitchells Plain District Hospital; GSH: Groote Schuur Hospital; n: number of participants

5. Discussion

This is, to our knowledge, one of the first longitudinal studies of the implementation of maternal HIV testing guidelines in a routine setting in SA. The majority of women eligible for HIV testing tested at least once (91%). Although testing completion at "booking" was high (98%), women "booked" late with only 49% "booking" in the first recommended window. While HIV testing implementation improved over time, with fewer missed testing opportunities in the second year after guideline change, there were substantial missed testing opportunities with nearly a third of women not testing within 3 months of/at delivery and only 10% of eligible women being tested in all three recommended testing windows.

The high initial HIV testing proportion in our study (91%) is encouraging however, with 9% of women never tested in pregnancy/delivery, it falls short of a) the global PMTCT target of having over 95% of pregnant women aware of their HIV status and b) the >95% "uptake of antenatal HIV testing" rate recorded for SA between 2010 – 2012 [15]. This observed difference may be due to our use of operational data from a single referral chain of health facilities in one area of Cape Town, including testing completeness in women presenting at delivery with no prior antenatal care, versus the use of nationwide aggregate antenatal survey data. This is underscored by the significant predictors of never HIV testing in pregnancy in our analysis: presenting for delivery "unbooked" vs. "booked" and older gestational age at "booking" (per additional week gestation), concurring with results from Zimbabwe [27]. These results suggest a need for additional interventions to improve the implementation of initial HIV testing among women who either "book" late in pregnancy or don't "book".

In SA "booking" before 20 weeks gestational age, regardless of HIV status, is a PMTCT-related indicator [15]. It is also recommended in national and WC guidelines that women are HIV tested at their first visit [8,10]. Reassuringly, the implementation of HIV testing at "booking" was excellent (98% coverage) but unfortunately many women "booked" late i.e. after 20 weeks gestation. Our analysis revealed that the median gestational age at "booking" for HIV-positive (at delivery) women was 24 weeks and the highest proportion

(1.6%) of HIV-positive diagnoses at enrolment was in the >22 - < 28 weeks gestation period. Further, a high proportion of women (15%) presented at delivery "unbooked" with HIV status unknown. Of the "unbooked" women who tested, 1.5% were HIV-positive which is possibly an underestimate as less than half of "unbooked" women received a HIV test. Untested women may have had a different HIV risk profile to tested women.

Reassuringly, implementation of maternal HIV testing in our setting improved over time following the adoption of the updated retesting guidelines, similar to results from Kenya [23]. Women were less likely to miss testing opportunities if they enrolled in 2015/2016 as opposed to in 2014. Notwithstanding, we observed several missed repeat testing opportunities; a third of women had an unconfirmed HIV status after delivery as they had either never tested or last tested ≥3 months before delivery. This is however lower than that observed in Kenya [23]. Only a small proportion (10%) of eligible women received all three recommended HIV tests. Understandably, women who deliver prematurely are less likely to have all three tests however the data show that poor implementation of delivery testing was responsible for the bulk of missed opportunities.

At delivery, women were more likely to HIV test at either of the two secondary level facilities (MPDH/MMH) versus MPMOU. At secondary facilities there were PMTCT nurses designated to do HIV testing. Women were often tested in the labour ward upon arrival, but otherwise had other opportunities to test in the post-natal ward if admitted after delivery. In primary care, women are often discharged within 6-8 hours of an uncomplicated birth. Nonetheless, women delivering at secondary facilities versus MPMOU were more likely to not test at all, possibly as "unbooked" (hence untested) women with high-risk pregnancies/deliveries are frequently transferred straight to secondary facilities for caesarean delivery, with no opportunity for testing in the labour ward. The transfer between facilities may also cause confusion regarding whether women were already tested.

HIV prevalence among women with a known HIV status at delivery was 21%, similar to the 19% reported for the WC [26]. Of the HIV-positive women the vast majority (95%) were known positive at enrolment indicating the maturity of the HIV programme with high overall testing coverage. It is also reassuring that the first of the 90-90-90 targets [15], that 90% of HIV-positive people know their status, has been met. It should however be noted that this proportion may be slightly overestimated due to missed positive diagnoses among women

that never tested. Furthermore, awareness of HIV status does not guarantee that women have initiated and adhered to ART. Future studies are required to assess viral load suppression among known positive women. The overall HIV incidence among women that initially tested HIV-negative was estimated to be 0.2% which is substantially lower than that previously reported in SA and SSA (3 – 4%), but similar to that of non-African countries (0.3%) [12,28]. While our study may substantially underestimate incidence due to the low completeness of repeat HIV testing, assessment of the most cost-effective number and timing of maternal HIV tests in different incidence settings, and feasibility of implementation, should be considered for future studies.

Strengths and limitations:

The use of individual-level longitudinal data allowed for a more accurate assessment of testing completion in recommended testing windows, based on each woman's progress through the PMTCT continuum as opposed to using aggregate data. The use of longitudinal data also enabled the description of a) the timing of HIV-positive diagnoses and b) HIV incidence estimates. Point-of-care testing is not normally digitized so to our knowledge this is the only data of this kind available in SA. We had a large sample size which included antenatal and delivery HIV testing data from primary through tertiary care facilities. Positively, our study demonstrated the real-world implementation of PMTCT testing guidelines; however, we were dependent on the quality of operational data and couldn't account for missing data. Furthermore, qualitative data were not routinely collected, and we could therefore not explore qualitative risk factors for missed testing opportunities. At visits other than "booking" and delivery, we did not have a record of visit data separate from testing data and therefore could not distinguish between visit coverage and re-testing coverage in the third trimester. Although we excluded women who attended any documented ANC visits at banc sites, we were unable to determine whether women had received point-of-care HIV testing at facilities not included in the study, or outside the WC province. The subset of women without recorded pregnancy outcomes may have had systematically different testing outcomes to those for whom outcomes were recorded and their exclusion from the dataset may therefore have introduced selection bias into the study results, thereby slightly overestimating testing completeness. Although the results of this

study may be externally valid to the WC, HIV testing is context-specific and results should be treated with caution when generalizing to other settings.

6. Conclusion

The results of this study illustrate that although there has been maturation of maternal HIV testing within the PMTCT programme over time, gaps remain in late pregnancy testing, particularly at delivery. Interventions are required at facility level to improve delivery HIV testing among women "booking" late/not "booking" and those that have high-risk pregnancies in order to limit the transition of undiagnosed HIV-positive women to the postnatal period without access to lifelong ART, feeding support and infant post-exposure prophylaxis. Additional research to assess a) the viral suppression among known HIV-positive women and b) the cost-effectiveness of PMTCT testing guideline implementation is required.

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PART D: APPENDICES

Appendix 1: Supplementary methods

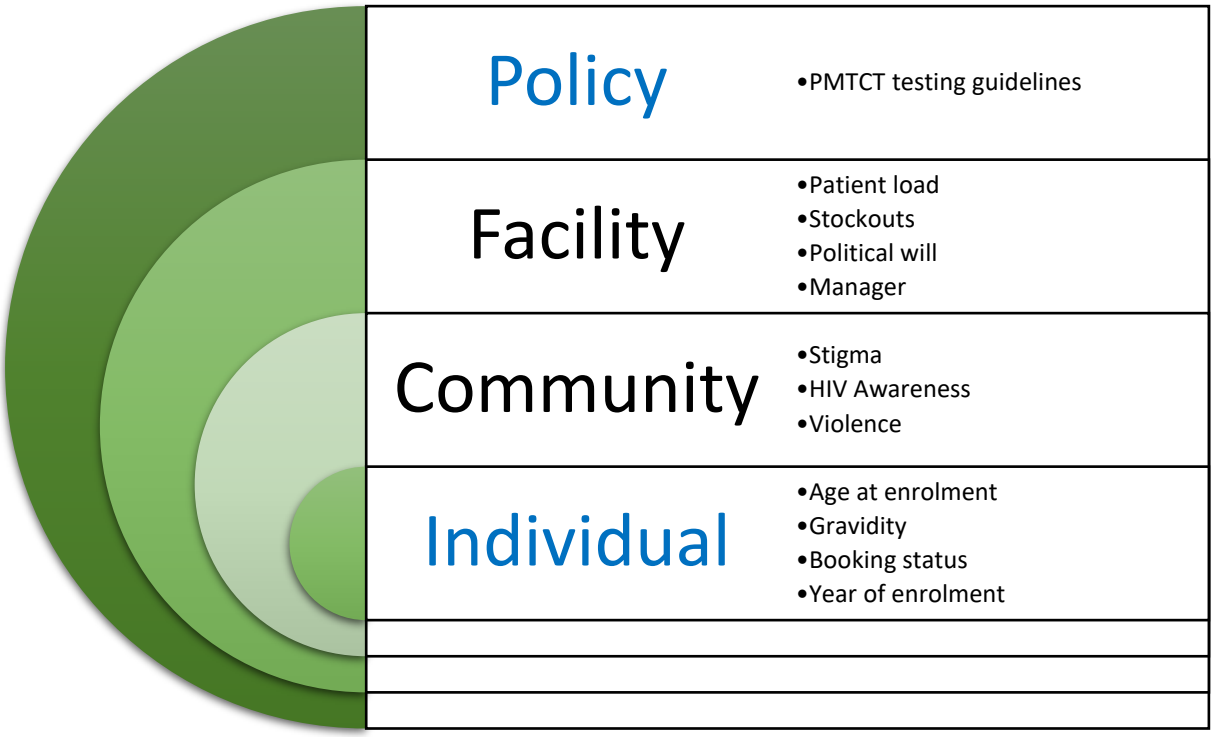

Figure S1. Conceptual framework demonstrating the potential factors associated with HIV testing during PMTCT. Policy and individual level factors were investigated in this study.

PMTCT: Prevention of mother-to-child transmission

Appendix 2: Supplementary results

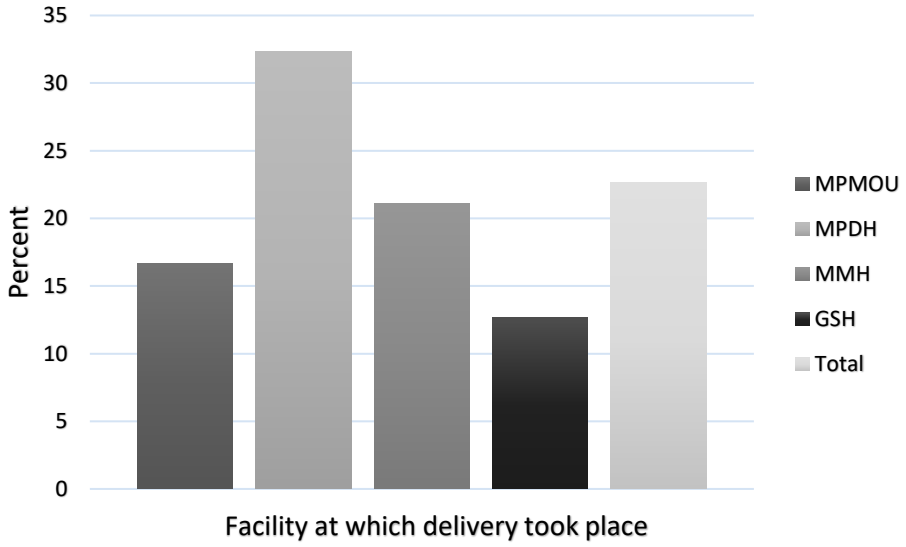

Figure S2. Delivery HIV testing completion at respective delivery facilities.

MPMOU: Mitchells Plain Midwife Obstetric Unit; MPDH: Mitchells Plain District Hospital; MMH: Mowbray Maternity Hospital; GSH: Groote Schuur Hospital

Table S1. Univariable and multivariable factors associated with failure to test at delivery among unbooked women (n=1016).

	No delivery HIV testing	
Variable	**OR (95% CI)**	**aOR (95% CI)**
Age at first visit (years)	0.95 (0.93; 0.97)	0.99 (0.96; 1.02)
Gravidity: 1	**Ref**	**Ref**
2	0.73 (0.50; 1.07)	0.78 (0.51; 1.18)
3	0.55 (0.37; 0.81)	0.66 (0.42; 1.05)
≥4	0.37 (0.26; 0.52)	0.49 (0.30; 0.80)
Premature delivery: Yes	**Ref**	**Ref**
No	1.66 (1.08; 2.56)	1.68 (0.96; 2.97)
Mode of delivery: Vaginal	**Ref**	**Ref**
Assisted	0.52 (0.09; 3.12)	0.22 (0.03; 1.48)
BBA	0.57 (0.38; 0.86)	0.78 (0.51; 1.21)
Caesarean section	1.37 (0.89; 2.09)	0.83 (0.48; 1.42)
Outcome: Alive	**Ref**	**Ref**
Still Born	0.47 (0.23; 0.97)	0.72 (0.31; 1.63)
Year of enrolment: 2014	**Ref**	**Ref**
2015/2016	0.35 (0.27; 0.47)	0.40 (0.30; 0.53)
Delivery facility: MPMOU	**Ref**	**Ref**
MPDH	1.96 (1.41; 2.73)	1.66 (1.09; 2.52)
MMH	1.26 (0.78; 2.01)	1.62 (0.87; 3.00)
GSH	0.66 (0.21; 2.09)	0.71 (0.20; 2.55)

BBA: Born Before Arrival; MPMOU: Mitchells Plain Midwife Obstetric Unit; MPDH: Mitchells Plain District Hospital; MMH: Mowbray Maternity Hospital; GSH: Groote Schuur Hospital

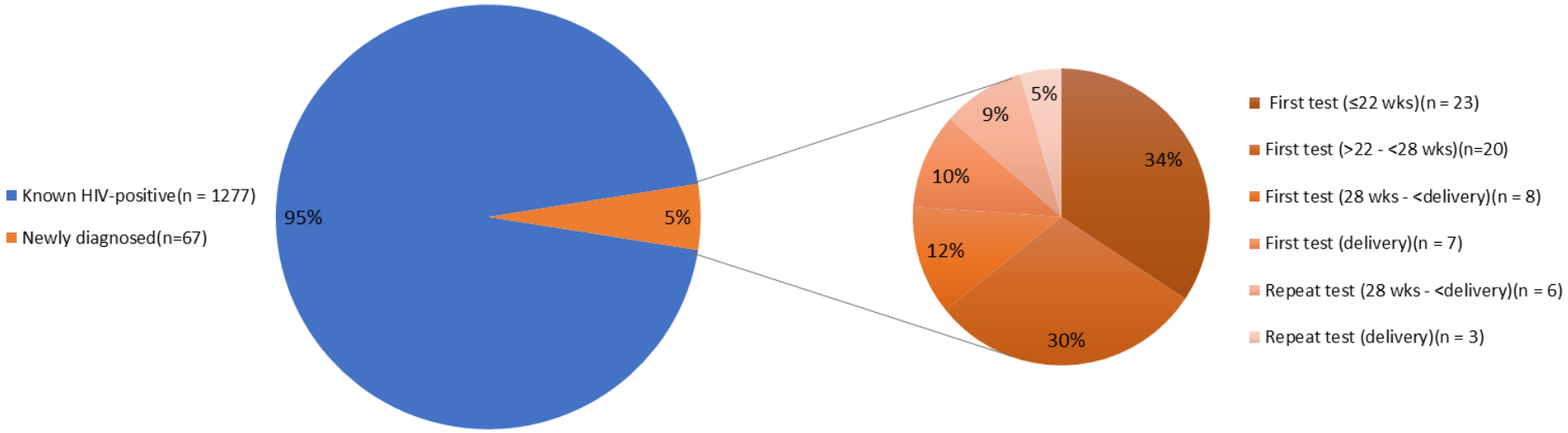

Figure S3. Diagnoses among HIV-positive women (n=1345).

Appendix 3: Closing the Gaps synopsis

Towards pediatric HIV elimination: Closing the gaps in prevention of mother-to-child transmission (PMTCT) programme coverage, early infant diagnosis and treatment. (Short title: "Closing the Gaps")

1. Background and project outline

Virtual elimination of vertical transmission of HIV is within reach in South Africa. Despite high antenatal HIV prevalence, implementation of currently available technology and guidelines in the South African Prevention of Mother-to-Child Transmission (PMTCT) programme has resulted in substantial reductions in vertically transmitted HIV to 3.5% across the country, and <2% in the Western Cape (WC). Yet, elimination remains elusive due to persistent coverage gaps and "drop-offs" at each of the steps required in completion of the PMTCT and infant care continuum, with upwards of 1000 vertically infected infants born in the Western Cape each year. We hypothesize that these persistent coverage gaps are the most important remaining barrier to near-elimination of pediatric HIV morbidity and mortality, irrespective of intensification of PMTCT regimens.

There is thus a need for research to identify strategies that provide an early warning system of coverage gaps both at the level of the health system and the individual, and link to care pregnant women and HIV-exposed/infected infants with such gaps who critically need antiretroviral therapy (ART) or interventions to prevent transmission.

2. Purpose and objectives:

The purpose of this study is to implement and evaluate three linked active surveillance activities integrated with the existing service platform that aim to iteratively identify and close PMTCT, early infant diagnosis and ART coverage gaps. The study will be carried out by the Centre for Infectious Disease Epidemiology and Research (CIDER) from the UCT School of Public Health and Family Medicine in partnership with the WC Department of Health (DoH). The study will be conducted at the Gugulethu Midwife Obstetric Unit (GMOU) in the

Klipfontein sub-district, and its referral facilities, Mowbray Maternity Hospital (MMH) and Groote Schuur Hospital (GSH). The three activities are as follows:

1. Routine cord blood surveillance (CBS) for HIV exposure and, if positive, the presence of antiretroviral drugs (ARVs): This will be linked to the existing programme of screening for congenital hypothyroidism. CBS will enable identification and urgent linking to care of HIV-exposed infants with no/suboptimal peripartum ARVs to ensure interventions to prevent postnatal transmission, prompt infant diagnosis and infant ART if infected.

2. A single integrated electronic PMTCT register (e-register) linking existing separate paper-based registers held at antenatal, obstetric and infant clinics in the Klipfontein subsdistrict, as well as NHLS laboratory data (maternal CD4, infant PCR). Unlike existing registers that report on aggregate coverage of individual steps in the PMTCT pathway, the combined e-register will track an individual pregnant woman's trajectory through PMTCT and identify where drop-offs and missed opportunities occur. The e-register will therefore support systems of urgent reporting of laboratory results of low CD4 counts in pregnant women and positive infant HIV-PCR test results to clinics, with tracing to ensure prompt ART initiation.

3. Clinical quality assurance and improvement using CBS and PMTCT e-register data. This will be developed in partnership with DoH service managers and integrated with existing subdistrict programme review processes.

These activities thus aim to close coverage gaps at 2 levels:

At an individual level: For individual mothers and infants interventions are designed to ensure appropriate linkages to care will be triggered at key points in the PMTCT cascade.

At a health system level: An auditable early warning system of coverage gaps across the entire program, and interrogation of the reasons for ongoing vertical transmission, will inform and be integrated into clinical quality assurance systems.

Objectives of the study are therefore as follows:

1. To compare PMTCT programme outcomes and effectiveness before and after implementation of these surveillance activities. Measures of programme outcomes and effectiveness to be compared will include:

• Vertical transmission proportion

• Proportion of women presenting at delivery without a previous HIV test

• Proportion of women with incident HIV infection during pregnancy

• Proportion of mother-infant pairs "dropping off" at each step of the cascade (e-register and CBS).

2. To assess the feasibility and success of implementation of the project by measuring, for example, CBS coverage, completeness and quality of PMTCT e-register data entry and linkage, proportion of those identified by the e-register and/or CBS as needing additional intervention who are successfully traced and linked to appropriate care, compliance with clinical quality assurance review meetings.

All data needed for the above objectives will be collected through implementation of CBS and the e-register.

3. Implementation and recruitment

Briefly we aim to implement the 3 activities as follows:

3.1. Cord blood surveillance

The project will build on the existing system of congenital hypothyroidism screening, using routine systems for collection of a specimen of cord blood, specimen transport, registration and testing. A research assistant will visit GMOU, MMH and GSH twice a week to support and monitor the collection of cord-blood specimens. Recruitment of pregnant women ≥18 years of age will take place at the antenatal booking visit at GMOU. As part of counselling and testing for routine opt-out antenatal HIV testing that is standard of care, a study counsellor will work with existing counselling staff to obtain informed consent (IC) to participate in the study. This will include consent for a rapid HIV test to be performed on a cord blood specimen taken at delivery and, if HIV positive, 2 dried blood spot specimens to be tested for the presence of ARVs. HIV tests will be performed at the NHLS laboratory at Red Cross Children's Hopsital and tests for ARVs at the UCT Department of Pharmacology. The process of obtaining IC will include explaining the risks and benefits of participation (including that testing may lead to more active tracing and follow-up of the patient if results indicate that there is a high risk of transmission), the alternatives to participation, and that

the decision to participate will in no way affect the medical care provided. Patients consenting to participate in the study will be provided with an information sheet and informed that they may withdraw from the study at any time. In particular, at delivery, women will be reminded that they have given consent for cord blood testing, and given the opportunity to withdraw from the study. For women who arrive at GMOU in labour without a previous antenatal booking, we will attempt to obtain consent during labour to participate in the study. This will be done to ensure that coverage of CBS is as complete as possible, and that "unbooked" women are also able to access the benefits of study participation. All consent procedures, information sheets and reminders of study involvement will be performed/translated into all local languages.

Infants at high risk of HIV infection (cord blood HIV positive, no/sub-optimal ARVs) will be traced and linked to care by a study community outreach worker working with existing health service PMTCT support staff. This will include counseling regarding the HIV diagnosis to the mother if this was previously unknown. Mother-infant pairs will be linked to routine PMTCT/MCH services so that interventions to reduce the risk of postnatal transmission as well as early infant PCR testing (with early ART if positive) can be provided. Data from HIV-exposed infants with ARVs present in cord blood will be linked to laboratory data to determine whether PCR testing occurs timeously. The same tracing staff will seek infants not tested by 8 weeks of age and link them to care.

2. Electronic PMTCT Register

PMTCT data from women delivering at GMOU as well as women referred from GMOU to MMH and GSH, will be linked with data from the antenatal and infant follow-up clinics associated with GMOU, as well as with laboratory data to establish a single PMTCT e-register. Linkage fields will include the WC unique patient health numbers, maternal and infant names, birth dates, delivery dates and infant birth dates. A very high proportion of true matches are readily linkable when the linkage sets are restricted by location (facility) or date (e.g. birth date of infant and delivery date of mother). The proportion of records that cannot be linked will indicate the disjunction in each step in the PMTCT continuum, providing early warning of coverage gaps.

The e-register will support urgent notification of clinics of laboratory results of maternal CD4 <350 cells/µl and positive infant PCR tests. These will be identified through daily updates of laboratory results from the NHLS to the research officer at CIDER for incorporation into the e-register. The research officer will work with existing reporting systems to inform the relevant clinic/health service staff of any positive test results. We will work with existing WC and City of Cape Town HIV/AIDS and PMTCT to ensure tracing and treatment initiation for these HIV-infected women and infants needing ART.

There will be no recruitment and we are requesting a waiver of informed consent for this part of the project. We will only be incorporating data already collected as part of routine care by the health services and for which informed consent was given when women consented to standard of care routine antenatal opt-out HIV testing.

3. Clinical quality assurance and improvement

Monthly program reviews will be implemented in partnership with Department of Health service managers and be informed by data arising from the PMTCT e-register and CBS. For example:

• Sentinel events of new cases of infant HIV identified through the e-register will be reviewed to identify reasons for transmission.

• Coverage gaps at each step of the PMTCT cascade in women on the PMTCT program as identified through the e-register will be reviewed.

• Coverage gaps in all steps of the cascade up to and including delivery as measured by CBS data will be reviewed.

No maternal or infant identifiers will be used or mentioned at all in these reviews.

4. Description of risks and benefits:

4.1. Potential risks to subjects and their likelihood and seriousness

The major risk for all 3 components will be breach of confidentiality - project staff will have access to individually identifiable maternal and infant HIV and ARV cord blood results, and trace high risk transmission mother-infant pairs. A small number of women will be recruited

for CBS in labour and this may pose a psychological risk. Patient autonomy may also be compromised and privacy breached, as the circumstances in labour may not provide adequate opportunity for counseling and informed consent according to service protocol. This could be considered morally controversial. However, it is argued that withholding the right to consent to HIV testing and treatment to a woman of unknown serostatus compromises her autonomy to have the choice of her infant receiving interventions to prevent vertical transmission if she is HIV infected, even if consent needs to be sought during labour. The study offers clear benefits to mother-infant pairs identified as HIV infected for the first-time at delivery (opportunity to receive proven effective interventions to prevent post-natal transmission, active follow-up and linkage to HIV/ART care) so it would be unethical to exclude women presenting for the first time when already in labour. This is the group for whom the benefits of participation may be the greatest. Rapid HIV testing in labour is recommended in other service settings e.g. “opt out” testing in labour for a woman of unknown serostatus is standard of care in the United States.

4.2. Adequacy of Protection Against Risks

The process of obtaining informed consent for CBS in such a way as to minimize risks, ensure that women fully understand the risks of participation and have autonomy to refuse participation or withdraw from the study have been described above. In particular, we will only use qualified HIV Counseling and Testing (HCT) counselors and will employ additional counselors to support DoH counselors to ensure adequate quality of the informed consent process. For women recruited during labour we will ensure that counseling is conducted in privacy and that the benefits and risks of cord blood HIV testing are fully explained. Since a pregnant woman in labour is particularly vulnerable, we will be sure that women clearly understand that the quality of health care they receive will not be compromised should they elect not to participate. Should a woman with no prior antenatal care present too late in labour for there to be time for her to be invited to participate in the study, the midwife will collect the additional cord blood specimen, and after delivery is complete, the woman will be invited to participate in the study and have the specimen tested for HIV/ARVs. Specimens from women who decline to participate post-delivery will be discarded.

Tracing and linkage to care of pregnant women eligible for ART and infants identified as HIV-infected or at high risk of vertical transmission will be done carefully and sensitively. Pregnant women/mothers of infants will be telephoned and asked to attend the clinic urgently for a health care appointment. Where telephonic tracing is unsuccessful, a home visit will be done and the patient asked to attend the clinic for a health care appointment. No laboratory results will be given to the mother telephonically or at the home visit. Results will only be given to the mother at the clinic appointment in a private room by qualified health service providers as per South African PMTCT and HCT guidelines ensuring patient confidentiality. Full post-test counselling will be given to the mother according to HCT guidelines.

All HIV counselling and testing (antenatally and during labour or post-delivery) will be offered by qualified health service providers as per HCT and PMTCT guidelines ensuring patient confidentiality and autonomy.

To minimize risks of breaching confidentiality, all electronic project data will be stored in a password-protected database on a secure server housed in the CIDER offices at the UCT Faculty of Health Sciences, with user level access control implemented. Any paper-based patient records will be stored in locked filing cabinets in locked room with access only to those directly involved in the study. Inclusion of identifiers in the databases is needed initially so that they can be linked and for tracing of mothers/infants. Identifiers will be removed from all databases (PMTCT e-register and CBS HIV and ARV results) as soon as possible once linkage and tracing are complete. Only staff directly involved in the project will have access to the data and will undergo Human Subjects Protection training prior to having access to any individually identifiable data. We will use the same measures to protect against breach of confidentiality as are currently in place in all CIDER projects. Thus far, no breach of confidentiality has occurred in any of these projects. Should a breach of confidentiality occur in this project, it will be noted and investigated.

4.3 Potential benefits

Historically, antenatal sentinel surveillance and monitoring of PMTCT programmes has been based on anonymous specimens and aggregate data. While these provide surveillance for the programme as a whole, they provide no opportunity to act on clinically important results, and thus fail to benefit the individual patient on whom testing has been performed.

This study thus has the following benefits:

• It will generate surveillance data and early warning systems that will trigger and inform PMTCT programme improvement, thus benefiting all HIV-infected mother-infants pairs in the area where the study takes place.

• It provides individual benefit to mothers and infants participating in the study by identifying pregnant women eligible for ART, HIV-infected infants and those at high risk of transmission and prioritizing provision of immediate PMTCT and maternal and infant HIV care interventions that are known to be effective and safe. All pregnant women ≥18 years of age will be invited to join the study and have access to these benefits.

• The surveillance systems will be developed in partnership with health services with a long term view to more widespread routine adoption, so that HIV-infected women and exposed infants from other areas will also benefit if the project is successfully expanded to other areas and integrated into routine surveillance.

• The findings of the study will inform PMTCT programmes broadly in terms of improving coverage and maximizing the benefits of ART for maternal and child health.

4.4. Balancing the major risks to subjects with the potential benefits of the project

***Breach of confidentiality*:** As every effort will be taken to ensure confidentiality, the small risk of it being breached can be considered to be acceptable given the potential not only to achieve PMTCT programmatic improvements, but also to provide individual benefit to study participants through tracing and linkage to care. Of note, the individual benefits could not be provided without the holding of identified laboratory test results, so this is an unavoidable risk.

Compromise of patient autonomy and psychological distress for women recruited during labour:

While optimal strategies for PMTCT comprise early antenatal diagnosis and treatment, testing pregnant women of either unknown serostatus or with acute infection at the time of delivery provides an additional opportunity for PMTCT. Given the availability of effective maternal and infant ART the potential immediate benefit to mother and child of a pregnant woman learning her serostatus peripartum has increased relative to the potential risks of offering HIV testing in this setting.

Appendix 4: UCT Human Research Ethics Committee approval (145/2013); PGWC Health Research approval (RP063/2013) (CTG)

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Faculty of Health Sciences Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
e-mail: sumayah.ariefdien@uct.ac.za
www.health.uct.ac.za/research/humanethics/forms

29 April 2013

HREC REF: 145/2013

Dear A/Prof A Boulle
CIDER
School of Public Health & Family Medicine
FHS

Dear A/Prof A Boulle

PROJECT TITLE: CLOSING THE GAPS IN PMTCT PROGRAM COVERAGE, EARLY INFANT DIAGNOSIS AND TREATMENT.

Thank you for addressing the issues raised by the Human Research Ethics Committee.

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

Approval is granted for one year till the 15 May 2014.

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.

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

Please quote the REC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

Western Cape Government
Health

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www.capegateway.gov.za

REFERENCE: RP 063 /2013
ENQUIRIES: Ms Charlene Roderick

Centre for Infectious Disease Epidemiology and Research
Falmouth Building
Faculty of Health Sciences
University of Cape Town
Observatory
7925

For attention: **Dr MA Davies, Dr EM Kalk, Prof J McIntyre, Prof A Boulle, Prof D Coetzee and Dr M Kroon**

Re: Towards paediatric HIV elimination: Closing the gaps in prevention of mother-to-child transmission (PMTCT)programme coverage, early infant diagnosis and treatment"Closing the Gaps"

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

Mitchells Plain Hospital **Ms Z Xapile** **Contact No. 021 391 5820**

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 report within six months of completion of research. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).
3. The reference number above should be quoted in all future correspondence.

Yours sincerely

DR NT Naledi
DIRECTOR: HEALTH IMPACT ASSESSMENT
DATE: 11/11/2013
CC **P OLCKERS** **DIRECTOR: MITCHELLS PLAIN / KLIPFONTEIN**

Appendix 5: UCT Human Research Ethics Committee approval (779/2018)

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

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

23 November 2018

HREC REF: 779/2018

A/Prof M Davies
CIDER
SPHFM Room 5.42
Falmouth Building-FHS

Dear A/Prof Davies

PROJECT TITLE: A LONGITUDINAL ANALYSIS OF THE COMPLETENESS OF REPEAT HIV TESTING AND THE PREDICTORS THEREOF, AMONGST HIV NEGATIVE PREGNANT WOMEN IN MITCHELL'S PLAIN, CAPE TOWN (Master's candidate-Miss S de Beer) sub-study linked to HREC/REF:145/2013

Thank you for submitting your study to the Faculty of 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 November 2019.

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)

We acknowledge that the student: Ms Shani de Beer 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

Appendix 6: Instructions for Authors Journal of the International AIDS Society

Research - full reports of data from original research studies

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

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

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