COVERAGE, QUALITY AND UPTAKE OF PMTCT SERVICES IN SOUTH AFRICA: RESULTS OF A NATIONAL CROSS-SECTIONAL PMTCT SURVEY (SAPMTCTE, 2010)

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Missed opportunities

EID service

EID service coverage

Uptake of PMTCT service

Loss to follow-up

Linkages

Health system factors

Risk factors of transmission

Executive Summary

Background and objectives

HIV is a significant contributor to child mortality in low and middle income countries.[1,2] In Sub-Saharan African countries more than a thousand children are newly infected with HIV daily.[3] Despite the rapid scale-up of services to prevent HIV transmission from mother-to-child (PMTCT services) in this region, poor service utilisation remains a major barrier. South Africa is signatory to the UNGASS declaration of commitment to provide universal access to antiretroviral (ARV) treatments for PMTCT, and to the UNAIDS target to eliminate mother-to-child transmission of HIV (MTCT) by 2015.[4,5] Even though effective packages of interventions have been introduced to enable the virtual elimination of mother-to-child transmission (eMTCT), the effectiveness of these interventions is ultimately influenced by the coverage of PMTCT services and retention rates as women progress through a cascade of PMTCT preventive, treatment and care services.

Few studies evaluate the coverage of PMTCT cascade services and gaps in PMTCT programmes nationally.[6-8] Although several targets have been set for PMTCT programmes, available data (routine programme data) used for tracking the achievement of these targets have limited validity. Thus in most high HIV prevalence countries (including South Africa), there is a lack of strong evidence on progress towards achievement of international targets. This study aimed to (i) measure national and provincial uptake of antenatal and early postpartum PMTCT cascade services and missed opportunities at each step of the PMTCT cascade services in South Africa, (ii) the study also aimed to explore health facility and individual level factors that explain geographical variations in the risk of mother-to-child HIV transmission and (iii) the last objective of the study assessed reasons for missed opportunities of early infant HIV diagnosis (EID) services. This is the first national study that provides estimates of uptake of antenatal and perinatal PMTCT cascade services using a national and provincial level representative sample.

Methods

Two quantitative studies were carried out in randomly-selected facilities within all nine provinces of South Africa. First, a situational assessment of these randomly selected facilities was undertaken using key informant (health care personnel) interviews and record reviews to ascertain guidelines and procedures for early identification of HIV-exposed infants (HEI), the coverage of early infant diagnosis services, the human resource capacity of the health system, and existing linkage and referral system for antenatal and postnatal PMTCT services. This was followed by the South African national PMTCT survey (SAPMTCTE) which involved a collection of infant blood samples and maternal interview data from mother-infant pairs (infants age 4-8weeks) attending six weeks immunisation service points in the selected facilities. Interviews were conducted with mothers to assess antenatal and peripartum PMTCT services received and maternal intention to request for infant HIV testing at six weeks immunisation visits. Data on gestational age at birth, infant birth weight and HIV status was extracted from the road-to-health-card (RtHC).

The HIV status of mothers was determined from maternal report or enzyme immunoassay (EIA) test conducted on infants dried blood spots (DBS). A weighted analysis (weighted for sample size realisation and population live births) was performed to assess uptake of services along the PMTCT cascade. Mothers who either self-reported an HIV-positive status or had an EIA positive infant were classified as HIV-positive mothers. Perinatal ARV regimen coverage was calculated from the total number of HIV-positive mothers who received maternal azidothymidine (AZT) or HAART for any duration during pregnancy plus infant nevirapine (NVP)/AZT received at birth. Descriptive methods were used to analyse national availability of EID services and approaches for identifying HEI at the six weeks immunisation visit. Logistic regression assessed key factors influencing maternal intention to receive EID. Logistic regression was also used to explore individual, health facility and provincial level factors that explain variability in mother-to-child-transmission rates.

Results

The study shows high (97.7%) uptake of antenatal HIV testing but substantial loss to follow-up on subsequent key steps along the PMTCT cascade. The study findings indicate that high attrition challenges the South African PMTCT programme with 10.4% of mothers at six week visit reporting not to know their HIV-positive status; not receiving CD4 count test / test result and dropout at referral for HAART accounting for a total of 22.6% and 10% missed opportunities for HAART treatment respectively.. In total, 78% of all (known and unknown) HIV-exposed infants received both maternal and infant antiretrovirals (i.e. maternal AZT or HAART for any duration during pregnancy plus NVP/AZT at birth).

Uptake of PMTCT cascade services varied between provinces - provincial uptake of CD4 count and maternal and infant ARVs (i.e. maternal AZT/HAART and infant NVP) ranged from 54%-89% and 65%-88%, respectively. Transmission rates also varied geographically ranging from 1.4% to 5.9%. Multivariate analysis of factors explaining geographical variations in mother-to-child-transmission rates identified two health system factors that are predictors of geographical variations observed in mother-to-child transmission, these are: low (<80%) provincial PMTCT cascade coverage (AOR 1.7, 95% CI 1.2 -2.6), and shortage of (≤2 health-care personnel doing VCT) health-care-personnel doing VCT (AOR 2.2, 95% CI 1.1 -4.3). Other significant factors associated with transmission include low (<2.5kg) birth weight, ARV regimens (receiving both maternal AZT/HAART and infant NVP v.s. receiving maternal only, infant only or no antiretrovirals (ARV)) and any breastfeeding. Achievement of the UNGASS universal PMTCT coverage target (≥80%) was associated with significantly lower (<3%) transmission rate.

Our assessment of infant HIV testing services at immunisation service points indicates the majority (68%) of facilities in South Africa offer targeted testing that relies on maternal notification of infant HIV-exposure or the road-to-health-card (RtHC) to identify HIV-exposed infants for six weeks infant testing. However, both

the RtHC and maternal reporting were poorly utilised. The HIV-exposure prevalence (32%) at six-week immunisation visits reported in our cross-sectional survey was similar with the HIV prevalence (29%) reported for pregnant women in the 2009 antenatal survey. Only 35% of known HIV-positive mothers intended to report their HIV-exposure at six week immunisation visit, and only 55% had RtHC that reflected their HIV-status. Thus facilities that use targeted approach potentially missed opportunities of early testing on significant percentage (38%) of HEI. Since the study offered provider-initiated counselling and testing to all infants, few of the infants actually missed HIV testing. In our study when PICT was offered to all mothers at six weeks immunisation visit, 95% of mothers agreed to give an infant blood sample for testing and to receive results. In regression analysis, poor maternal reporting for EID was associated with feeling discriminated, missing maternal/infant antiretrovirals, and inadequate knowledge about HIV transmission.

Conclusion

This assessment shows that South Africa is on track to meet the UNGASS universal access target (≥80%) for maternal and infant antiretroviral regimens. Contrary to previous reports (based on routine programme data), our study shows that ARV regimen coverage in South Africa is lower than the UNAIDS 90% effective ARV regimen target. Despite this, in three provinces that achieved the UNGASS (≥80% ARV regimen coverage) target, average transmission rate was significantly lower (<3%).

The study demonstrates variations in mother-to-child transmission rates were directly related to variations in uptake of the PMTCT cascade services and gaps in health systems infrastructure (particularly human resource shortage). Geographical variations in human resource distribution and subsequent differences in uptake of PMTCT services contributed to significant geographical differences in mother-to-child transmission. Strengthening the health system and reducing leakage at key dropout points /steps of the PMTCT cascade should be prioritized in order to

maximize the effectiveness of the PMTCT programme. The study identifies knowledge of HIV status, CD4 count, HAART initiation and early infant HIV diagnosis as key dropout points. The lack of on-site CD4 count service, gaps in courier and transportation systems and the CD4 count requirement for initiation of HAART are mentioned in the literature as the major barriers for low coverage of CD4 count and delay in HAART initiation. In light of the significant number (22.6%) of HIV-positive mothers in this study whose eligibility for HAART was not assessed (and thus HAART was not initiated), this study supports the adoption of the WHO Option B treatment guideline in South Africa which removes the CD4 count requirement for initiation of HAART. However, though the adoption of the WHO Option B treatment guideline has removed the CD4 count requirement, there is still a need to improve access to HAART treatment (e.g. by emphasising on decentralisation of HAART initiation through nurse initiated HAART treatment) as dropouts at antiretroviral referral points could pose major challenge for HAART initiation. Our findings on EID services indicate relying on identification of HEI for EID services through maternal request for testing or documentation on the RtHC contributes to lower uptake of EID services. Immunisation service points should give provider-initiated counselling and testing (with maternal or infant HIV antibody testing to identify the HIV exposure status of infant) to six weeks mother-infant pairs with undocumented/unknown HIV status.

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ABBREVIATIONS AND ACCRONYMS

3TC	Lamivudine
ADDRF	African Doctoral Dissertation Research Fellowship
AIDS	Acquired Immunodeficiency Syndrome
ANC	Antenatal Care
ART	Antiretroviral therapy
ARV	Antiretroviral (drug)
AZT	Azidothymidine
CDC	Centres for Disease Control and Prevention
CHAI	Clinton Health Access Initiative
CHWs	Community Health Workers
DHIS	District Health Information System
DNA	Deoxyribose nucleic acid
DBS	Dried blood spot
EC	Eastern Cape
EIA	Enzyme immunoassay
EID	Early infant diagnosis
FS	Free State
GP	Gauteng
HIV	Human Immunodeficiency Virus
HSRU	Health Systems Research Unit of the Medical Research Council
HAART	Highly active antiretroviral treatment
KZN	KwaZulu-Natal
LP	Limpopo
MCWH	Maternal Child and Women's Health
MPH	Masters in Public Health
MP	Mpumalanga
MRC	Medical Research Council
MTCT	Mother-to-child transmission (of HIV)
NC	Northern Cape

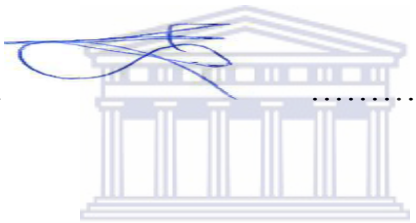
NDOH	National Department of Health
NHLS	National Health Laboratory Services
NICD	National Institute for Communicable Diseases
NSP	National Strategic Plan, South Africa, 2007-2011
NVP	Nevirapine
NW	North West
PCR	Polymerase Chain Reaction
PMTCT	Prevention of Mother-To-Child Transmission of HIV
RtHC	Road to Health card/ chart
SACEMA	South African Epidemiological Modelling and Analysis
SAPMTCTE	South African PMTCT service Evaluation/survey
SoPH	School of Public Health, University of the Western Cape
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
UNGASS	United Nations General Assembly, Special Session
UWC	University of the Western Cape
WC	Western Cape
WHO	World Health Organisation

DECLARATION

I hereby declare that this dissertation represents my own works and has not been presented either wholly or in part for a degree at the University of Western Cape or any other university.

Student: Selamawit Alemu Woldesenbet

Signature …… ……..



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- Mothers and their infants who participated in the survey
- MRC survey supervisors and data collectors

DEFINITIONS

Acceptability of PMTCT service: the degree to which the PMTCT service meets the social and cultural needs and standards of the community, which in turn influences uptake of PMTCT service. [9]

Access (to health services): the perceptions and experiences of people as to their ease in reaching health services or health facilities in terms of location, time, and ease of approach.[10]

Affordability refers to the direct (doctor's fees, travel and medical costs) and indirect costs (e.g. absenteeism from work) that affect access to service.[11]

Availability of service - we use this term in particularly to refer to the delivery (or availability) of services at peripheral level health care units (i.e. primary health care units).[10]

Caregiver
The person who feeds and looks after the child most of the week. This includes parents, legal guardians, family members, nannies, or friends who routinely feed, bath, change nappies, or in particular reference to this study, bring child for routine health services.

Coverage: the extent of interaction between the service and the people for whom it is intended. Coverage is not to be limited to a particular aspect of service provision, but ranges from resource allocation to the achievement of the desired objective.[12]

Early (six weeks) HIV Transmission rate amongst HIV-exposed infants
Number of DNA PCR positive infants and EIA (enzyme immunoassay) positive infants divided by the number of EIA positive infants at 4-8 weeks.

Effective ARV regimen coverage
Effective coverage is defined as the magnitude of the realised health gain from the intervention relative to the potential health gain possible with the optimal performance of the providers for a given health system.

Mother-infant pairs are considered as they received effective ARV regimen if eligible mothers (CD4 ≤350) received HAART and non-eligible mothers received ARV prophylaxis from 14 weeks (or earlier if receiving HAART) of pregnancy through delivery. Infants should receive daily dose of nevirapine for at least 6 weeks (not breastfeeding) or as long as breast milk is given. (*See definition of total ARV regimen coverage*)

Health care personnel
Health care providers and health care workers.

Health care provider
Any person providing health services in terms of any law, including in terms of the:

- Allied Health Professions Act, 1982 (Act No.63 of 1982)
- Health Professions Act, 1974 (Act No. 56 of 1974)
- Nursing Act, 2005 (Act No. 33 of 2005)
- Pharmacy Act, 1974 (Act No. 53 of 1974) and
- Dental Technicians Act, 1978 (Act No. 19 of 1979)

Health care worker
Any person who is involved in the provision of health services to a user, but does not include a health care provider. This includes lay counsellors and community caregivers.

HIV-exposed infant
An infant born to an HIV-positive mother and/or having a positive HIV antibody test result using DBS EIA.

HIV-infected infant
An HIV-exposed infant having a positive HIV DNA PCR result.

HIV-uninfected infant
An HIV-exposed infant having a negative HIV DNA PCR result.

HIV-positive mother
Defined for this survey as mothers whose infants have a positive DBS EIA.

HIV status unknown
Refers to people (including children) who have not taken an HIV test or who do not know the result of their test.

Infant
A child from birth to 12 months of age.

Mother-to-child transmission (MTCT)
Transmission of HIV from an HIV-positive woman during pregnancy, delivery or breastfeeding to her child. The term is used because the immediate source of the infection is the mother, and does not imply blame on the mother.

MTCT Rate
Defined for this survey as a numerator of HIV-positive infants (PCR positive) and denominator of HIV-exposed infants (infant EIA antibody positive).

PMTCT-cascade
For the purpose of this study, PMTCT cascade is defined as the following interventions: maternal HIV-testing and receiving result; if mother is HIV-positive:

receiving CD4 count test, and CD4 count test result; and appropriate ARV prophylaxis/treatment for mother and infant.

Quality of PMTCT service
Quality of PMTCT service refers to the degree to which PMTCT services are provided with high standard and excellence as set in PMTCT protocols/ guidelines, to ultimately increase the likelihood of desired health outcomes for mother-infant pairs.

Total ARV regimen coverage - Maternal azidothymidine (AZT) or HAART received for any duration during pregnancy plus infant nevirapine (NVP)/AZT received at birth (maternal and infant ARV prophylaxis/ HAART) was considered as a marker for total perinatal ARV regimen coverage.

Universal access/coverage –Particularly for this thesis, this term is defined as ≥80% total ARV regimen (maternal AZT or HAART received for any duration during pregnancy and infant NVP/AZT taken at birth) coverage.

Uptake of PMTCT services
Uptake refers to utilisation of PMTCT service by mother-infant pairs. For this study the following PMTCT cascade uptake measures are defined (*of which the receiving of both maternal and infant ARV is considered as the perinatal PMTCT cascade coverage):*

Uptake of maternal antenatal HIV testing - refers to the proportion of mothers interviewed at six weeks immunisation visit who reported receiving antenatal HIV testing.

Uptake of maternal HIV test result: refers to the proportion of interviewed mothers who reported receiving antenatal HIV test result.

Uptake of maternal CD4 testing result - refers to the proportion of infant EIA positive or reported positive mothers who had CD4 count test and received result during antenatal period.

Uptake of maternal ARV prophylaxis - refers to the proportion of infant EIA positive or reported positive mothers who reported **receiving** antiretroviral prophylaxis during pregnancy.

Uptake of maternal HAART - refers to the proportion of infant EIA positive or reported positive mothers with CD4 count ≤350 who reported receiving ARV treatment during pregnancy.

Uptake of **Infant ARV prophylaxis** - refers to the proportion of infant EIA positive or reported positive mothers whose infant received ARV prophylaxis immediately after delivery

Uptake of Maternal and infant ARV/total ARV regimen coverage - refers to the proportion of infant EIA positive or reported positive mothers who reported both mother and infant received ARVs (i.e. maternal ARV/HAART and infant ARV prophylaxis)

Utilization (of health services): experience of people as to their receipt of health care services of different types. [10]

Chapter 1: INTRODUCTION, AIM AND OBJECTIVES

1.1. Introduction

HIV is a significant contributor of child morbidity and mortality in developing countries.[1,2] An estimated 390 000 children aged less than 15 years old globally were newly infected with HIV in 2010; over 90% of them through mother-to-child transmission.[13] In sub-Saharan African countries more than a thousand children are newly infected with HIV every day. Without treatment, about half of these infected children will die before their second birthday.[14] The risk of MTCT without any intervention ranges from 15% to 30% in non-breastfeeding population and 25% to 35% in breastfeeding population with breastfeeding till 6 months.[15] With specific interventions in non-breastfeeding populations, the risk of MTCT can be reduced to less than 2%, and to 5% or less in breastfeeding populations.[16,17]

International policies emphasise on a four-pronged approach to prevent mother-to-child transmission, which includes: 1) Primary prevention of HIV infection among women of childbearing age; 2) Preventing unintended pregnancies among women living with HIV; 3) Preventing HIV transmission from a woman living with HIV to her infant; and 4) Providing appropriate treatment, care and support to mothers living with HIV and their children and families.[4]

In 2001, at the United Nations General Assembly Special Session (UNGASS), countries committed themselves for a universal coverage of PMTCT programmes and to halving of HIV infection in children by 2010. [4] South Africa is one of the signatory countries to the UNGASS Declaration. Since this declaration, South Africa has taken several steps to scale-up PMTCT interventions:

- The PMTCT programme was piloted in 2001 in 18 pilot sites. This was followed by full scale-up of the programme in all primary health care centres across all nine provinces. The programme started with single dose nevirapine (NVP) for mothers at the onset of labor and to their new-born within 72 hours after birth. The PMTCT programme package also included antenatal voluntary counselling

and testing, infant feeding counselling, provision of free formula milk for women who choose not to breastfeed and infant rapid antibody testing at 12-18 months. In 2005, PCR testing at 6 weeks was added in the package of care for the PMTCT programme.[18]

- In 2008, the PMTCT guidelines were revised to include the initiation of AZT at 28 weeks with single dose NVP at the onset of labor for mothers with CD4 count greater than 250 cells/µl, and initiation of maternal HAART for mothers with CD4 count less than or equal to 250 cells/µl or with stage IV disease. In addition, single dose nevirapine and 7 days AZT was recommended for HEI immediately post-delivery.[18]
- In April 2010, the Department of Health revised the PMTCT guideline to incorporate new protocols in line with the WHO 2010 (Option A) guideline. The new protocol recommended initiation of AZT at 14 weeks to pregnant mothers with CD4 count above 350 cells/µl, with nevirapine during labour and single dose of Tenofovir (TDF) + Emtracitabine (FTC) during or immediately post-delivery. For women with CD4 cell counts less than or equal to 350 cells/µl provision of maternal HAART is recommended. Infant NVP is given daily for at least 6 weeks (if on HAART or not breastfeeding) or until one week after cessation of breastfeeding. Immediate (irrespective of CD4 count) initiation of ARV treatment is recommended for HIV-infected infants diagnosed.[19]
- Recently, in April 2013, South Africa adopted the WHO Option B treatment guideline. This guideline recommends initiation of HAART for all HIV-positive pregnant mothers (regardless of CD4 count) as soon as possible after diagnosis until one week after cessation of breastfeeding, unless mother requires treatment for her own health in which case treatment will continue for life.[20]

In 2011, UNAIDS recommitted countries to eliminate new HIV infections among children by 2015.[5] The achievement of the UNAIDS goal relies on a successful implementation of a set of PMTCT interventions called the PMTCT cascade.[15] In sub-Saharan African countries despite the rapid scale-up of PMTCT services, poor service utilisation remains a major barrier for prevention of mother-to-child

transmission.[21] This study analyses coverage, uptake and quality of 'the PMTCT cascade service'– defined as - a sequence of steps needed to deliver preventive, treatment and care services to HIV-infected mothers and their infants to prevent mother-to-child HIV transmission and infant mortality.

The paper is organized in 5 sections. The first chapter gives a general introduction to the problem, context and rationale of the study and presents the research questions, aims and objectives of the study. The second chapter reviews existing literature. The third chapter elaborates on methods and materials used. Chapter four presents the results of the study in three sub-sections in the form of manuscripts for publication. Finally, chapter five presents the conclusion and recommendations of the study.

1.2. Conceptual framework of the research

In order for PMTCT programmes to be successful, a number of steps have to be undertaken (fig 1). In particular all pregnant women should receive:

(1) Antenatal care

(2) Good quality antenatal HIV counselling and testing including receipt of HIV test results;

If HIV-positive:

(3) CD4 cell count

(4) Effective maternal and infant ARV regimen;

(5) Appropriate infant feeding counselling;

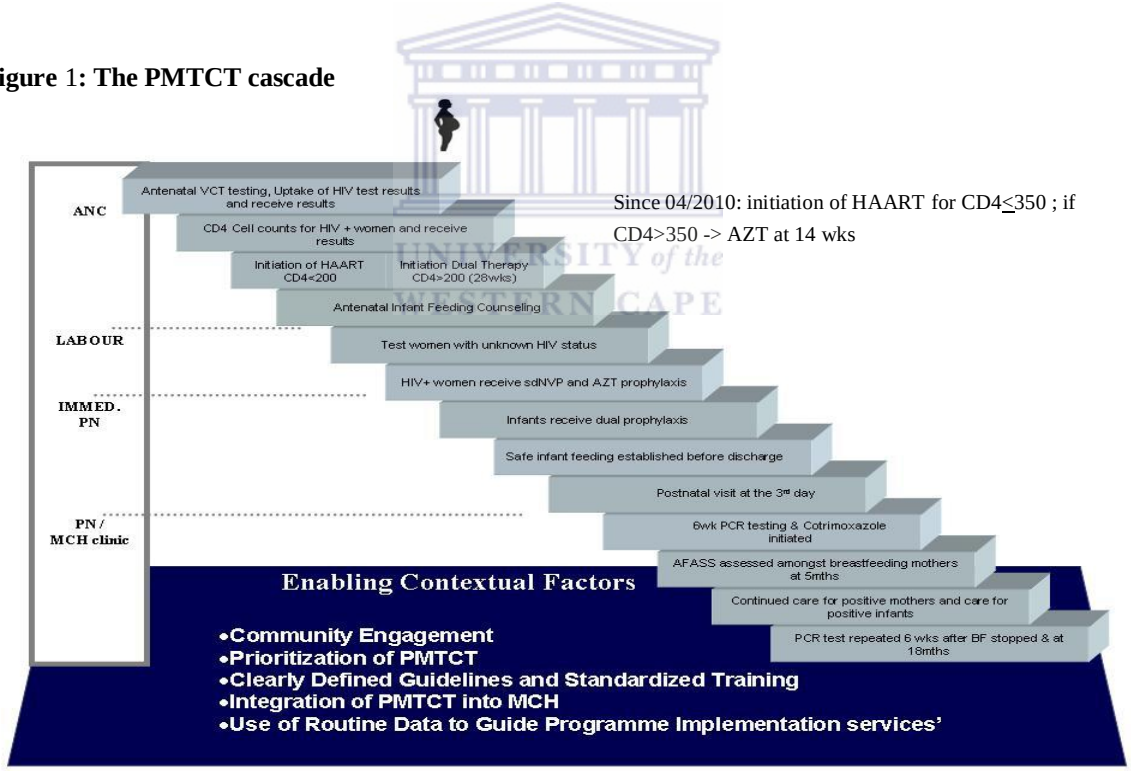
(6) Continuity of care, including follow-up counselling; continuous support for optimal infant feeding (regardless of feeding choice) and linkages to other services, such as neonatal and child health care, as well as HIV care and treatment, and;

(7) Infant PCR testing at or before 6 weeks (linked with the first immunisation), after cessation of breastfeeding, and a rapid test at 18-months.[22]

Loss at one or more of these PMTCT cascade steps diminishes effectiveness of the PMTCT programme.

Several factors could influence uptake of the PMTCT cascade services including health system factors that affect service uptake, user-related/ individual factors and broader socio-cultural factors. Health system/structure issues such as staffing level, availability and cost of antiretrovirals, capacity of health personnel to prescribe appropriate regimens, loss of laboratory specimens being transported from facility to laboratory (or loss of result back to facility); shortage of supplies (in facilities), failure to follow-up mother or infants' status, and giving wrong information/sub-optimal quality of counselling could lead to loss /dropout from the PMTCT cascade. Individual factors such as mothers' knowledge of PMTCT, socioeconomic and demographic characteristics, pregnancy history, as well as broader socio-cultural factors such as fear of stigma, lack of interest, cultural, family and social barriers are factors that influence successful completion of the PMTCT cascade services. [3,23-26]

Figure 1**: The PMTCT cascade**



1.3. Problem statement and motivation for the study

The achievement of high coverage and uptake of services along the PMTCT cascade is crucial for national and international mother-to-child transmission elimination

goals. South Africa has set targets to achieve above 95% uptake of PMTCT services along the cascade, by year 2015.[27] Available data is limited to track progress towards achievement of these targets. Routine programme data obtained from the district health information system (DHIS) does not provide information about the proportion of women who move successfully through each step of the PMTCT cascade. This is because, DHIS provides aggregated data and lacks a system (unique identifier) to link follow-up and repeat services given to mother-infant pairs. Hence, routine programme data (DHIS) cannot be used for measuring loss to follow-up of mother-infant pairs at each level in the PMTCT cascade. Furthermore, DHIS data is paper-based in most provinces of South Africa and relies on accurate documentation of information at facility level, followed by accurate transcription and transfer of this data to district, provincial and national levels. Studies indicate often, due to inadequate monitoring of data collation, the quality of the DHIS data is poor, resulting in questionable validity.[21,28] A study that compared PMTCT data submitted to DHIS with data on PMTCT registers (for reports in the same time period) in 3 large districts of KZN indicated that data elements for key PMTCT indicators was not reported in 49.7% of the time and were "inaccurate" 87% of the time.[28] The same study further reports that the primary site for a breakdown in accurate transfer of data is during the tallying and collation of data from the PMTCT registers. Therefore, DHIS data currently has limited usefulness to measure PMTCT programme effectiveness and uptake of PMTCT services along the cascade.

A small number of periodic surveys are conducted in South Africa to gather data on health and HIV related indicators (table 1). The national antenatal survey, conducted annually in the 52 districts of South Africa, provides measures of HIV prevalence among pregnant women at district, provincial and national level.[29] The Human Science Research Council (HSRC) national HIV prevalence, incidence and behaviour and communication survey measures HIV prevalence in the general population and among children. The 4th round of the HSRC survey gathered more data on access to health services and health status of infants and their mothers. This data is not fully released yet. In the last three consecutive HSRC surveys (2002,

2005, and 2008), the sample size of infants participating in the study was not adequate to allow HIV prevalence (or mother-to-child HIV transmission) measurement among infants. Also no data on PMTCT service related indicators was collected in the last three consecutive HSRC surveys. [30] The demographic health survey (DHS) and the general household survey (GHS) gather national data on general health indicators, but no PMTCT related data is gathered in either survey. [31,32]

Our study is the first study globally that attempts to provide a national estimate of uptake of services along the PMTCT cascade using a national and provincial level representative sample. The study aims to give a baseline national and provincial level estimate of uptake of PMTCT services that can be used for tracking progress towards achievement of national and international targets.

Table 1:National surveys assessing maternal and child Health and /or HIV related indicators

National surveys assessing maternal and child Health and /or HIV	key maternal and child measures assessed	HIV variables assessed	sample size	geographical unit where estimates are made	periodicity of survey
ANC national survey[29]	Syphilis prevalence among pregnant women	HIV prevalence among pregnant women	large sample size (33446 pregnant women)	National, provincial and district level	Annual
the HSRC South African National HIV Prevalence, Incidence, Behaviour and Communication Survey[30]	Hospitalization history and health status of children	HIV prevalence among children; HIV testing among reproductive age; HIV knowledge and behaviour	Not adequate sample size for measuring MTCT among infants (sampled 3988 total children in 2002);	National	Conducted every 3 years (2002, 2005, 2008)

SA DHS 2003[31]	Neonatal, infant, and child mortality ; Vaccinations ; Prevalence and treatment of acute respiratory infection, and diarrhoea; Feeding practices; Maternal mortality ratio; Antenatal care; Tetanus toxoid vaccination; Iron tablets/anti-malarial drugs; Place of delivery; Assistance during delivery; Characteristics of delivery; Delivery complications; Problems in accessing health care; fertility preferences ; contraception use; Use of smoking tobacco	knowledge of HIV/AIDS and sexual behaviour among youth and adult	large sample sizes (7756 households)	National (designed to give results by province, race and urban/rural)	conducted every 5 years
the GHS[32]	Teenage pregnancy, Health service utilization and quality	none	Large sample size (>25000 households)	National, provincial and district level	Annual

The study was conducted at six weeks immunisation visit targeting 4-8 weeks old infants brought for six weeks immunisation. Hence, we measure uptake of PMTCT services for services provided during pregnancy and early postpartum (4-8 weeks of infant age) period, whilst we do not assess PMTCT services provided during the late (> 4-8weeks) postnatal period.

The study has two components: a situational assessment preceding the main survey that aimed to assess the coverage of early infant HIV diagnosis service and capacity of health system to provide EID services. This was followed by a PMTCT survey which entailed collection of infant blood samples and maternal interview data from mother-infant pairs (infant age 4-8weeks) attending 6 weeks immunisation service.

1.4. Research questions

1) What is the national uptake of antenatal and perinatal services along the PMTCT cascade? Are there dropout points along the PMTCT cascade? Is South Africa on track to achieve international targets?
2) What are the health facility and individual level factors that explain geographical variations in mother-to-child transmission rate in South Africa? What influence does PMTCT service coverage have on transmission rate?
3) What are the challenges and gaps in implementing early infant diagnosis services at six weeks immunisation visits of primary health care facilities in South Africa? What percentage of facilities provide EID services at immunisation service points? What approach do facilities use to identify HIV-exposed infants from six weeks immunisation visits? What are the factors that influence maternal intention for receiving six weeks EID service?

1.5. Aim and specific objectives

1.5.1. Aim

- To assess uptake, and quality of PMTCT services in South Africa

1.5.2. Specific objectives of the study

1. Determine national uptake of antenatal and perinatal PMTCT cascade services and missed opportunities for PMTCT services
2. Determine health facility and individual level factors that explain geographical variations in mother-to-child transmission.
3. Determine reasons for low uptake of early infant diagnosis services in South Africa

1.6. Significance of the study

This study provides the first national (for South Africa) baseline estimate of uptake of services along the PMTCT cascade at a provincial and national level. These results can be used to track progress towards achievement of national targets set for steps within the PMTCT cascade. The study highlights gaps/missed opportunities along the

PMTCT cascade that policy makers, managers and health facility staff could use to plan and prioritize strategies to address identified gaps in the coverage and uptake of the PMTCT programme.

The situational analysis component provides a comprehensive assessment of gaps and challenges in the implementation of EID services within the routine primary health care system. This component reports on provision of EID services at six weeks immunisation visits and analyses challenges and gaps in identifying and offering EID services to HIV-exposed infants at six weeks immunisation visits. Given that PMTCT has been a high priority in the international and national response against HIV/AIDS, this study can give baseline data that can be used to monitor the impact of resources channelled into PMTCT interventions to increase uptake and quality of PMTCT services.

Chapter 2: LITERATURE REVIEW

2.1. Burden of HIV infection in women and children and mother-to-child transmission

HIV/AIDS is a leading cause of morbidity and mortality among women of reproductive age (15-49) worldwide.[13] According to UNAIDS estimate half of the 34 million people living with HIV globally are women of reproductive age.[3] Women in sub-Saharan African countries constitute more than half (59%) of the people living with HIV/AIDS in the region.[3] The HIV prevalence trend among pregnant women in sub-Saharan African countries has showed little or no decline in the past 15 years.[3]

HIV infection in children accounts for a significant proportion of child morbidity and mortality worldwide. [1,2,33] In 2010 an estimated 390,000 children (under 15 years) contracted new HIV infections globally.[3] Although significant progress has been made in recent years, reducing new infant HIV infections from the peak of 560,000 in 2002/03 to 390,000 in 2010, the rate of the decline particularly in sub-Saharan African countries is not sufficient enough to eliminate new infant HIV infections worldwide.[3] The global plan to eliminate new HIV infections among infants requires reduction of the number of new infections to below 5% (<43,000 new infections) by 2015.[5]

HIV is one of the leading causes of death among children in Southern African countries. [1,2,33] In 2009, death due to HIV among children under 5 years was estimated to be 162,000 globally.[33] HIV/AIDS related child (under 5 years) mortality rate in 2009 in the African region is estimated at 198 per 100,000 population.[34] The Millennium Development Goals aim to reduce the death due to HIV among children by half in order to reach to the global target of reducing HIV related child deaths to below 81,000 by 2015.[3,35]

There is significant variation within regions in HIV prevalence trends among children and women of reproductive age group. In high income countries, the advent of highly active antiretroviral therapy, caesarean section, the utilisation of

appropriate technology, and better resource allocation has enabled the virtual elimination of mother-to-child transmission of HIV, reducing transmission rates to <2%. In most resource-rich countries infant HIV infection is a sentinel health event.[36,37] For instance, in the US, only about 67 infants were born HIV-infected in 2005.[36] Whilst in developing countries mother-to-child transmission is cause for significant proportion of infant morbidity and mortality.[37] According to UNAIDS estimate, 90% of the 1,800 new infant HIV infections and 1,400 HIV related illnesses occurring among children everyday occur in the developing world.[38]

In South Africa three times as many young women (13.6%) aged 15 to 24 years are living with HIV as young men (4.5%).[13] According to the 2011 antenatal survey, the overall national HIV prevalence among antenatal women aged 15-49 years is 29.5%.[29] According to the antenatal survey findings, the HIV prevalence over the last three surveys has stabilised around this level. In 2008 2009, and 2010 the HIV prevalence was 29.3% , 29.4% and 30.2% respectively. [29] However, there are variations in HIV prevalence rates across provinces. In 2011, the Northern Cape reported the lowest estimate of 17.0% while KwaZulu-Natal had the highest antenatal HIV prevalence in the country at 37.4%.[29] Mpumalanga has shown an increase in HIV infection from 35.1% in 2010 to 36.7% in 2011. [29]

Based on the above figures (antenatal HIV prevalence of 29%), it is estimated that close to 300,000 babies in South Africa are born exposed to HIV. [29] Without access to a programme to prevent mother-to-child transmission of HIV, around 90,000 (approximately 30%) of these babies will be HIV-infected every year by age six weeks.[15] Routine PCR testing laboratory data for infants aged <2 months indicates mother-to-child transmission in 2009 was 11% nationally, ranging between 8.1% (in Western Cape) and 13.1% (in Limpopo).[39] With the estimated 11% mother-to-child transmission rate, annually 33,000 infants become HIV-infected perinatally. The 2010 report from routine district health information system estimates a slightly higher (40,000) number of HIV-infected children.[3] With comprehensive PMTCT

interventions the neonatal infection rate could be reduced to less than 5% (<15,000), thus saving between 18,000 and 25,000 lives annually.

2.2. Global PMTCT targets and strategies

Prevention of mother-to-child transmission programmes influence the achievement of three MDG goals declared by the global health community: MDG 4 aims to reduce the mortality rate among children under 5 by two thirds; MDG 5 aims to reduce the maternal mortality ratio by three quarters; and MDG 6 targets to halt and begin to reverse the spread of HIV.[35] The 2001 UNGASS declaration also commits the 189 WHO signatory countries to reduce the proportion of infants infected with HIV by half in 2010 and to ensure universal access (greater than 80% coverage) to effective antiretroviral treatment, voluntary counselling and testing and provision of continuum of care.[4] Achieving these targets require adequate resource allocation and an emphasis on provision of high quality PMTCT services.

In 2005 an ambitious target was set by a high-level global partners forum in Abuja to attain an HIV-free and AIDS-free generation worldwide.[40] The United Nations General Assembly High-level Meeting on AIDS in June 2011 further endorsed this goal by adopting the political declaration on HIV/AIDS to eliminate new HIV infections among children by 2015.[5] Twenty two countries (India and 21 countries in sub-Saharan Africa) with a high burden of MTCT have been identified as priority countries for intensified support to achieve the UNAIDS HIV elimination goal. [5] With the endorsement of the new infant HIV infection elimination goal, countries target to increase coverage of PMTCT services to ≥95%.[5,41]

In order to achieve the MDG and UNAIDS goals, the UNGASS four pronged strategy is recommended which includes the following comprehensive PMTCT services: (i) primary prevention programmes to avoid HIV infection among women in reproductive age; (ii) provision of an integrated reproductive health programme, including provision of family planning to avoid unintended pregnancies; (iii) the routine offer of HIV counselling and testing at antenatal clinic, enrolment into

PMTCT programme and provision of ARV treatment/prophylaxis and postnatal follow-up/support for infant feeding; and (iv) treatment and care of HIV-infected infants and their mothers.

All four components of the UNGASS strategies need to be implemented in order to achieve the PMTCT goals. However current evidence shows PMTCT programmes are usually focused on the third and fourth prongs of UNGASS strategies and often neglect the first two prongs that are very crucial for elimination of new infant HIV infections. For instance, the 2009 UNAIDS report for low and middle income countries indicate whilst the coverage of antiretroviral medications for prevention of mother-to-child transmission has increased from 15% in 2005 to 53% in 2009, the contraceptive prevalence in sub-Saharan African countries remains low at 25%.[13] Emphasising the need for a comprehensive programme, a demographic model developed by Mahy et al, indicates even if effective antiretroviral treatments are provided using the 2010 WHO guidelines to 90% of HIV-positive mothers worldwide, the number of new infant infections cannot be reduced to elimination level by 2015, unless all four UNGASS prongs are implemented and the following progress is achieved: new HIV infections among reproductive women is reduced by half, unmet family planning needs are eliminated, the duration of breastfeeding is limited to 12 months and coverage of effective antiretrovirals is increased to 90%.[42]

2.3. Review of previous and current PMTCT antiretroviral guidelines

The first WHO recommendation to use short course ARV regimens to prevent mother-to-child transmission programme was issued in 2000 after evidence showing provision of short course ARV prophylaxis for HIV-positive pregnant mothers and their new born could result in a two to three fold reduction in mother-to-child transmission rates.[43-45] Following this finding, WHO recommended provision of azidothymidine (AZT) alone or in combination with lamivudine (3TC) or single dose nevirapine (sdNVP) to HIV-positive pregnant mothers for prevention of mother-to-child transmission.[45]

Most PMTCT programmes in developing countries were launched with the affordable and simple regimen single dose nevirapine (sdNVP) given at labour to the mother and to the infant within 72 hours after birth. However although sdNVP was less expensive and easy for scale up at national level, studies that examined the efficacy of sdNVP identified that single dose NVP only target transmission during labour and delivery and does not prevent antenatal and postnatal transmission; whilst dual therapy (AZT +sdNVP) given from 28 weeks of pregnancy till after 1 week of child birth was found more efficacious in preventing antenatal and early postnatal transmission.[16,46-48] Exposure to single dose maternal and infant NVP was also associated with increased occurrence of viral resistance. The HIVNET 012 study detected viral strains resistant to NVP at 6–8 weeks postpartum among 25% of women who received sdNVP.[49] The SAINT study in South Africa found a 67% rate of NVP resistance at four weeks postpartum among women who had received two doses of NVP.[50] Other studies showed adding up to a week of postpartum tail of twice-daily AZT/3TC to sdNVP might reduce the risk of resistance.[51]

Following the above findings the WHO guideline was updated twice in 2004 and 2006.[52,53] The 2004 revised guideline recommended to give maternal AZT from 28 weeks of gestational age and a one week infant prophylaxis in addition to sdNVP in order to prevent antenatal, labour and early postnatal transmission. The 2006 revised guideline added a one week maternal postpartum AZT for the mother in addition to the regimens recommended in the 2004 guideline. The 2006 guideline also recommended lifelong ART for women with CD4 counts ≤200 cells/µl or stage 3 or 4 clinical diseases.

Although these guidelines that recommended initiation of ARV prophylaxis from 28 weeks were distributed in 2004 to all national authorities, several years later many developing countries did not have adequate infrastructure to shift from sdNVP treatment to combination therapy for prevention of mother-to-child transmission.[52] The WHO guidelines also suggested countries consider readiness of their health system infrastructure before implementing the dual therapy guideline. Therefore, in

many sub-Saharan African countries sdNVP continued to be used as an interim measure while steps were being taken to enable more effective regimens to be delivered. [52] Currently, although many countries have shifted to a combination therapy for prevention of mother-to-child transmission, reports from low and middle income countries indicate significant health system and infrastructural problems still challenge the successful implementation of the PMTCT programme.[24,25,54]

In most provinces of South Africa sdNVP was the antiretroviral choice of treatment for prevention of mother-to-child transmission until 2008. In 2008 the national guideline was reviewed in accordance with the WHO 2006 guideline and recommendation was made to provide AZT from 28 weeks until delivery and 7 days infant post-exposure ARV and single dose NVP for HIV-positive pregnant mothers and their infants.[18]

Single dose nevirapine still continues to be used in some settings in developing countries. In 2010, thirty three countries globally reported that sdNVP was given for PMTCT mothers.[3] However, the overall percentage of women globally receiving sdNVP has significantly reduced from 49% in 2007 to 11% in 2010.[3] The 2010 WHO guideline states that sdNVP should be phased out from all countries.[20]

The new WHO guideline released in 2010 recommends two options (Option A or Option B) for prevention of mother-to-child transmission. Option A recommends initiation of HAART for all women who have CD4 cell counts of ≤350 cells/ µl, irrespective of WHO clinical staging, and for all women in WHO clinical stage 3 or 4, irrespective of the CD4 cell count. HIV-infected pregnant women who do not need HAART for their own health are recommended to start ARV prophylaxis from as early as 14 weeks of gestation (second trimester) or as soon as possible thereafter. For infants receiving breast milk, daily administration of infant NVP is recommended from birth (within 6−12 hours) or as soon as feasible thereafter, until 1 week after all exposure to breast milk has ended or, if breastfeeding stops before the age of 6 weeks, for a minimum of 4 to 6 weeks following birth.[20]

Option B recommends provision of HAART to all HIV-infected pregnant women irrespective of CD4 count or clinical stage starting from as early as 14 weeks of gestation (or as soon as possible thereafter) until delivery, or, if breastfeeding, until one week after all infant exposure to breast milk has ended. In this option, irrespective of the mode of infant feeding, it is recommended that maternal HAART should be coupled with daily administration of NVP (or twice-daily AZT) to the infant from birth (within 6−12 hours) or as soon as feasible thereafter until 4 to 6 weeks of age.[20]

Recently WHO announced Option B+ as an alternative treatment option for preventing mother-to-child transmission. This option recommends initiation of lifelong HAART to all HIV-positive pregnant mothers irrespective of CD4 count or clinical staging.[55] The evidence base on ethics, medical safety, economic and programme feasibility of Option B+ is sparse.[56] Currently most African countries have adopted either Option A or Option B treatment guidelines, whilst Malawi, and more recently Rwanda, have adopted Option B+ treatment guideline.[57,58] The new WHO guidelines are believed to be a major paradigm shift for PMTCT. The effectiveness of these options however remains to be assessed in operational settings rather than in clinical trials settings.

2.3.1. Current evidence on efficacy of antiretroviral regimens and rates of mother-to-child transmission

Prior to the adoption of the WHO 2006 guidelines, published scientific evidence and guidelines (particularly from Africa and Asia) focused on prevention of mother-to-child transmission occurring during labour and delivery. Whilst recently, with increasing evidence showing greater contribution of breastfeeding for mother-to-child transmission, more studies are exploring the efficacy of antiretrovirals for prevention of postnatal transmission.

Available evidence shows high transmission rate is associated with incident infections or untreated (not receiving antiretroviral prophylaxis/treatment) infections.

Transmission with incident infections (new infections occurring during pregnancy or breastfeeding) are estimated to be as high as 30% during peripartum and 28% postnatally within 6 months of maternal infection if no antiretroviral treatment is received.[59] Based on a number of randomized and non-randomized studies the peripartum (in-utero and intrapartum) transmission rates when no prophylaxis/treatment is given from several reports ranges from 15.3%-25.5%.[43,47,59-62] The Petra study conducted in Tanzania, South Africa and Uganda in a breastfeeding population reported 15.3% transmission rate at 6 weeks postpartum in the placebo (not received any prophylaxis or treatment) arm of the study.[60] Other studies conducted in formula feeding populations in US and France, and Thailand reported 25.5% and 18.9% in-utero transmission rates respectively among groups that did not receive any prophylaxis/treatment.[43,61] In two studies conducted in breastfeeding populations in Cote d'Ivoire the transmission rate at 4-6 weeks in the placebo arm (group not receiving any prophylaxis or treatment) of the studies were 21.7% and 21.8%, respectively.[47,62]

Several studies that assess the efficacy of different types of antiretroviral regimens confirm that significant reductions in MTCT can be achieved by providing effective ARV regimens. These studies assess the efficacy of HAART in comparison with ARV prophylaxis at different levels of CD4 count, the best timing for initiation of treatment and efficacy of maternal based versus infant based antiretroviral treatments/prophylaxis.[63] [64] [65,66] The Kesho Bora study was a randomized control trial that assessed the efficacy of HAART given from 28-36 weeks of gestation until cessation of breastfeeding for mothers with higher CD4 count (200-500 cells/µl).[63] The study found a 4.1% and 5.8% reduction in HIV transmission and HIV-free survival rate respectively at 12 months by providing HAART to women with CD4 count 200-500 cells/µl compared to providing AZT and sdNVP prophylaxis for women with the same CD4 count. This study was the first randomised controlled trial that provided evidence on the PMTCT benefit of initiating HIV-positive pregnant women with HAART even though they do not need it for their own health.

Similarly, the MTCT-plus study compared cohorts of HIV-infected women initiated on HAART at 24 weeks with women who were initiated on ARV prophylaxis at 28 weeks.[67] The women who were initiated on HAART had CD4 count ≤200 cells/ µl whilst those received ARV prophylaxis had CD4 count >200 cells/ µl. This study found a lower perinatal transmission rate (3.3%) among those who received HAART compared to those who received short course ARV prophylaxis with higher (>200 cells/ µl) CD4 count (5.7%). The results from this study suggest that the effect of ARV prophylaxis is lower compared to HAART irrespective of initiation of ARV prophylaxis at higher CD4 count level.

The Kisumu study is another study that initiated HAART for all breastfeeding HIV-positive mothers at 34 weeks of gestation till 6 months postpartum (breastfeeding cessation) reported that initiating HAART at higher CD4 count prevents transmission more effectively.[68] This study reported a lower (5.5%) transmission rate at 12 months among mothers with CD4 count >250 cells/ µl compared to mothers with CD4 count ≤ 250 cells/µl (6.7%) despite both groups receiving HAART.

Other studies indicate that duration of HAART is an important predictor of transmission. An observational study published by the Kesho Bora study group that assessed efficacy of antiretroviral treatment initiated during pregnancy for women with advanced (stage 4 or with <200 CD4 cells/ µl) HIV disease stage found that antiretroviral initiated at late stage of pregnancy (median time 7 weeks till delivery) among women with advanced HIV-1 disease resulted in a higher HIV transmission risk (7.5% transmission at 18 month) compared to ARV prophylaxis given to women with higher CD4 count (>500 cells/ µl) during pregnancy and delivery (5.8% transmission rate at 18 month).[64] The study highlighted adequate viral suppression will be difficult to achieve at delivery with a short duration of HAART provided to women with advanced HIV-1 disease, thus recommended to initiate HAART as early as possible for women with advanced HIV-1 disease.

Similarly, the Dream study which analysed the HIV transmission rate among a cohort of mothers who received lifelong HAART from 14 weeks (<350 cells/ µl) or from 25 weeks (<350 cells/ µl) till weaning concluded that short duration of prenatal HAART (<30 days) is strongly associated with higher (AOR:2.4) infant HIV-1 transmission and/or death at 6 months postpartum compared to HAART initiated 30 days prior to delivery. Thus the study highlighted the importance of early initiation of HAART for women eligible to receive HAART.[69]

Other studies compared lifelong maternal HAART with infant ARV prophylaxis given for the duration of breastfeeding for prevention of postnatal transmission.[65,66] The BAN study which compared maternal triple antiretroviral prophylaxis with infant nevirapine prophylaxis suggests that both (maternal and infant ARV) interventions reduced the risk of transmission equally, however infant nevirapine was more advantageous as it is low cost and has manageable toxic effects.[65]

The above and other studies illustrate the benefit of extended duration of HAART and initiation of HAART at higher CD4 counts. Transmission rates reported from the above studies varied due to different duration of treatment and disease stage. The transmission rates among women who received HAART in the MTCT-plus study was much lower (3.3% early transmission and 1.9% late postnatal transmission) compared to women who received HAART in the Kisumu (5.5% at 12 month) and the Kesho Bora studies (3.3% at 6 weeks and 5.6% at 12 months) mainly due to varied duration of treatment.

According to reports from several studies, including ones mentioned above, perinatal transmission rates can be reduced to 9.4% - 12.3% with single dose Nevirapine.[47,65,70,71] The SWEN study conducted in Ethiopia, India and Uganda reported a six weeks cumulative transmission rate of 9.4% for women receiving single dose nevirapine (in the control group).[70] A multi-centred random controlled trial study in South Africa reported 12.3% transmission at 8 weeks among those who received single dose nevirapine.[71]

The peripartum transmission rate is significantly lower (ranging from 2.3% to 5.3%) when dual therapy is provided per the WHO 2006 guideline.[16,47,59,67] A randomised controlled trial conducted in Thailand during 2001-2003 reported peripartum transmission rate of 2.3% among formula fed infants who received dual therapy (maternal and infant AZT and NVP).[16] The ANRS Ditrame study conducted in a predominantly breastfeeding population in Cote d'Ivoire reported a six weeks transmission rate of 5.3% among those who received maternal and infant AZT and sdNVP.[47] In the same study the addition of maternal 3TC reduced six weeks transmission to 4.7%. Another study in Cote d'Ivoire among primarily formula-fed population reported a four weeks transmission rate of 3.1% among those who received maternal AZT +3TC+sdNVP and infant AZT and sdNVP.[67] The low transmission rate in this group was also due to the high CD4 count of mothers, as all mothers had CD4 count >350 cells/ µl.

The Kesho Bora study showed that with provision of ARV prophylaxis from 14 weeks of gestation for mothers with CD4 count 350-500 cells/ µl, and with extended postnatal ARV regimen for infants until one week after breastfeeding the transmission rate at 6 weeks could be lowered to 2.9%.[63] In the same study among mothers who received dual prophylaxis (AZT and sdNVP per the WHO 2006 guideline) with CD4 count 350-500 cells/ µl the peripartum transmission rate was 3.4%.

Postnatal transmission rates with no postnatal antiretroviral provision are estimated to be 1.57% and 0.51% per month of any breastfeeding for CD4 count ≤350 cells/ µl and CD4 count >350 cells/ µl, respectively.[59] Initiating HAART for those with CD4 count ≤350 cells/ µl during pregnancy could reduce the risk of postnatal transmission to 0.16% per month of breastfeeding.[59] For mothers with CD4 count above 350 cells/ µl, provision of infant NVP using Option A WHO guideline or providing maternal HAART using WHO Option B guideline could reduce postnatal transmission to 0.2% per month of breastfeeding.[59]

The above transmission rate reports in the context of antiretroviral treatment and prophylaxis are measured in clinical trial settings rather than at operational settings. Hence the operational effectiveness of currently recommended antiretroviral regimens remains to be assessed at a programmatic level.

2.3.2. Maternal and infant adverse events and drug resistance

Antiretroviral treatment provision for HIV-positive women requires careful consideration of the balance between the mother's health needs, the need to reduce transmission, and the adverse effects of antiretroviral treatments. Few studies report adverse effects and drug resistance of antiretroviral treatment in the perinatal and postnatal periods.

In the MTCT-plus study drug related maternal adverse events were more common among women who received HAART compared to women received short course ARV prophylaxis.[67] The adverse events reported in women who were on HAART included grade 3 or 4 adverse events attributed to HAART, mucocutaneous rash attributed to NVP, grade 4 liver toxicity attributed to NVP, and severe anaemia attributed to AZT. But none of these adverse events were fatal. In the same study, infant birth weight was low among infants whose mothers received HAART compared to infants exposed to maternal ARV prophylaxis.

The Kesho Bora observational (cohort) study reported a higher rate of low birth weight but lower ARV related toxicity among women and children exposed to HAART compared to those exposed to short course ARV prophylaxis.[64] In this study, low birth weight was twice as high in the HAART group compared to the ARV prophylaxis group, although this was not significantly different which was stated in the paper as due to sample size limitation. The lack of significant difference could also be due to lack of actual difference in birth weight between the two groups comapred (i.e. the difference noted could be due to chance alone). Mothers in both the Kesho Bora and the MTCT-plus studies were on HAART because they were at

advanced stage of the disease; hence it is not known whether the cause for low birth weight is exposure to HAART or due to the mothers advanced disease stage. Other studies report hematologic abnormalities on infants were observed in the ARV prophylaxis group more than in the HAART group.[72]

Development of drug resistance is another concern in the provision of antiretroviral treatment for prevention of mother-to-child-transmission. A secondary analysis from the Kisumu study reports occurrence of drug resistance mutation among 67% of HIV-positive infants whose mothers received a NVP based or nelfinavir based triple ARV regimen from 34 weeks throughout the breastfeeding period.[68] The study reports ingestion of antiretroviral drugs through breast milk may have contributed to the emergence of HIV drug resistance mutations and recommend while a combination ART treatment is a successful PMTCT intervention, selection of less resistant ARV drugs and early infant diagnosis to identify HIV-positive infants before they develop drug resistance is crucial. Similarly, the PACTG P1030 study reports a quarter of a cohort of HIV-infected infants were infected with drug-resistant HIV after taking nevirapine (NVP)-containing PMTCT regimens.[73]

Given, the WHO Option B treatment recommendation to provide HAART until cessation of breastfeeding and to stop HAART after cessation of breastfeeding for mothers with high CD4 count, the impact of interrupting HAART after termination of breastfeeding has been assessed by few studies. A secondary analysis of the Kesho Bora randomized controlled study shows interrupting prolonged HAART prophylaxis among mothers with CD4 count >350 cells/ µl had no effect on HIV-1 progression following cessation of HAART compared to women in the ARV prophylaxis group.[72] In the same study, the women in the HAART group had lower disease progression during the time they were on HAART compared to the ARV prophylaxis group. Adverse events in mothers and infants were similar in both the HAART and ARV prophylaxis group. A similar finding was reported in the Dream study. In the Dream study, HAART interruption following extended PMTCT use was

associated with improved health parameters in the first 3 years following interruption.[69] Both studies suggest that interruption of HAART with cessation of breastfeeding does not lead to any adverse effect or deterioration of health.

In summary, results from the above studies indicate that highly active antiretroviral treatment has higher efficacy compared to antiretroviral prophylaxis at any CD4 count level. Duration of treatment and initiating HAART at higher CD4 count provided more advantage to achieve lower transmission rates. Whilst more side effects were documented with initiation of HAART, the studies have showed that side effects were not fatal and no side effect was reported by stopping HAART after cessation of breastfeeding. However more studies are needed in order to understand the safety of highly active antiretroviral treatment as countries rollout the new (Option B and B+) treatment guidelines.

2.3.3. Biomedical and Health System risk factors for MTCT

Transmission rates are affected by a number of factors including viral, maternal, obstetrical, fetal and infant factors. Maternal and viral related factors include: lower CD4+ counts, advanced clinical stage, high maternal viral load, procedures during pregnancy that cause placental/amniotic sac inflammation, long duration of ruptured membranes, procedures during delivery (episiotomy), mode of delivery (vaginal delivery) and viral genotype (HIV type C) are reported as factors that increase the risk of mother-to-child transmission.[47,59,67,74-82] There is limited evidence on the effect of viral geno type on transmission, although a few studies suggest viral geno type as a probable risk factor of transmission.[75] The strong link between viral load and transmission is reported in several studies.[77,80,81] In a New York study women with detectable level of viral load had almost six times higher risk of transmission than those who had undetectable viral load.[81] Transmission rates are also higher in incident (new infection during pregnancy or breastfeeding) maternal infections.[59]

Elective caesarean section has been shown to be a protective factor in some prospective studies [74,76] In a study by Newell transmission rate was 3.8 times higher in children born before 34 weeks of gestation.[78] The risk of transmission in breastfeeding also varies. Mixed-feeding, the presence of infection - breast conditions such as mastitis, oral thrush, nipple cracks - increase MTCT risk during breastfeeding.[79,82] Exclusive breastfeeding with postnatal maternal HAART reduces transmission significantly.[59]

Whilst there are studies that assess the association between socio-economic (SES), cultural, demographic and health system factors and coverage of services, few studies assess the association between these health system and socioeconomic factors and transmission rates.[a] Stringer et al. report failed coverage of nevirapine was associated with younger maternal age (<20), and fewer antenatal visits (2 or 3).[7] In a study in Lusaka, non-adherence to NVP was associated with home delivery or hospital delivery showing the impact of poor integration of PMTCT service at hospital and community level.[83] In the same study poor infant health status was also associated with poor adherence to NVP. However, these studies do not assess the direct relationship between SES/health system factors and transmission.

Few studies report significantly influential SES factors on transmission. A study in Kenya report neither socioeconomic status nor cultural factors (disclosure/stigma) were associated with transmission.[84] A study in South Africa reported maternal age of > 25 years as significant risk factor for transmission.[85] A study in Rwanda showed unmarried status carried higher risk of undisclosed HIV status, and undisclosure of HIV status was independent risk factors of transmission [86]

Other studies show the link between knowledge of HIV, education, adherence to treatment and MTCT using a combination of theoretical and empirical evidences.[87,88] Wenger et al. report a good level of understanding about HIV by the patient, a belief

[a] Key words used in Medline search: risk factors and transmission, socioeconomic status and transmission, health systems and transmission, risk factors and infant HIV infection, socioeconomic status and infant HIV infection, health systems and infant HIV infection, nevirapine coverage and risk factors.

that HAART is effective and prolongs life and recognition that poor adherence may result in viral resistance and treatment failure, could impact favourably upon mothers ability to adhere to treatment.[89]

The link between adherence to treatment and transmission rate was demonstrated by Boateng et al.[90] No study could be found that assess the impact of health system factors (including PMTCT service coverage and health infrastructure) on transmission rate. Modelling studies however illustrate transmission rates that can be achieved with different levels of PMTCT services coverage. According to these studies higher (>90%-95%) PMTCT service cascade coverage is required in order to reduce transmission rates to virtual elimination level.[41,42]

2.4. Coverage of PMTCT services – the PMTCT cascade

2.4.1. PMTCT service coverage globally

Antenatal HIV testing

The latest UNAIDS data (2010) indicate nearly two thirds (65%) of pregnant women in low and middle income countries do not receive antenatal testing.[3] The antenatal testing coverage in Eastern and Southern African countries is slightly higher (most southern African countries have above 80% coverage) compared to east, south and south-east Asia which had 18% and 30% antenatal testing coverage in 2009 and 2010, respectively.[3]

UNAIDS reports in 2010 approximately 68% of the estimated total number of 1.49 million pregnant women living with HIV know their HIV-positive status.[3] Countries that have implemented innovative strategies to improve the antenatal testing coverage have shown significant progress in increasing their antenatal testing coverage. Rwanda is one of these countries which has substantially improved antenatal testing rates from 16% in 2003 to 80% in 2009 through using a family centred approach and male involvement.[3,91] Reports indicate most countries (98 out 119 UNAIDS reporting countries) have now adopted policies on provider-initiated counselling and HIV testing for all pregnant women.[3] However although the policy

exists on paper, a number of pregnant women visiting antenatal clinic in sub-Saharan African countries miss antenatal testing due to gaps in translation of policy.[3]

Uptake of antiretrovirals

In 2010 the coverage of effective maternal antiretroviral (both prophylaxis and therapy excluding sdNVP only regimen) for prevention of mother-to-child transmission globally was 48%.[3] Additionally 11% of pregnant women received single dose nevirapine which was no longer recommended.[3] The UNAIDS target is to increase maternal antiretroviral coverage to above 90% by 2015. In addition, with the updated WHO 2010 guideline, 90% of women are expected to be covered with postnatal maternal or infant antiretroviral treatment or prophylaxis during the breastfeeding period.

The number of HIV-positive women assessed for eligibility of HAART in 2010 was 45% globally. Thirty four percent (34%) of eligible women received HAART.[3] In developing countries infrastructural gaps (such as lack of on-site CD4 count service, gaps in courier and transportation systems) and poor referral and tracking systems remain as major reasons for low coverage of HAART.[54,92,93]

Uptake of Early infant diagnosis(EID) services and cotrimoxazole

In 2010 from 65 countries reporting on EID coverage, 28% of infants were reported to have been tested for HIV in the first two months of life.[3] Southern African countries including South Africa (68%), Lesotho (78%), Namibia (62%), Swaziland (54%) and Botswana (53%) reported above 50% coverage of services to diagnose early infant HIV infection.[3] Coverage of ARV therapy among HIV-infected children was 23% in 2010.[3] Both early infant diagnosis and paediatric ARV initiation services need more attention globally in order to achieve the UNAIDS target to provide early ARV treatment for all HIV-infected infants by 2015. In addition, cotrimoxazole coverage was 13% and 23% in 2009 and 2010 respectively, also

showing poor coverage of this essential drug for prevention of opportunistic infections among uninfected HIV-exposed infants.[3]

2.4.2. National PMTCT service coverage in South Africa

Limited reliable national data exists on the coverage of PMTCT cascade services in South Africa. The national accelerated plan sets national targets to achieve 95% coverage on the following PMTCT indicators by 2011: 95% HIV testing rate (among pregnant women), 95% ARV (dual prophylaxis both for infant and mother) prophylaxis coverage, and 95% six weeks PCR testing (and initiation of cotrimoxazole) coverage.[94] DHIS data reports current national aggregated uptake of these PMTCT indicators, and had limitations as explained in section 1.3 above. Given these caveats the following data are currently available.

Antenatal HIV testing and HIV prevalence among antenatal women

According to DHIS data *antenatal attendance rate* in South Africa is high, at 94%, and antenatal HIV testing rate has impressively increased from 49.9% in 2005/06 to 86.7% in 2008/09.[95,96]

Uptake of CD4 count and ARV prophylaxis

The DHIS data on uptake of CD4 cell count testing and receipt of results is incomplete with data missing and of unreliable quality (with reports above 100% coverage), hence there is limited data on national uptake of CD4 count services.

According to the 2009 DHIS report, there has been an overall increase in the uptake of ARV prophylaxis/treatment from a national uptake of 65% in 2006/07 to 83% in 2009. However, according to the UNICEF country progress report, in the same year 37% of women received single-dose nevirapine only, despite a change in national policy that includes short course AZT from 28 weeks.[96-98] The same report indicates

only 56% of HIV-exposed infants received ARV prophylaxis to prevent mother-to-child transmission of HIV.[98]

Uptake of Early infant diagnosis services

Routine data on uptake of EID services comes from the DHIS and from the National Health Laboratory Services (NHLS). DHIS reports the number of babies who are PCR tested at six weeks after birth as a proportion of estimated live births to HIV-positive women. However this is a new indicator that was only introduced into DHIS data in 2008, and there is no national figure yet due to differences in the denominator used between provinces (Western Cape province use a birth cohort register to track cohort data for mother-infant pairs while other provinces estimate the denominator) and missing data. NHLS data indicates that uptake of EID services for infants age <2months has increased from 31.4% in 2008 to 51.4% in 2010.[39] However both data use number of live births as a denominator, hence do not reflect the true PCR testing that would be measured if actual cohorts of infants were tracked. Similar to this, the antenatal HIV testing rate, and the uptake of CD4 count and ARV indicators are measured using proxy denominators rather than actual tracking of data for mother-infant pairs starting at antenatal visit.

Although inadequate, due to limited data availability, these uptake indicators have been used nationally and internationally to track countries progress towards achievement of national and international goals. However, a critical indicator for the impact of the PMTCT programme is the proportion of women who successfully go through and complete the PMTCT cascade.

2.5. Challenges in the PMTCT programme

2.5.1. Dropout /attrition from the PMTCT cascade

HIV-positive pregnant mothers and children born from HIV-positive mothers require PMTCT follow-up services starting from first antenatal visits in early pregnancy till 18-months of infant's age. Although many countries are moving towards national

coverage of services for PMTCT, loss to follow-up during antenatal, delivery and postnatal periods remain a major challenge. According to a recent review by Khalembo and Zgambo (2012), cumulative losses in sub-Saharan African PMTCT programmes are estimated to range from 20% to 28% during antenatal care, about 70% at four months postpartum and close to 81% at six months after birth.[99] The same study reports very few children under the age of one get diagnosed with HIV and receive treatment. Similarly, a four-country African study of HIV-positive mothers showed half of the children exposed to HIV during pregnancy and childbirth did not receive nevirapine at the time of delivery.[7]

A number of community- and provider-related operational and cultural reasons for loss to follow-up are documented in the literature.[100-106] These include: fear of stigma, discrimination, household conflict/divorce on disclosure of HIV status; lack of support from husbands; not being prepared for HIV testing; social and cultural taboos; long waiting times at the antenatal clinics; and inability to afford transport costs related to the long distances to hospitals.

In South Africa the PEARL study reports 17.6% of all mothers who were dispensed with maternal nevirapine did not take (ingest) the nevirapine.[7] The study reports younger mothers and those who made fewer visits to the health facility before giving birth were significantly less likely to have taken the dose of nevirapine, and their infants were less likely to have received a dose of nevirapine after birth. A descriptive study conducted by Jones SA, Sherman, G and Varga, A in the Coronation Women and Children's Hospital South Africa reports socioeconomic factors such as poverty, geographical relocation and a lack of paternal support affect the capacity of families to comply with the PMTCT follow-up programme.[107] Women's education also plays a major role in accepting and honouring PMTCT follow-up visits. Two studies from Malawi and Ethiopia report mothers who were less educated were less likely to attend PMTCT follow-up services.[108,109] At health facility level, lack of functional community based organizations (CBOs) working with PMTCT and paediatric HIV programmes is often reported as a major barrier in

tracking lost to follow-up mothers and infants. On the contrary, good coordination between the health care facilities and the community and computerised tracking systems are reported to enable tracing loss to follow-up mother-infant pairs – yet in most developing countries these best practices are not implemented widely.[110]

The above and other research evidence adequately show provider related gaps and social barriers that influence the performance of PMTCT follow-up programmes. These identified gaps remain to be addressed in most sub-Saharan African countries.

2.5.2. Health systems constraints

Health services in sub-Saharan African countries face severe resource constraints to run a successful PMTCT programme. Lack of health care infrastructure, limited human resource, and competing public health priorities within limited health care budgets remain major challenges in the implementation of the PMTCT programmes in sub-Saharan African countries.[24,25]

The capacity of health care facilities is a major determinant factor for provision of PMTCT services. In resource-rich countries, one of the promoting factors for low transmission rates is the high coverage of PMTCT services that are ensured through usage of appropriate technology, adequate human resources, and uninterrupted supply of antiretrovirals. Availability of such resources in high income countries has enabled implementation of innovative interventions such as universal antenatal testing, integrated MCWH and PMTCT services and computerised tracking systems. In developing countries, although internationally recommended interventions, such as universal testing are adopted at policy level, their consistent implementation is challenged by health systems constraints such as shortage of human resources.[3,24] The literature recommends strategies such as geographical redistribution of professional health care personnels, task shifting and capacity building, which could be used to curb the human resource shortage problems in sub-Saharan African countries.[23]

On the other hand, the literature shows inaccessible or non-functional health facilities, and long distances are major impediments for pregnant women to access PMTCT programmes.[111] There also exists lack of clarity regarding positioning of PMTCT within the health service delivery context. Whilst there exist different integration models to provide PMTCT interventions as part of existing facility and community based MCWH (maternal, new-born and child health) programmes, challenges such as severe shortage of human, logistical and technical resources, as well as funding weaknesses interfere with the full implementation of integrated PMTCT programmes.[26]

2.5.3. Access to Antiretroviral drugs and decentralisation of HAART services

Although inadequate, some progress has been made in increasing the coverage of antiretroviral treatment in developing countries. Thus far providing antiretroviral prophylaxis to pregnant women living with HIV has prevented more than 350 000 children from acquiring HIV infection globally since 1995.[3] Approximately 85% of these new infant infections averted were from sub-Saharan African countries.[3] As of December 2010 the antiretroviral coverage among people in need of treatment in low and middle income countries was 47%.[3] Women represented 53% of people who received HAART and 51% of those who are in need of HAART.[3] Overall a 27% increase of HAART coverage is observed in low and middle income countries between 2009 and 2010.[3] The number of health facilities providing HAART treatment in 2010 also increased by 22% since 2009 in sub-Saharan African countries, this represented an average number of 484 people receiving antiretroviral therapy per health facility in sub-Saharan African countries compared to 297 globally.[3]

South Africa has the largest antiretroviral (HAART) treatment programme in the world, with about 1.8 million people estimated to be taking antiretrovirals by April, 2011.[112] antiretroviral services are also available in more than 2552 approved

facilities countrywide.[112] Roughly 50% of individuals in need of HAART were receiving treatment in South Africa in 2011.[3,113]

However, with the new (2010) WHO guideline that recommends initiation of ARV treatment for all mothers (Option B) or for mothers with CD4 count below 350 cells/ µl (Option A), the number of mothers that need to go on HAART increased by about 50%, and HAART spending (drugs, tests, service delivery costs) is expected to grow from around $3.3 billion to $9.5 billion by 2015.[114] In South Africa it is estimated that with the new South African adult and adolescents treatment guideline implementation in 2010 (eligibility at ≤350 for pregnant women and TB/HIV co-infected; early paediatric treatment; and immediate treatment for adults with CD4 ≤200 cells/µl for all others) people who are in need of treatment will increase from 1.5 million in 2010/11 to about 3.2 million by 2016/17.[115]

In order to meet the increasing demand of antiretrovirals, WHO promotes a public health approach to HAART delivery.[23] In this approach, standardised simplified treatment protocols, decentralised service delivery, negotiating drug prices, and selection of less costly ARV treatment are recommended. Task shifting is also recommended as a vital step for simplifying and enabling expanded provision of HAART.[116]

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2.6. Methodologies to measure MTCT and PMTCT Services Cascade

Prospective follow-up cohort study

Although there is no national study conducted to determine transmission and coverage of services along the PMTCT cascade, there is research conducted to estimate transmission and coverage of PMTCT cascade services in selected sites, using different approaches (methods) to establish the coverage of PMTCT cascade.

The most rigorous but expensive approach, which was used by the Good Start study, is a prospective home based follow-up of a cohort of mother infant pairs - at three

purposively selected sites - recruited during the antenatal or immediate post-delivery period. The Good Start study conducted a medical record review at delivery and followed mother-infant pairs at 3,5,7,9,12,16,20,24,28,32 and 36 weeks post-delivery.[117] Blood samples were collected at 3, 24 and 36 weeks. This type of method has high internal validity and gives robust estimates of the PMTCT cascade, as well as 9-month outcome measures of infant HIV-free survival rates. However, the cohort approach is resource-intensive, time consuming, and is not always generalizable at country level due to the limited representativeness of the cohort, bias due to loss to follow-up and the "Hawthorne" effect[118] (subjects improve or modify their behaviour simply in response to being followed, since investigators would be ethically bound to provide cohort participants with the best possible care e.g. referral of mother and infants for HIV care and treatment), members of the cohort could thus be poorly representative of the population as a whole. In addition, prospective approaches, although ideal, are not practical for routine monitoring in most developing countries given their expense and complexity.

Facility based cord blood surveillance plus a population based survey

The PEARL study used a facility-based process data and cord blood surveillance plus a structured evaluation and a community-based survey to assess coverage of the PMTCT cascade and transmission rates.[7,21,119] The PEARL study recommends the modification of the Demographic and Health Survey (DHS) to include gathering of data on maternal HIV history, PMTCT programme enrolment, interventions received, infant feeding practices and household child mortality. This recommendation has been argued to be challenging due to requirements of sample size larger than currently allocated sample sizes for DHS.

The facility based component of the PEARL study involved a collection of umbilical cord blood sample from 43 randomly selected facilities in 4 African countries aiming to measure antiretroviral prophylaxis coverage. The study defined coverage of antiretrovirals for preventing mother-to-child transmission as the proportion of mother–infant pairs with confirmed nevirapine ingestion. Maternal ingestion was

confirmed by the presence of nevirapine in the cord blood, and infant ingestion was confirmed by reviewing relevant documentation. This study assessed maternal adherence to nevirapine by testing umbilical cord specimens. The study found 27% of mothers did not adhere to the treatment prescribed.[7] The results from this study however could only represent mothers who deliver at institutions. This approach is likely too costly and complex for country wide implementation.

Facility based surveys

Surveys with retrospective information gathering are another approach to collect PMTCT cascade and transmission data.[6] This approach needs shorter study periods, and in areas with high immunisation attendance rate, population level representative outcomes could be reported from facility-based surveys conducted at 6 weeks immunisation visits. [6] Retrospective gathering of information may introduce recall bias, unless recall periods are short. The results from facility based surveys will not represent infants who do not attend or who died before 6 weeks immunisation visits. In research settings, conducting a national facility based survey could have high cost, but if facility based surveys could be incorporated into routine 6 weeks immunisation services, this method will be most cost-effective. Facility-based surveys are not also ideal for measuring longer term postnatal outcomes due to high loss to follow-up rate often occurring due to societal barriers, distance, financial and time commitment needed from participants to attend regular facility-based follow-up visits. Community based studies (e.g. home visits) are more appropriate for follow-up studies as participants can be visited in their home/or at other nearest/convenient location.

In conclusion, the main difference among the three methodologies discussed in this section is with their study population (facility-based versus population-based) and study design (cross-sectional versus cohort). Whilst each method has its own advantages and limitations (explained above), in countries with high immunisation coverage, cross-sectional facility based surveys may be the most efficient method for evaluating PMTCT programmes for the early postpartum period.[120] Nonetheless,

cross-sectional studies conducted to date are limited to certain geographical areas and do not provide estimates of the national coverage of the PMTCT cascade.[6,121] Thus, a national study is required to monitor progress towards achievement of national and international targets set to reduce mother-to-child transmission rates.

Chapter 3: METHODOLOGY

3.1. Study components and study design

Two quantitative studies were carried out in randomly selected facilities within the nine provinces of South Africa. First, a cross-sectional facility-level situational assessment was undertaken in 680 selected facilities using key informant (health care provider) interview and record review methods to assess the coverage of EID services and the capacity of the health system to provide PMTCT and EID services.

Following the situational assessment, a facility based cross-sectional survey (SAPMTCTE survey) was conducted to gather caregiver interviews and infant blood samples from caregiver/mother-infant pairs (4-8 weeks infants) attending six weeks immunisation (1st DTP Dose) visits in sampled facilities. The HIV status of the infants was determined based on the approach recommended by Rollins et al.[6] – HIV antibody testing was performed on infant blood samples (dried blood spots) to screen for the presence of maternal HIV antibody, which was a marker for HIV-exposure of infant, this was followed by DNA PCR test for those infants who are HIV-exposed. This study design was field tested and proven to be effective in the South African context. [6,121] The high attendance rate (>95%)[122] of six weeks (DTP1) immunisation services in South Africa provided an opportunity to provide estimates that closely represent all 4-8 weeks old infants. Antenatal and PMTCT histories and infants blood samples were collected from all infants visiting six weeks immunisation regardless of whether the mother and/or infant received any PMTCT interventions. This method was relatively rapid to undertake compared to longitudinal study designs.

The combined data from the two study designs ((i) facility level situational assessment and (ii) the six weeks individual level PMTCT survey) enabled this study to examine the effect of health service measures (i.e. service availability, guidelines for service provision, human resource and other infrastructure) on service utilisation (uptake/coverage of services) and PMTCT outcomes (transmission rates).

3.2.Sample size, sampling design and justification thereof

Facility sampling, sample size and sample frame

A two-stage stratified sampling method was used to select sample facilities for both studies. In the first stage, target facilities (Primary sampling units - PSUs) for both the situational assessment and PMTCT survey were randomly sampled using a probability proportional to size sampling methodology. The sampling frame comprised all public primary health clinics (PHCs) and community health centres (CHCs) throughout the country. Three thousand three hundred ninety (3390) CHCs and PHCs reportedly administering 1st DTP doses in the South African national district health information system (DHIS 2007) were eligible for inclusion in the sampling frame.[123] Satellite and mobile clinics were excluded as they only operate for a few hours a week. Private facilities and public hospitals were not primary sites for immunisations therefore they were not included in the sampling frame.

Facilities in the sampling frame were stratified into four groups based on the 2007 DHIS data and the 2009 antenatal HIV prevalence estimates: small facilities with <130 annual immunisation (DTP1) coverage, medium size facilities with 130 -300 annual immunisation (DTP1) coverage, large (annual immunisation/DTP 1 coverage >= 300) facilities with antenatal HIV prevalence below 29% (the national HIV prevalence estimate), and large facilities (>= 300 annual immunisation /DTP1coverage) with antenatal HIV prevalence above or equal to 29%. [123,124]

This sample size was calculated to enable providing a national and provincial level estimate of transmission rates and PMTCT cascade coverage. The sample size of medium and large facilities was determined based on antenatal HIV prevalence and transmission rate estimates using the following methodology:

1. The overall infant HIV prevalence of each province was estimated using the antenatal HIV prevalence data, the transmission rate estimates from two KwaZulu-Natal (KZN) surveys (estimates of transmission rates for SdNVP and no treatment were taken from Rollins[6] while the transmission rate for Dual

Therapy comes from the recent KZN survey[125]) and the coverage of ARV prophylaxis in each province from DHIS report. (Appendix I)

2. In the next step precision levels were specified. The first sample size calculations were based on a fixed relative precision of 30% across all provinces. The Western Cape Province had the lowest estimated infant HIV prevalence (with 1.9% infant HIV prevalence at six weeks). Specifying a 30% relative precision for Western Cape led to a sample size of nearly 4000 infants for this province alone. The numbers for the other provinces are also indicated in the table (appendix I). This approach resulted in an imbalance in field work effort required. The biggest effort would be required in the province with the lowest expected prevalence. It was felt that given the low infant HIV prevalence in Western Cape a larger relative precision would be acceptable. For the Western Cape Province it was felt that a $\pm$1% precision would be adequate for public health purposes. With this precision, the upper limit of the 95% confidence interval was around 3% and this equates to a relative precision of 51%. For the provinces with a higher expected prevalence a reasonable precision was needed. In Gauteng province infant HIV prevalence is estimated at 8.2% and therefore a higher precision was required to monitor this transmission. A$\pm$2% precision was decided to be reasonable. The precision required and specified for the nine provinces thus vary from $\pm$1% to $\pm$2%. In general provinces with a higher prevalence had a lower (better) relative precision. The relative precision implemented in each province is indicated in the table (Appendix I). The benefit of this is that better equity in sample size is achieved between provinces.
3. Sample size was calculated using nQuery Advisor Version 7 software for specified precision levels for each province (Appendix I)
4. Sample size was doubled using design effect of 2 to take into account for the clustering effect at facility level (Appendix I)
5. Based on the above calculation of sample size, for the six weeks PMTCT survey a total sample size of 12200 infants nationally and 700-1800 infants provincially was required.

6. The sample size calculated for the province (700-1800 infants) was allocated proportionally (population proportionate to size) between the strata (medium, large and large and high prevalence strata) in each province.
7. For each stratum, using immunisation data from DHIS, the median number of children expected in a fixed time period (3-4 weeks) was calculated. This number was then used to determine the number of clinics that need to be sampled in each stratum in each province to obtain the number of children specified in Appendix I.
8. Clinics were then randomly sampled proportional to size (PPSSYS) within each stratum using the detailed information of the sampling frame. The method operates under the without-replacement-type selection as described in Lehtonen (1994).[126] This sampling method was implemented in excel.

The sampling design of each province is given in Appendix I. It contains the summarised information from the sampling frame and the number of facilities and the number of infants sampled to provide the sample size required.

Provincial sample size adjustment and justifications

In three provinces the following sample size adjustments were made:

Eastern Cape has a large number of medium sized facilities (130-300 immunisations per annum) therefore requiring that a substantial number of these facilities be sampled. This would lead to an unfeasible sampling burden in this province. For this reason we oversampled facilities in the larger stratum and under sampled facilities in the smaller stratum. This oversampling fraction is 6%.

Mpumalanga used the same sampling strategy described for the Eastern Cape Province. The oversampling fraction was 7%

Northern Cape has the largest geographical coverage in the country and has enormous distance between facilities. Hence, taking into account our logistical capacity, decision was made to limit the number of facilities sampled in each of the stratum, and in compensation for the reduced number of facilities, the duration of

time spent in each facility for data collection was increased to a median number of 4 weeks.

Based on this, nationally, 580 facilities (34-79 provincially) were selected from medium and large size facilities for inclusion in the situational assessment and SAPMTCTE survey (Appendix I). For the situational assessment, an additional 100 facilities (10-20 facilities per province) were randomly sampled from small (< 130 immunisation) facilities, thus the total number of facilities sampled for situational assessment were 680 facilities. Small facilities were not included in the six weeks PMTCT survey as it was not logistically feasible, hence 580 facilities were planned to be visited for the six weeks survey.

3.3.Situational assessment

The situational assessment was conducted between January and May 2010 on 580 facilities that were sampled for the situational assessment and PMTCT survey and an additional 100 facilities sampled for situational assessment only as described in the previous section. The second stage sampling in the situational assessment was the selection of key informants. Three health workers and a district information officer were purposefully selected from each facility for key informant interviews as follows: one clinic manager (or representative manager in the absence of a manager), one immunisation nurse and one child health (IMCI) nurse who were on duty at the time of the assessment, and the health information officer of the district (where available each facility's information officer) were interviewed in each facility using structured questionnaires (appendix II). In facilities that had more than one immunisation nurse/IMCI nurse on duty, one nurse from each unit was randomly (simple random sampling) selected. A self-administered structured questionnaire was used to obtain quantitative data from respondents. The questionnaire was adapted from previously tested tools (Doherty, Besser and Donohue (2003) and Doherty and McCoy D et al. (2005)).[127,128] Participants were interviewed face-to-face by trained fieldworkers. A four days training was given for field workers using standard manuals (SOPs). The

questionnaire was piloted in two clinics prior to field work. Data was collected over a one month period in each province.

Both open ended and close ended questions were used to collect the data. The questionnaire had four sections: a section for facility managers, a section for immunisation nurses, a section for IMCI nurses, and a section for district information officers.

Topics covered in the questionnaire include:

Organization of the health system for identifying HIV-exposed infants, infant HIV testing, transportation of HIV-related maternal and infant blood specimens, postnatal maternal HIV testing and linkages to HIV-related care. This included:

- human resources for EID and PMTCT services;
- distribution of PMTCT/ARV services;
- procurement and stock control of supplies for infant HIV testing;
- systems that exist for routine transport of DBS specimens;
- communication / referral systems for HIV-related care;
- Current policies and procedures relating to EID ;
- Attitudes of maternal, child and women health (MCWH) staff towards early infant diagnosis and,
- Community involvement

Data on quarterly immunisation numbers and quarterly uptake of antiretrovirals was extracted from record reviews.

Written, signed, informed consent was collected from each facility manager/immunisation nurse/information officer and child health nurse participated in the situational assessment. The information sheet for participants was prepared in English language describing the purpose of the study, confidentiality of data, and benefit of conducting the situational assessment. The information sheet explained that data reporting will be aggregated, at a strata and provincial level. Hard copy questionnaires (Appendix I) were used for data collection of the situational

assessment. The data was captured on excel and was transferred to STATA SE (version 12, Texas, 77845 USA) for analysis.

Descriptive analysis, including frequency tables, ranges and cumulative numbers were used for analysing data. During data analysis the following variables were created:

Approaches for early infant HIV diagnosis (EID) were categorized as follows:

- Universal HIV testing: offering testing to all infants visiting for six weeks immunisation service regardless of prior maternal HIV status
- Targeted Testing: HIV-testing of known HIV-exposed infants
- Provider-initiated counselling and testing (PICT) for undocumented and uncertain HIV status infants: is defined as the routine provision of HIV testing to six weeks immunisation infants whose HIV status is unknown or uncertain.

The implementation and effectiveness of the above three EID service approaches was examined using service utilisation data from the six weeks PMTCT survey (this is discussed in detail in chapter 4 - Paper 3).

3.4.The six weeks PMTCT survey

3.4.1. Study population

The study population for the six weeks PMTCT survey was infants aged 4-8 completed weeks and their caregivers/mothers visiting Public Clinics and CHC (primary sampling units) for administering 1st DTP dose to the infant.

3.4.2. Sample size and sampling

The desired sample size of the six weeks survey was the collection of 12200 maternal interviews and infant blood samples from mother-infant pairs visiting the selected 580 facilities for this component of the study. The sample size allocated for each stratum was divided equally for each facility in the stratum giving a self-weighted sample. The second stage sampling for this component of the study was the sampling

of mother-infant pairs from each facility. A fixed number (i.e. the allocated sample size for each facility) of mother/caregiver-infant pairs were consecutively or randomly (depending on the size of the facility) selected from each facility over a planned three to four weeks recruitment period. The sample size allocated for each facility was the median number of infants expected within the sampling window (3-4 weeks) across the population of facilities within the stratum as determined from the detailed information of the sampling frame (appendix I).

3.4.3. Participant inclusion and exclusion criteria for survey

Participant inclusion criteria

Infants were eligible for participation in the study if they are in the age range 4-8 completed weeks, attending clinic for 1st DTP immunisation and mother/caregiver consents to participation (consent for maternal or caregiver interview and/or infant DBS). Orphaned children brought to the clinic by caregivers who consent to participation in the study (consent was taken from caregiver for interview and/or infant DBS) were included. The PMTCT cascade analysis included all mothers with interview data regardless of infant DBS collection and HIV test.

Participant exclusion criteria

The following were exclusion criteria: severely ill infants needing emergency medical care or urgent referral to the next level of care e.g. infants who were vomiting or have convulsions, or are lethargic or unconscious or have severe pneumonia or severe dehydration. For the PMTCT cascade, caregivers (other than mothers) were excluded from analysis as PMTCT programme data for mothers cannot be obtained from caregivers (other than mothers) interview.

3.4.4. Data collection

Data collectors (trained field workers) recruited mothers/caregivers from the clinic/CHC waiting room during immunisation days. The data collectors introduced

themselves and the study verbally and in written form using a standardised information sheet. If the mother agreed to the interview, the nurse and the participant moved to a private location in the clinic/CHC. After the participants understand the purpose of the study, expectation from the subject, the long and short term benefits and risks of the study, the right to refuse to participate or withdraw, and the confidentiality of all information taken from the participants, written signed informed consent (Appendix II) was obtained from each eligible caregiver/mother. Interviews were conducted with mothers using full questionnaire, and a shortened version of the questionnaire (PMTCT questions were excluded from caregivers' questionnaire) was used for caregivers, legal guardians and fathers. The questionnaire was adapted from several validated tools (Rollins et al., 2007 & 2009; HSRC, undated; Nyblade & MacQuarrie, 2006; Tlebere et.al., 2007; Jackson et al. 2007).[6,117,125,129 130,131] Mothers were asked questions regarding utilisation of specific HIV-prevention services including HIV testing; receipt of HIV test results; if HIV-positive: CD4 count testing; receiving antiretroviral prophylaxis or highly active antiretroviral treatment (HAART) and intention to test infant at six weeks immunisation. Printed pictures of samples of antiretrovirals were showed to mothers, following antiretroviral questions, to assist them to identify the antiretrovirals they (or their infant) received. Data on gestational age at birth, infant birth weight and HIV status was extracted from the road-to-health-card (RtHC).

3.4.5. Laboratory tests

Blood specimens were collected from infants for HIV testing after mothers/caregivers were given pre-test counselling by the study nurse and agreed for infant testing. All specimens were tested in one accredited central laboratory, National health laboratory (NHLS), Johannesburg. Blood samples were sent from clinics to the central laboratory using the routine transportation system used by facilities. A serologic test, an enzyme immunoassay (EIA) (Greenscreen HIV 1/2 Ab EIA version 2, Bio-Rad Laboratories, France), was used to determine presence of HIV-antibody in collected specimens. All antibody positive and 10% of antibody negative specimens were

retested using a second enzyme immunoassay (EIA) (Vironostika HIV Uni-form II plus O, Marcy-L'Etoile, France). Discordant results were checked using Western blot. Specimens with one or two EIA result were tested using a qualitative deoxyribonucleic acid (DNA) polymerase-Chain- Reaction (PCR) test to determine infant HIV infection. EIA positive result indicated HIV-exposure of infant, and a PCR positive result showed HIV infection of infant.

3.4.6. Data management and analysis

Data collection for the PMTCT survey was done using electronic questionnaires (Appendix II) that were loaded on low cost mobile phones using the Mobile Researcher software management solution. This reduced cost and time needed for data capturing and data cleaning.

Analysis of the PMTCT cascade data was started by observing the sample realisation in each stratum of each province. The sample realisation was established and the sampling weights were adjusted to reflect the sample size realisation. A formal survey analysis was done which included the specification of the different sampling stages and the finite number of PSU's involved. A weighted analysis was performed for each province as well as estimating the national uptake of PMTCT services (PMTCT cascade). Unweighted cell counts are presented where it is important to show the sample size in each category. District level analysis could not be done as the sample size was not adequate for providing district level estimates.

Definition of Service coverage terms

- **Acceptability of PMTCT service**: the degree to which the PMTCT service meets the social and cultural needs and standards of the community, which in turn influences uptake of PMTCT service. [9]
- **Access (to health services):** the perceptions and experiences of people as to their ease in reaching health services or health facilities in terms of location, time, and ease of approach.[10]

- **Affordability** refers to the direct (doctor's fees, travel and medical costs) and indirect costs (e.g. absenteeism from work) that affect access to service.[11]
- **Availability of service** - we use this term in particularly to refer to the delivery (or availability) of services at peripheral level health care units (i.e. primary health care units).[10]
- **Coverage:** the extent of interaction between the service and the people for whom it is intended. Coverage is not to be limited to a particular aspect of service provision, but ranges from resource allocation to the achievement of the desired objective.[12]

- **Uptake** is used to refer to utilisation of services. Uptake was calculated for the following PMTCT cascade indicators using maternal report data:

  1) Percentage of mothers who received ANC HIV testing

  2) Percentage of mothers who received antenatal HIV test result

  3) Percentage of reported HIV-positive or infant EIA positive mothers who had CD4 count test (and received CD4 count result)

  4) Percentage of reported HIV-positive or infant EIA positive mothers who took ARV prophylaxis/HAART during pregnancy

  5) Percentage of HIV-exposed infants (from maternal report or EIA result) who received ARVs immediately after delivery, and

  6) Percentage of mothers who had intention to test infant at six weeks immunisation visit.

The final outcome that represents the coverage of the perinatal PMTCT cascade is the receiving of maternal AZT or HAART for any duration during pregnancy and infant NVP/AZT taken at birth.

- **Utilization (of health services):** experience of people as to their receipt of health care services of different types. [10]
- **Universal access/coverage** –Particularly for this thesis, this term is defined as ≥80% total ARV regimen (maternal AZT or HAART received for any duration during pregnancy and infant NVP/AZT taken at birth) coverage.

Multivariate analysis using both situational assessment and six weeks survey data

A logistic regression model was fitted to compare transmission differences between provinces that achieved universal coverage (≥80% ARV regimen coverage) of ARV regimens and provinces that did not achieve universal coverage. The auxiliary information obtained through the six weeks questionnaire and the situational assessment facility level data were combined and analysed using the survey analysis framework. This framework takes into account the sampling weights the survey design and the cluster sampling of participants. The following variables were considered in adjusting this model: from individual level factors, marital status, maternal age, education, socioeconomic status, planned pregnancy, number of life time pregnancy, gestational age at birth, infant birth weight, and history of child sickness (sickness treated at a clinic or a hospital level) since birth; and at facility level, human resources, referral system, availability of on-site ARV clinic, task shifting and community involvement were included. All estimates are reported with 95% confidence limits. Detail data analysis step is presented in chapter 4 (paper 2).

A second logistic model was fitted to examine individual level factors influencing maternal intention to receive EID at six-week visit among known HIV-positive mothers. Variables used for adjusting this model are presented in chapter 4 (paper 3).

Data imputation

All variables included in the final model of the multivariate analysis were imputed using multivariate imputation by chained equation (MICE) method. Variables that closely explain the missing variables were specified and STATA SE 12 was used in performing the multiple imputations. This method creates multiple imputation for each missing data and accounts for uncertainties introduced with imputed missing data at analysis stage by running a series of regression models which are conditional upon other variables in the data.

3.4.7. Informed consent

Written, signed, informed consent was obtained from each eligible caregiver/mother (see Information Sheet and Consent form in Appendix II). Informed consent was prepared in the preferred language of the participants. The information sheet was written in plain lay words to be easily understood by participants and has a SMOG score of <8. The Flesch-Kincaid Grade Level is 4.7 meaning that the consent form is easy to read by an average student in the 4-5th grade (around 9-11 years old). In the PMTCT study, pre-test counselling was given to all mothers, following which mothers were requested for consent to collect heel prick blood sample with an option to know the HIV test result of the infant. Mothers who agreed to infant testing were given confidential linked (names were written on lab forms) testing. Confidentiality of identifying information was assured by limiting the number of people who have access to identifying information. The national laboratory technicians (NHLS) who process the testing of the blood specimen were the only parties who had access to infant identifying information (the laboratory technicians had access to identifying information as they were responsible for returning of results to the health facility). These laboratory technicians had no access to interview data collected from mothers. Mothers could refuse if they did not want to have the infant HIV test result. For mothers who refused to have named infant HIV results, anonymous testing was offered, in which case specimens were collected without taking infants/mothers name, but a barcode was used for data linking. If infant was brought by caregiver other than mother, they were given an option for anonymous testing, however if caregivers indicated the mother/guardian is interested to know the HIV status of the infant, confidential linked testing was given and appointment card was sent to the mother to collect the infant result at 10-14 weeks. Results were returned through the routine system. A confidential Study ID (BARCODE) was given to each participant consent form and questionnaire for the purpose of data linking and audit, and to provide the infants blood test results. Data collectors were properly trained and carried identification. The data collectors ensured that the prospective subject is provided with all the necessary information about the study, and that participation in the study is not influenced by coercion, undue influence or intimidation. Care was

taken to ensure that HIV-infected mothers who refuse the study understand that their infant should still be tested and can be tested without participating in the study.

All aspects of the project were carried out according to strict standard operating procedures (SOPs). Detailed instruction was written explaining the step-by-step process of: recruitment of caregiver/mother-infant pairs, informed consent procedure (and confidentiality), interview (interpretations of questions), process of blood sample collection and transportation, referral of mothers/infants to receive the necessary care, monitoring the field data collection process and data management and an analysis.

3.5. Ethical Approval for the Study

Ethical approval for the PMTCT survey was obtained from the Medical Research Council, National Department of Health, the provincial research ethics committees (as applicable) and from the United States Centres for Disease Control and Prevention Associate Director for Science (Appendix II). Ethical approval for the situational assessment was sought from the Medical Research Council (Appendix II), and the provincial research ethics committees (as applicable). Approval and buy-in was obtained from National and Provincial Departments of Health before commencing the fieldwork.

3.6.Quality control/quality assurance measures

During data collection, field supervisors were assigned for each province to manage the field work activity and act between fieldworkers and project coordinators for logistics and other queries from field sites.

3.7.Validity/Reliability

The six weeks immunisation visit has a very high attendance nationally (over 95%) suggesting limited selection bias using this approach.[123] Actual 6 week immunisation coverage at each sampled facility was reviewed to estimate possible bias due to lower

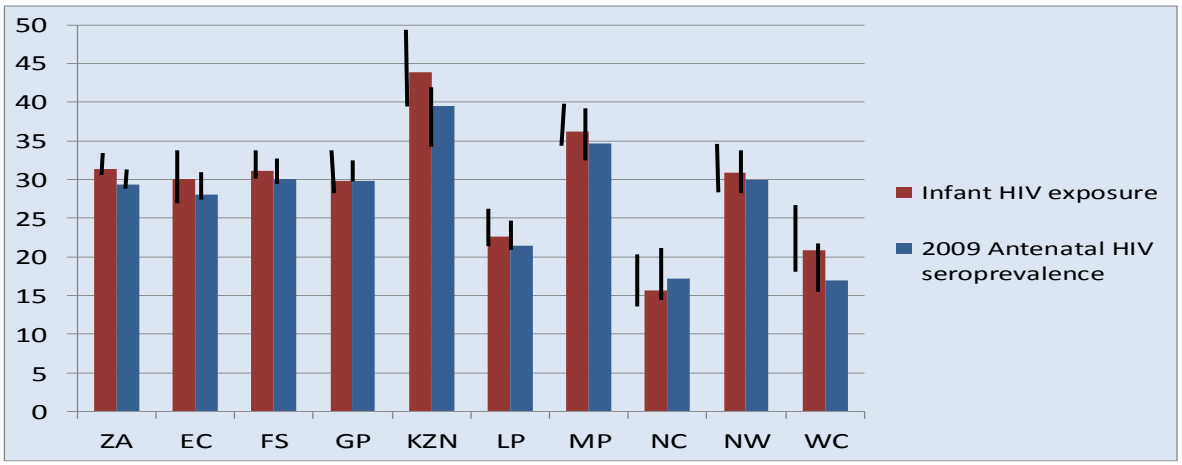
than expected coverage. A few facilities (<5) were found with lower than expected immunisation coverage, and these facilities were re-categorised/moved into their appropriate strata (small, medium or large strata) and a replacement facility was sampled for their substitution.

To validate our data, the demographic characteristics (i.e. maternal age distribution) and the HIV exposure prevalence of our survey was compared with the antenatal survey maternal age distribution and HIV prevalence data. Both our survey and the antenatal survey data have comparable age distribution and infant HIV exposure prevalence (table 2 and fig 2).

Table 2: Comparison of age distribution between the antenatal survey and the six week PMTCT survey

Maternal age in years	PMTCT survey 2010 (%)	ANC survey 2009 (%)
<15	0.1%	0.3%
15 - 19	15.9%	18.7%
20 – 24	30.1%	31.1%
25 – 29	25.4%	23.9%
30 – 34	16.1%	14.5%
35 – 39	8.1%	8.1%
40 – 44	2.3%	2.2%
45 – 49	0.3%	0.2%
>49	1.7%	0%
Not specified	0%	0.8%

Figure 2: Comparison of the PMTCT survey infant HIV exposure prevalence and the antenatal survey HIV sero-prevalence data



Bias in data collection, measurement & analysis

Potential Selection Bias

Potential bias in this study includes the following:

a) The uptake rate we report in this study is not an expression of service uptake at a population level. We calculated uptake for mothers that attended the 6 weeks immunisation visit. However, 6 weeks immunisation visit has a very high attendance in South Africa (>95%), suggesting limited selection bias using this approach

b) Neonatal deaths were not included in this study; hence the PMTCT cascade results from this study cannot represent utilisation of PMTCT service by mothers whose infants died before 6 weeks immunisation visit.

d) Only clinics and community health centres were included in this study, while these are the primary care facilities providing well child services in South Africa they may not be representative of all types of health facilities.

e) This study provides facility, not community-based estimates of uptake of PMTCT cascade. However as DTP1 immunisation rates are high (>95%) in South Africa, the results can closely represent infants in the age of 4-8 weeks old in the population. [122]

f) The study does not also provide estimate on uptake of PMTCT service given at late postnatal period (>4-8 weeks of infant age).

g) Missed opportunities (for enrolment in PMTCT programme) among mothers infected late in pregnancy may not be identified if maternal antibodies are not yet present in the baby's blood or as some studies show if extended ARV use may delay infant HIV diagnosis [132]

Potential Information Bias

a) There is always potential for recall bias, however the relatively short recall period (recall period of <1 year) should reduce this potential bias. Non response rates were high for CD4 count and duration of treatments due to the long recall period. We therefore did not use these two variables for multivariate analysis.

b) Social desirability bias and fear of disclosure and stigma may cause mothers to either over or under-report participation in the PMTCT programme. Confidentiality

was assured and discussed as part of the informed consent process and a private place was secured for the conduct of interviews. HIV prevalence calculated from infant DBS test shows most mothers reported their true HIV status.

c) National Health Laboratory Service (NHLS) and National Institute for Communicable Diseases (NICD) conducted the validation EIA testing on dried blood spot (DBS) samples. The result of this validation test showed that the sensitivity and specificity of the EIA test ranges from 89.1-95.2 (sensitivity) and 99.6-99.9 (specificity). Established sensitivity and specificity of the HIV testing was operational, but this was minimized through proper handling of specimens and assurance of laboratory quality control.

3.8. Work plan

Table 3: Time frame for the 6 week SA PMTCT survey project

Description of activities	2009	Jan-May 2010	June – Dec 2010	2011	Jan-March 2012	April 2012 - April 2013	May 2013
Timeline for the main PMTCT survey							
Planning and finalisation of questionnaire, SOPs	X						
Selection of field workers		X					
Training of field workers		X					
Data collection			X				
Data entry, data cleaning, and preliminary analysis				X			
Timeline for PhD							
Proposal writing				X			
Data analysis					X		
Write-up of 3 manuscripts						X	
Submission for external examiners							X

3.9. Contribution of the student to the study

Ms Woldesenbet is a Senior Scientist at the MRC. She was responsible for the overall planning, coordination and implementation of the situational assessment study, and the planning and coordination of the 2010 PMTCT survey until July 2010. During

survey implementation Ms Woldesenbet's responsibilities included overseeing field work in three provinces and overseeing the work of two scientific coordinators who managed the field work in the other six provinces. From July 2010 she was also mainly in charge of reviewing and cleaning the data from the survey (in her role as Scientific Manager). The PMTCT survey main objective was to estimate the MTCT among infants aged 4-8weeks old. The second and third objective of the PMTCT survey was to report on uptake of PMTCT cascade and factors associated with transmission rate. The findings of the main objective of the study were written by the principal investigators (Dr. Ameena Goga, Prof. Debra Jackson, and Dr. Thu-Ha Dinh). The principal investigators oversaw the overall coordination and implementation of the study and had the final decision on the scope of the study (including decision on main objectives and depth of data/information gathered), study procedures and budget allocation. They employed staff, including Ms Woldesenbet to implement the study. In accordance with previous discussions with the Principal Investigators Ms Woldesenbet was responsible for data management, analysis and write-up of reports and manuscripts from the situational assessment study and the 2nd and 3rd objectives of the PMTCT study which make up her PhD analysis and thesis. Data weighting was done by an MRC statistician. The rest of the analysis in this thesis was done by the student (Ms Woldesenbet), with guidance from the principal survey statistician, PhD supervisor and PIs and inputs from co-authors.

Chapter 4: RESULT AND DISCUSSION

4.1. Paper 1: Uptake of PMTCT services

TITLE: Uptake of prevention of mother-to-child transmission (PMTCT) services in the South African PMTCT programme: Findings from the first South African PMTCT (SAPMTCTE) survey, 2010

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Abstract

Objectives

This study aimed to assess uptake of antenatal and perinatal PMTCT services and missed opportunities for PMTCT service in a national survey conducted in nine South African provinces.

Methods

A cross-sectional survey was conducted among 4-8 weeks old infants receiving first immunisations in 580 facilities selected from the nine provinces of South Africa using a multistage stratified sampling method. Interviews were conducted with mothers to assess uptake of antenatal and peripartum PMTCT services. HIV status of mothers was determined from maternal report or enzyme immunoassay (EIA) testing of infants' dried blood spots. A weighted analysis was performed to assess uptake of antenatal and perinatal PMTCT services.

Results

From 10299 mothers with unknown or HIV-negative status prior to pregnancy, 97.7% reported receiving antenatal HIV testing and test results. 3209 (32.2%) infants were HIV-exposed (HEI) per maternal report (known HEI 89.6%) or infant blood EIA test (unknown HEI 10.4%). 75% of HIV-positive (per maternal report or EIA result) mothers received a CD4 count test and 67% received their CD4 count test results. Of those mothers who reported CD4 count ≤350cells/µl, only 64% received highly active antiretroviral treatment (HAART). In total 82% of all mothers of HEI (known and unknown) received HAART or azidothymidine (AZT) prophylaxis during pregnancy and 78% received both maternal HAART/AZT and infant nevirapine/AZT.

Conclusion

Substantial loss to follow-up occurred at CD4 count and antiretroviral treatment (HAART) initiation points. Given the observed high dropout at CD4 count point and related delays in initiation of HAART, this study supports the recent adoption of the WHO Option B treatment guideline in South Africa which recommends initiation of HAART to all HIV-positive mothers regardless of CD4 count. The adoption of the new guideline should be accompanied by decentralisation of HAART services (NIMART) to prevent loss to follow-up at antiretroviral referral points.

Key words: prevention of mother-to-child transmission, uptake of PMTCT, PMTCT cascade

Background

Evidence now shows elimination of mother-to-child transmission can be a realistic goal for resource limited countries.[1] Providing the most effective antiretroviral regimen for HIV-positive pregnant women using Option A or Option B WHO treatment guidelines can reduce the risk of mother-to-child transmission (MTCT) to less than 5% in a breastfeeding population and to <2% in non-breastfeeding populations.[2,3] In a clinical trial setup, both Option A and Option B WHO treatment guidelines are proven to be efficacious in reducing the risk of mother-to-child transmission.[2,4] At programmatic level however, delivering a comprehensive prevention of mother-to-child transmission of HIV/AIDS (PMTCT) programme to HIV-positive mothers and their infants requires longitudinal follow-up of both mothers and infants and delivery of high quality PMTCT preventive, treatment and care services called the PMTCT cascade services.

Globally only 48% of the estimated 17 million HIV-positive women receive ARVs for prevention of mother-to-child transmission.[5] The literature indicate achievement of the paediatric HIV elimination goal requires at least >95% uptake of antiretroviral treatments among HIV-positive women.[6] In countries that implement the WHO treatment Option A guideline, CD4 count testing is a crucial component for initiating effective ARV regimens.[5]

A number of studies have been carried out to measure uptake of the PMTCT cascade and missed opportunities in sub-Saharan African countries.[7-14] Most of these studies are small in scale,[7,9-11,14] or measure uptake of simple regimens (single dose nevirapine) rather than combination antiretrovirals.[8,12,13] A recent systematic review of PMTCT studies indicates uptake of simple regimens (single dose nevirapine) in four low income sub-Saharan African countries was on average 55%.[15] The study highlights the lack of operational research studies that measure uptake of combination ARV regimens.

This paper presents data on uptake of antenatal and perinatal PMTCT services and missed opportunities at a national level in the context of the WHO 2010 Option A treatment guideline in South Africa. The study was conducted between June and December 2010 during a time when most provinces of South Africa were at an early stage of adopting the WHO Option A treatment guideline**.** We identify key dropout points in the PMTCT cascade services, including their policy implications, and provide national and provincial level baseline data on uptake of WHO Option A guideline in South Africa.

Methods

Study design

A cross-sectional survey was conducted from June to December 2010 among mother/caregiver-infant pairs visiting immunisation service points within public primary health care facilities (PHCs) and community health centres (CHCs) in all nine provinces of South Africa. The primary and secondary objectives of the survey were to provide national and provincial level estimates of mother-to-child transmission (MTCT) rates and uptake of PMTCT services, respectively. This study analyses the national uptake of PMTCT services and identifies drop out points at each step of the PMTCT service pathway.

Sample size and Sampling

The desired sample size for the study was the collection of interview data and infant blood samples from 12200 mother-infant pairs. Sample size was calculated with a projected transmission rate of 7% with dual therapy, 15% with sdNVP, and 29% for untreated MTCT. A precision level of 1%-2%, an estimated 29% of HIV-exposure among infants and a design effect of 2 was considered in calculating sample size. Further details on parameters used for sample size calculation and provincial details are presented elsewhere.[16]

The sampling frame comprised all PHCs and CHCs throughout the country. Satellite or mobile clinics, small facilities (immunisation number below 130 per annum), private facilities and public hospitals were not included in the sampling frame. A stratified multistage sampling method was used to select sample facilities. Facilities in the sampling frame were stratified into three groups based on the 2007 district health information system (DHIS) immunisation data and the 2009 antenatal HIV prevalence estimates: medium size facilities with 130 -300 annual immunisation (DTP1) coverage, large (≥ 300 annual DTP 1 coverage) facilities with HIV prevalence below the national HIV prevalence estimate (<29%), and large facilities (≥300 annual DTP1coverage) with HIV prevalence above or equal to the national HIV prevalence estimate (≥29%). Probability proportional to size sampling method was used to select five hundred eighty (580) medium and large size facilities for inclusion in the survey and 3-4 weeks were spent in each facility to collect interview data and infant dried blood spots (DBS) from mother-infant pairs attending six weeks immunisation visit.

Data collection

10820 mother/caregiver-infant pairs visiting six weeks immunisation services were approached and screened for eligibility. Mothers/caregivers were requested for consent to participate in the study if infants were between 4-8weeks of age and had no emergency illness. Those who gave consent were interviewed on reasons for the visit, antenatal and peripartum PMTCT services received, and knowledge about MTCT and PMTCT services attended.

After the interview was conducted, pre-test counselling was given to each mother individually and mothers were requested for their written informed consent to receive infant HIV testing. Mothers who agreed to infant testing were given confidential linked testing and results were returned to mothers through the health facility using the routine system. Anonymous testing was offered if mothers /caregivers did not want the result.

Data were collected on electronic (cell phone) questionnaires and then transferred to STATA SE (version 12, Texas, 77845 USA) for analysis.

Statistical analysis

Infants were included in this analysis if they were brought by their mother and the PMTCT section of the questionnaire was answered. A weighted analysis was performed to describe the socio-demographic characteristics of participants. HIV status of mothers was determined from self-report of mothers or from enzyme immunoassay (EIA) (Genscreen HIV antibody assay) test done on infants DBS. EIA test result was considered a biomedical marker for maternal HIV status. Mothers who either self-reported an HIV-positive status or had an EIA positive infant were classified as HIV-positive mothers. These mothers were considered as the target population for the PMTCT programme. Mothers who reported HIV-negative status with negative or no infant EIA test result were considered as HIV-negative mothers and classified as non-target for the PMTCT programme. A Socioeconomic score (SES score) was created from availability of the following working items in the house: stove, refrigerator, radio, TV and car. Results are weighted for sample size realisation and the 2010 live birth distribution across provinces.

We calculated a weighted proportion of mothers who had antenatal testing and who received an antenatal test result, proportion of reported HIV-positive mothers, proportion of HIV-exposed infants (per EIA test or maternal report) whose HIV-exposure status was known and reported by the mother; and proportion of all HIV-exposed infants (known and unknown) whose mother received a CD4 count test, CD4 count test result, maternal ARV prophylaxis/HAART and both maternal and infant ARVs. Maternal AZT or HAART received for any duration during pregnancy plus infant nevirapine (NVP)/AZT received at birth was considered as a marker for uptake of both maternal and infant ARV regimen. Percentage of known HIV-exposed infants who dropped out at each step along the cascade and missed opportunities for PMTCT services due to unknown infant HIV-exposure status are reported.

The survey protocol was approved by the institutional review board of the Medical Research Council of South Africa and the Office of Associate Director of Science at the Centers for Disease Control and Prevention, United States of America. All study participants provided written informed consent.

Results

Description of the study population

Ten thousand eight hundred twenty (10820) mothers/caregivers who brought infants to sample clinics for six weeks immunisation service were approached and screened for eligibility (fig 3). Mother-infant pairs who were eligible were requested for consent to participate in the survey. Ninety-nine percent (10735) of total screened mother/caregiver infant pairs were eligible and agreed to an interview, of which 10357(97%) mothers who responded to maternal sections of the survey were included in this analysis. Of mothers interviewed, 9896 (96%) had both interview data and laboratory results. This yielded 81% (9896) national sample size achievement of the desired/planned 12200 sample size.

The socio-demographic characteristics of the study population are presented in table 4.The majority of participants were single mothers (74.4%), whose infants are from African/black race (98.6%), and had finished 1-5 years of high school education (77.6%). The average maternal age was 25.9 years. Most (60.2%) pregnancies were unplanned and the majority of mothers attended the first antenatal care visit in their second (48%) or third (12.5%) trimester.

Uptake of services along the PMTCT cascade

From the total 10357 mothers interviewed on the maternal section of the study, 58 (<1%) mothers reported knowing their HIV-positive status prior to pregnancy. From the remaining 10299 mothers with unknown or HIV-negative status prior to pregnancy, 98.7% reported receiving HIV testing during antenatal visits (fig 4).

Almost all (97.7%) mothers who received HIV testing received their test results. Of those who tested and received their test result, 29.5% reported being HIV-positive as opposed to 32.2% (3209) total HIV-exposed infants identified from both infant EIA test and maternal report.

Figure 4 presents weighted estimates of maternal knowledge of infant HIV-exposure status and attendance of the PMTCT programme among both known and unknown HIV-exposed infants. According to our estimate, of the 3209 HIV-exposed infants in the study, 89.6% were known HIV-exposed infants as reported by mothers and 10.4% were unknown HIV-exposed infants - eight percent (8.2%) reported HIV-negative status and the remaining 2.2% reported unknown HIV status (fig 5 step A and B).

Of all HIV-positive mothers, 75% (2339) received a CD4 count test and 67% (2110) received their CD4 count test results (fig 5 step C and D). In total 22.6% of HIV-positive mothers missed CD4 count test or result – 14.6% did not have CD4 count test, and 8.0% did not receive their CD4 test result (fig 5 step B–D, step B-C, and step C-D respectively).

Of all HIV-positive mothers (known and unknown), 29.5% of mothers received HAART and 52.5% of mothers received maternal ARV prophylaxis (AZT) during pregnancy. In total 82% (2584) of all HIV-positive mothers (known and unknown) received maternal HAART or ARV prophylaxis (AZT). Among those who received HAART, 37%, 57% and 6% of mothers were initiated on HAART before pregnancy, during pregnancy and after delivery respectively. AZT prophylaxis was started at 14 weeks or earlier in 5% of mothers, 47% started AZT prophylaxis between 14 weeks and 28 weeks, and 24% received AZT prophylaxis at or after 28 weeks. Close to a quarter (24%) of mothers who received AZT prophylaxis did not recall the duration.

Infant NVP was received by 83.2% of all HIV-exposed infants. Among those who received infant NVP, 41% of HIV-exposed infants were on NVP prophylaxis for 4

weeks or more, 45% received NVP for less than 4 weeks, and the rest 14% of mothers did not recall duration of infant NVP.

Figure 6 presents the regimen mother-infant pairs received. Seventy eight percent (78%) of all HEI received both maternal (AZT and HAART) and infant ARVs. The remaining 2.6% received single dose maternal and infant NVP, 4.3% received maternal ARV only, 2.7% received infant NVP/AZT only, and 1.4% of known HEI and 10.4% unknown HIV-exposed infants missed both maternal and infant ARVs.

Lifelong antiretroviral treatment (HAART)

Among 1797 mothers who reported their CD4 count number, 49% (881) had CD4 count ≤350 cell/µl. Of the 881 mothers with CD4 count ≤350 cell/µl, 74% (652) were referred to ART clinics for initiation of HAART and 64% (564) reported they received HAART (fig 7).Ten percent (10%) of mothers eligible for HAART were referred to ART clinics but did not receive HAART (4% reported they did not go to ART clinic and 6% reported visiting the ART clinic but were not initiated on HAART). In total 36% of eligible mothers with CD4 count ≤350 cell/µl missed lifelong ART (fig 7 A-C). However, almost all (97%) eligible women who did not receive HAART received maternal ARV prophylaxis.

Uptake of HAART was relatively higher (77.3% 95% CI: 71%-82%) among mothers with CD4 count ≤200 cell/µl compared to mothers with CD4 count 200-350 cell/µl (56.0% 95% CI:51%-61%). All provinces initiated HAART for both women with CD4 count ≤200 cell/µl and CD4 count 200-350 cell/µl as recommended in the new WHO and South African guidelines. Across provinces between 30% and 60% of mothers who were initiated on HAART had CD4 count 200-350 cells/µl.

Discussion

The study shows high uptake of antenatal HIV testing (97.7%) and more than 75% uptake of both maternal and infant ARVs among all HIV-exposed infants. Significant

improvement has been made in increasing uptake of PMTCT service in South Africa. Since the national scale-up of the PMTCT programme in 2003/2004 the uptake of antenatal testing has doubled.[17] A number of interventions, including the introduction of universal offer of testing at antenatal clinics, and increased access to ARV treatments, have made a notable contribution to the success of the South African PMTCT programme. Despite this success, the country is still one of the highest burden countries globally with 30% HIV prevalence among antenatal women and an estimated 40000 new infections occurring annually among infants.[18,19] Hence achieving the new infection elimination goals in South Africa requires intensive effort to substantially increase the uptake of *effective* ARV regimens among all HEIs.[6] Certain gaps that may challenge the achievement of this target are identified in this study.

The study identifies high attrition rate of mother-infant pairs between HIV diagnosis, CD4 count test and initiation of highly active antiretroviral therapy with 10.4% of mothers who do not know their HIV-positive status, 14.6% of known HIV-positive mothers who do not receive a CD4 count test, additional 8% of mothers who do not receive their CD4 count results and 10% of mothers who do not initiate ART despite eligibility and referral to ART sites.

Most mothers had at least one antenatal HIV test (97.7%) during pregnancy. Despite this, 10.4% of mothers did not know their HIV-positive status. Our study did not assess timing of testing and uptake of late pregnancy repeat tests. However, in light of increasing research that shows higher rate of new infections during pregnancy,[20] both early and repeat antenatal tests should be considered essential for all mothers attending antenatal services unless HIV-positive status is confirmed prior to pregnancy or at the first antenatal visit.

Several studies have reviewed challenges surrounding the current centralised CD4 count testing system.[21-23] Challenges that have been found to be the main contributors to the drop out at CD4 count service points in the current centralised system are

supply chain failures, unreliable specimen transport systems, long turnaround times, and distance. As demands for CD4 count testing increase, these challenges will continue to prevail unless laboratory systems necessary to support an effective testing service are strengthened.

Point-of-care CD4 diagnostic tests can improve access to CD4 count and turnaround time for results.[24] However, the feasibility of implementing this strategy in resource limited countries including the cost of placing CD4 count machines in each clinic, human resource, logistic and infrastructural needs of such laboratory tests at peripheral levels is not well established. Best practices from studies in sub-Saharan African countries recommend simple strategies such as on-site same day blood draw for CD4 count test which could increase uptake of CD4 count testing.[11]

While innovative studies are urgently needed to advance cost-effective and feasible solutions that simplify the provision of CD4 count service, governments should also consider the alternative WHO Option B treatment as a strategy to curb the operational challenges of increasing uptake of effective ARV regimens. The South African government recently adopted the WHO Option B treatment guideline. The adoption of this guideline will improve care to the close to one quarter (22.6%) of mothers (and their infants) who drop out at CD4 count service and those that receive less effective ARV regimens without assessment of their eligibility for HAART.

A recent analysis of cost-effectiveness of the WHO treatment Options A and Option B guidelines shows that treatment Option B is more cost-effective than treatment Option A due to the paediatric HIV costs averted by initiating ARVs early for all HIV-positive mothers regardless of CD4 count.[25] However, the study notes poor adherence to treatment and loss to follow-up after delivery could lead to virologic failure and shorter maternal life expectancy. In the South African programme, the WHO Option B is launched with a fixed dose combination therapy (a single dose therapy given once a day). This is expected to significantly lower the pill burden (and side effects) on patients, and improve adherence to treatment.

However, the other concern in this study was the significant proportion (10%) of mothers who dropped out after referral to antiretroviral treatment sites. Research in sub-Saharan African countries indicates that gaps in the referral and tracking systems of PMTCT programmes are major barriers for early initiation of HAART.[26,27] With the adoption of treatment Option B in South Africa, the readiness of antenatal facilities to introduce nurse initiated ARV treatment (NIMART) should be assessed. In areas where ARVs are not initiated at antenatal sites, drop out at antiretroviral referral points could pose a significant challenge for early initiation of ARV treatments.[28]

Our findings on the two key drop out points (CD4 count, and referral to ARV sites) are similar to other studies in South Africa and sub-Saharan African countries.[29] In a study in KwaZulu-Natal, CD4 count testing points and initiation of HAART are reported as the key drop out points in the antenatal PMTCT programme.[30] Other studies in Sub-Saharan African countries also report similar findings.[15,29,31]

According to our study findings, although the 2010 guideline was adopted in South Africa in the same year as our study was conducted, all provinces initiated HAART for mothers whose CD4 count was between 200 and 350 cells/µl per the new guideline. More than half (52.3%) of mothers also received ARV prophylaxis before 28 weeks as opposed to 24.1% of mothers who received ARVs at or after 28 weeks as per the old guideline.

Reports indicate most sub-Saharan African countries have lower coverage of ARV regimens compared to the PMTCT coverage we report for South Africa. The PEARL study in Zambia, and Cote d'Ivoire reported 30%, and 17.9% umbilical cord maternal and infant NVP coverage and 89% and 70.1% maternal NVP coverage from record review respectively.[8,13] Our ARV uptake rates are lower than uptake rates reported from routine data in the UNAIDS country report. The UNAIDS country progress report gathered from countries routine data for 2010 reports >95% of antenatal testing and maternal antiretroviral treatment coverage for South Africa.[5]

Reports from routine data may overestimate the coverage of PMTCT programme as these reports are limited to women that are in the PMTCT programme (known HEI) only, and the data collation system of routine data may introduce double-counting when data from different sources are aggregated.

Our study has several limitations. Although the study measured uptake of PMTCT services at national and provincial level, children who had already died by the age of 4–8 weeks, children who did not receive first immunisation at public facilities and children who received first immunisation after 8 weeks of age were not included in this study. However most immunisations occur in primary health care facilities and attendance of six weeks immunisation clinic in South Africa is high (>95%), hence our results represent most infants. Repeat antenatal testing, timing of antenatal testing, uptake of early infant diagnosis, cotrimoxazole coverage and uptake of postnatal PMTCT services are not captured in this study. Due to the structure of our questionnaire, only those mothers who had not had an antenatal test responded to the question asking about 'prior knowledge of HIV status'. Hence the number of mothers who reported to know their HIV-positive status prior to pregnancy (<1%) may be an under representation. Lastly the data on all PMTCT cascade indicators was collected from interviews with mothers. Recall bias could be expected on certain PMTCT cascade indicators, although the duration of recall is not very long (<52 weeks).

Conclusion

This is the first national survey in South Africa presenting data on coverage and missed opportunities for PMTCT services at national and provincial level. Studies conducted prior to this study in South Africa or elsewhere are smaller in scale or measure coverage of simple regimens (single dose nevirapine) implemented at initial rollout phase of the PMTCT programme. The study findings highlight CD4 count and initiation of ART as key drop out points that require urgent attention and innovative solutions. Given the observed high dropout at CD4 count point and related delays in initiation of HAART, this study supports the recent adoption of the WHO Option B

treatment guideline in South Africa which recommends initiation of HAART for all HIV-positive mothers regardless of CD4 count. The adoption of the new guideline should be accompanied by decentralisation of HAART services (NIMART) to prevent loss to follow-up at antiretroviral referral points.

Acknowledgment: CDC, NRF, NICD/NHLS, UNICEF, Mickey Chopra, Tanya Doherty, Nathan Schaffer, Thabang Mosala, Wondwossen Lerebo, Katherine Robinson, Nobuntu Noveve, provincial supervisors, data collectors, mothers and infants,

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Table 4: **Socio-demographic characteristics of the study population by eligibility for PMTCT programme**

	HIV-positive mothers (mother HIV infected or infant HIV-exposed) [# (%)] N1 = 401,947 (n1=3209)
Maternal and infant Characteristics	Number (%)
Maternal Age	
Mean (Range)	27.6(15-46)
Maternal Education	
None	95 (2.7)
Grade 1-7	624 (18.3)
Grade 8-12	2410 (76.3)
Above Grade12	78 (2.6)
No information	2 (0.05)
Marital status	
Single	2445 (78.8)
Married/cohabiting	740 (20.5)
Widowed/Divorced	24 (0.8)
No information	0
SES score created from working items (CI)	-0.11 [-0.21, -0.03]
No of live children	
1	922 (28.1)
2	1215 (38.2)
≥ 3	1072 (33.7)
Planned Pregnancy	
Yes	1209 (36.9)
No	1989 (62.8)
Missing	11(0.4)
Gestational age at first ANC	
1st trimester	
2nd trimester	723 (20.1)
3rd trimester	1545 (49.7)
Missing	378 (12.5)
	563(17.7)
Infant gender	
Male	1594 (49.8)
Female	1615 (50.2)
Infant Race	
Black	3134 (98.6)
Coloured	69(1.3)
White, Indian and other	6 (0.1)

Figure 3: 2010 SAPMTCTE interview data study profile

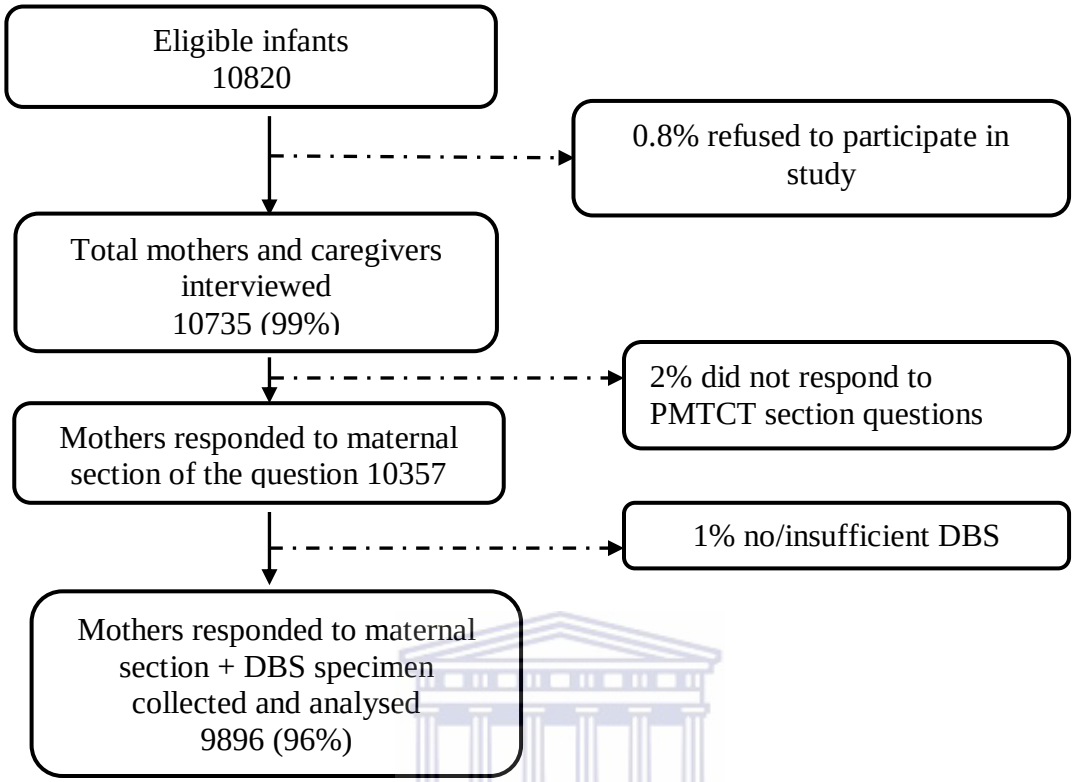


Figure 4: Uptake of antenatal HIV testing, national result, South Africa 2010 survey

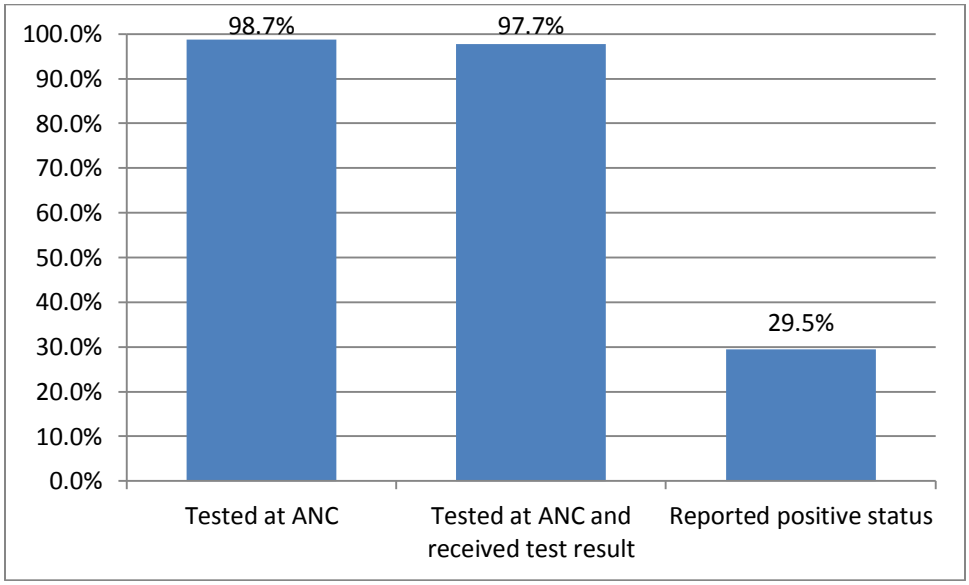


Figure 5: Uptake of services along the PMTCT cascade, national result, South Africa 2010 survey

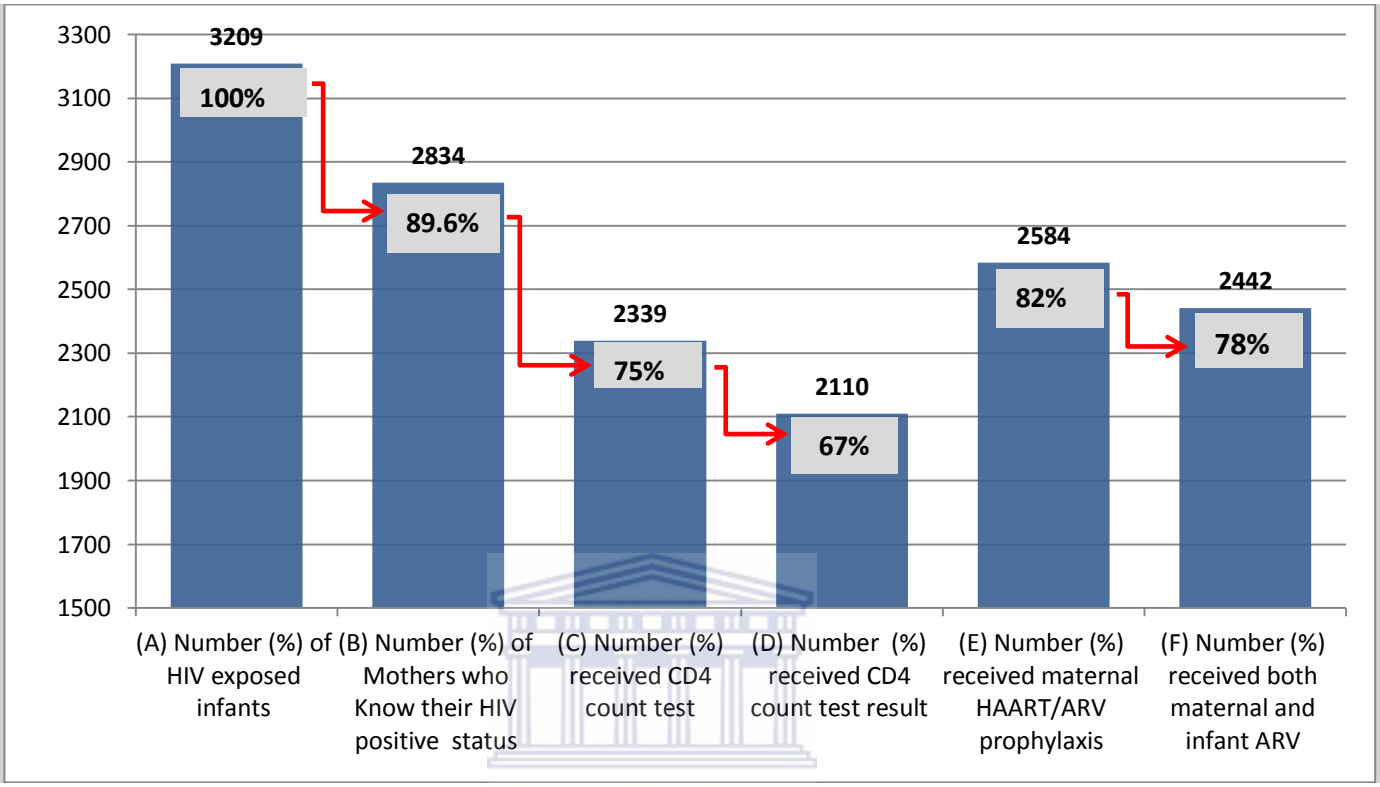


Figure 6: Antiretroviral Regimens received by mother-infant pairs

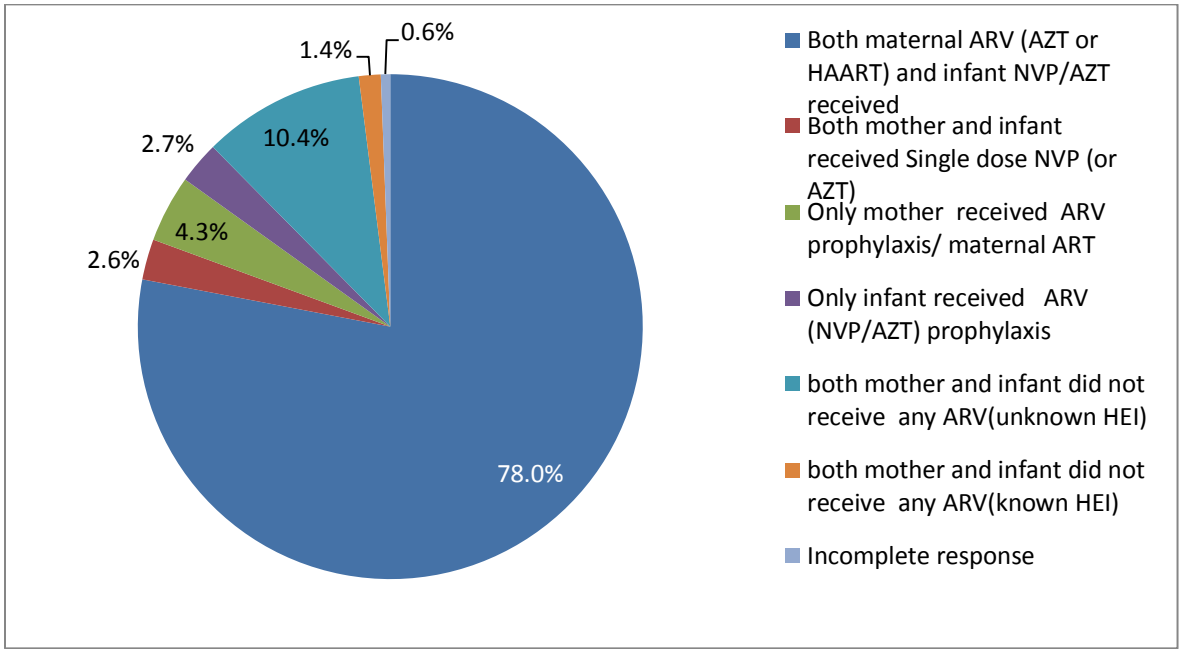
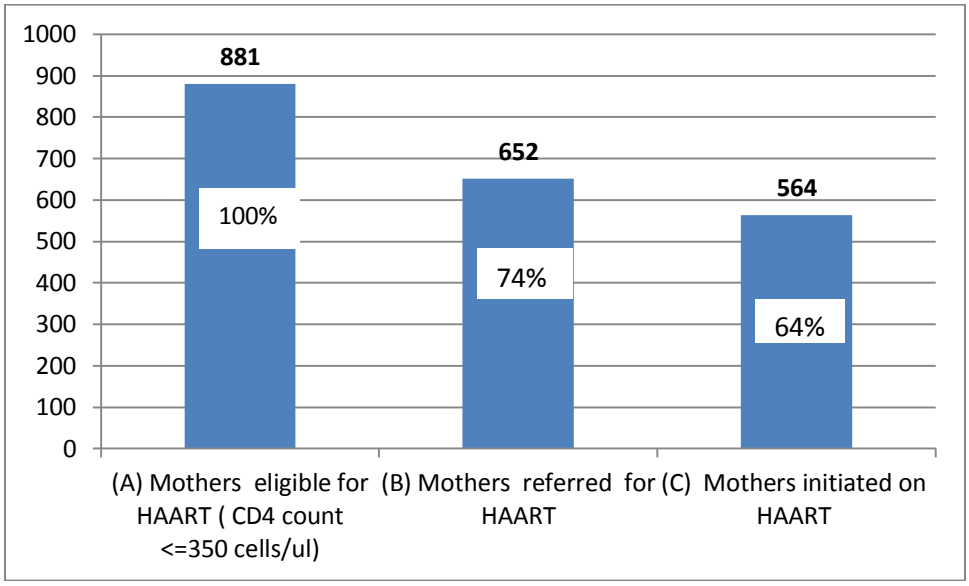


Figure 7: Cascade for lifelong ART



4.2. Paper 2: PMTCT coverage and Transmission

TITLE: Achievability of perinatal mother-to-child transmission elimination targets with prevention of mother-to-child transmission (PMTCT) service coverage levels lower than 95%

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Abstract

Objectives

Global targets aim to virtually eliminate mother-to-child transmission of HIV (MTCT). The 2010 overall national perinatal HIV transmission rate in South Africa is reported at 3.5%, however wide geographical differences (ranging 1.4%-5.9%) in MTCT were documented. We sought to determine reasons for these geographical differences.

Methods

A situational assessment was conducted among public facilities randomly selected from all nine provinces of South Africa using health worker interviews and record reviews. This was followed by a national survey which involved caregiver interviews and collection of blood samples (for HIV testing) from infants attending six weeks immunisations in sampled facilities. Maternal report of receiving antenatal antiretroviral treatment/ prophylaxis for any duration during pregnancy plus infant nevirapine (NVP)/ azidothymidine (AZT) received at birth was considered as a marker for total perinatal antiretroviral coverage. Provinces were categorised into two groups according to achievement of the UNGASS universal (defined as at least 80% coverage) antiretroviral coverage target. Individual, health facility and provincial level factors were considered in multivariate analysis.

Results

By 2010 three provinces achieved the target for universal access (≥80%) to antiretroviral treatments (range 80%-88%). The remaining six provinces had an average antiretroviral coverage of 69% (range 64%-76%). The average transmission rate in the three provinces that achieved ≥80% antiretroviral coverage was 2.8% compared to 4.9% in the six provinces that achieved <80% antiretroviral coverage. In a multivariate analysis provinces that did not achieve universal coverage had significantly higher transmission risk [OR 1.7, 95%CI 1.2 -2.6] compared to provinces that achieved universal coverage.

Conclusion

Our study shows PMTCT services coverage is a significant determinant of geographical variations in MTCT rates. The achievement of 2.8% transmission rate with 80-88% antiretroviral coverage contrasts with results from modelling studies that report the requirement of 95%-100% antiretroviral coverage for achieving perinatal MTCT elimination targets.

Key words: geographical variations, mother-to-child transmission of HIV, PMTCT cascade, universal access

Background

Global targets aim to reduce the risk of mother-to-child-transmission of HIV (MTCT) to below 2% perinatally and 5% by 18-months postnatally.[1] By mid-2010, an estimated 390 000 children globally were infected with HIV through mother-to-child transmission.[2] Reaching the global target for reducing new infant HIV infections from current levels to below 2% perinatally and 5% (43000) postnatally by 2015 requires substantial decline in the number of new infant HIV infections.[2]

Mother-to-child-transmission rates have been shown to have wide variations across populations and geographical areas. In South Africa substantial subpopulation level transmission rate differences have been reported. The Good Start study reported MTCT rates ranging from 8.6% in a well-functioning peri-urban site (Paarl) to 13.7% in a poorly functioning rural site (Rietvlei).[3] In the prevention of mother-to-child transmission (PMTCT) survey completed recently (2010), overall national perinatal HIV transmission rate in South Africa was reported at 3.5% (95%CI, 2.9-4.1), however there was wide variation between provinces in the perinatal transmission rate ranging between 1.4%-5.9%.[4] What explains this variation in transmission rates across provinces is not well understood.

To date no study attempts to assess the impact of PMTCT services coverage on transmission rate. A few mathematical modelling studies estimate the level of PMTCT services coverage required in order to significantly reduce population level MTCT rates.[5,6] Results from these modelling studies indicate a minimum of 95%-100% PMTCT coverage is required in order to approach the 2% perinatal and 5% postnatal (18-months) MTCT targets.[1,5]

In 2001, the United Nations General Assembly (UNGASS) set a target to ensure universal access (80% coverage) to effective antiretroviral treatment by 2010.[7] Recently new and ambitious targets have been set to achieve 90% coverage of PMTCT services.[1] Whilst there are progress reports and data from modelling

exercises tracking the achievement of these targets, no study has used real data to measure population level MTCT reductions achieved as a result of the attainment of the above targets.

This study aims to explore health facility and individual level factors that explain geographical variations in mother-to-child transmission rate across the nine provinces of South Africa, using national survey data collected from randomly selected public primary health care facilities within the nine provinces of South Africa. By doing this, the study assessed the level of MTCT rates achieved as a result of the attainment of the UNGASS ≥ 80% provincial PMTCT cascade coverage target.

Methods

Study design, sample size, sampling

Two quantitative studies: (i) a cross-sectional situational assessment of health facilities and (ii) a facility-based six weeks cross-sectional survey among mother/caregiver-infant pairs were conducted at public primary health care facilities randomly selected from the total 3390 public primary health care facilities (PHCs) and community health centres (CHCs) in South Africa.

A stratified multistage sampling design was used to select the study facilities. Facilities in each province were stratified into four groups based on their six weeks annual immunisations number (extracted from the 2007 district health information System) and antenatal HIV prevalence of the district (from 2009 antenatal survey) as follows: small facilities with <130 annual immunisation, medium size facilities with 130 -300 annual immunisation, large (annual immunisation >= 300) facilities with antenatal HIV prevalence below the national HIV prevalence estimate (29%), and large facilities (>=300 annual immunisation) with antenatal HIV prevalence above or equal to 29%.[8]

The sample size of medium and large facilities was determined based on antenatal HIV prevalence and transmission rate estimates (detailed description of sample size is

presented elsewhere[4]). Five hundred and eighty (580) facilities were selected from medium and large size facilities using probability proportional to size sampling method. Additional 100 facilities (10-20 per provinces) were purposively selected from small facilities. This gave a total of 680 facilities selected from small, medium and large facilities.

Situational Assessment

The situational assessment was conducted from January to May 2010 in the total 680 facilities selected from small medium and large facilities. This component of the survey targeted collection of data on human resources, referral systems, record keeping, linkage and organization of the PMTCT programme using structured interviews with clinic managers, health information officers, immunisation nurses, PMTCT nurses and sick-child (IMCI) nurses.

SAPMTCTE survey

Following the situational assessment from June to November 2010, a cross-sectional survey was conducted among mother/caregiver-infant pairs visiting immunisation service points in the 580 facilities selected from medium and large size facilities. The 100 facilities selected from small facilities were not included in this component of the survey due to logistic feasibility. A fixed number of mother/caregiver-infant pairs were enrolled from each facility over a planned three to four weeks recruitment period. The desired sample size for the study was the collection of interview data and infant blood samples from 12200 mother-infant pairs. Sample size was calculated with a projected transmission rate of 7% for dual therapy, 15% for sdNVP, and 29% for untreated MTCT. A precision level of 1%-2%, an estimated 29% of HIV-exposure among infants and a design effect of 2 was considered in calculating sample size. Further details on parameters used for sample size calculation and provincial details are presented elsewhere.[4]

10 820 mother/caregiver-infant pairs visiting six weeks immunisation service were approached and screened for eligibility by trained nurses. Mothers/caregivers were

requested for consent to participate in the study if their infants were 4-8 weeks old and had no emergency illness. Those who gave consent were interviewed on antenatal and peripartum services received socioeconomic status, and knowledge about PMTCT and PMTCT services attended. The infant Road-to-health-card was checked for documentation of maternal and infant status, gestational age at birth and birth weight.

After interview, pre-test counselling was given to each mother individually and if mothers consented, infant blood samples (dried blood spots) were collected from heel prick. Dried blood spot (DBS) specimens were tested for HIV by means of an enzyme immunoassay (EIA) (Genscreen HIV antibody assay). A positive EIA result showed HIV-exposure of infant. A qualitative DNA PCR (Amplicor HIV-1 DNA PCR version 2.0 assay, Roche Diagnostics, Branchburg, NJ) test was performed on all EIA positive DBS to determine whether the infant was currently HIV-positive. Infant test results were returned to mothers through the health facility using the routine transportation system. De-identified infant test results were linked with the interview data using patient identifier (barcode).

Statistical analysis

Hard copy questionnaires were used for data collection of the situational assessment. The SAPMTCTE survey data was collected on electronic (cell phone) questionnaires. The PMTCT survey and the situational assessment data were combined on STATA SE (version 12, Texas, 77845 USA) for analysis. Survey design data analysis method was applied in all univariate and multivariate analysis. Data was weighted for sample size realisation and number of live births in each province.

Provincial (province level) perinatal ARV regimen coverage was calculated from the total number of known and unknown HIV-positive mothers in the province who received maternal azidothymidine (AZT) or HAART for any duration during pregnancy plus infant nevirapine (NVP)/AZT received at birth (maternal and infant ARV prophylaxis/ HAART) – this was considered as a marker for perinatal PMTCT

cascade coverage. Provinces were categorised into two groups based on their achievement of the UNGASS universal access (defined as achievement of at least 80% antiretroviral coverage) target for ARV regimens. Provinces that achieved≥80% maternal and infant ARV prophylaxis/HAART coverage were classified as provinces that achieved the universal PMTCT coverage target; and provinces that achieved below 80% total ARV regimen (maternal and infant ARV prophylaxis / HAART) coverage were categorised as provinces that did not achieve the universal PMTCT coverage targets for 2010.

Whilst our marker for ARV regimen coverage (maternal and infant ARV prophylaxis/ HAART) permits monitoring of the total coverage of maternal and infant ARV regimens, this indicator does not distinguish whether appropriate type of regimen was received or for how long the treatment was received. For this reason, CD4 count number was used to calculate the number of mothers eligible (CD4 count ≤350 cells/µl) for initiation on HAART, and consecutively HAART coverage was calculated for each province. However, six out of the nine provinces had poor response rate for CD4 count number, therefore we could not use the HAART coverage data to assess coverage of appropriate ARV regimen. In three of the provinces we had a relatively higher CD4 count number response rate, thus HAART coverage data was used to explain differences in the three provinces transmission rates. We also had incomplete data for calculating duration of treatment.

Multivariate analysis of factors affecting mother-to-child transmission rate using multiple logistic regression model included analysis of individual biological, clinical and behavioural factors, facility level factors (health systems characteristics) and provincial coverage of the PMTCT cascade. A logistic regression model was fitted to compare transmission differences between provinces that achieved universal coverage (80%) of ARV regimens and provinces that did not achieve universal coverage. The dependent variable for this analysis was –infant HIV infection. Independent variables were taken from both the situational assessment and the six weeks survey data. The following variables were considered in adjusting this model:

from individual level factors, marital status, maternal age, education, socioeconomic status (SES), planned pregnancy, number of life time pregnancies, gestational age at birth, infant birth weight, and history of child sickness since birth. At facility level, human resources, referral system, availability of on-site ARV clinic, task shifting and community involvement were included. List of variables included in the final model are presented in table 7.

SES score was created from five socioeconomic indicators namely: stove, refrigerator, radio, TV and car. All variables except gestational age at first antenatal visit and CD4 count had 85% and above response rate. Data was imputed using chained equations multiple imputation method for all variables included in the analysis. Data imputation was considered for CD4 count data, but with six of the nine provinces having more than 50% of data missing, imputed CD4 count data could not be used for multivariate analysis. For the three provinces that had a relatively higher (>60%) response rate for CD4 count number (two of the province had >75% response rate and one province had 63% response rate), we used imputed data to explain provincial transmission differences.

The survey protocol was approved by the institutional review board at Medical Research Council of South Africa and the Office of Associate Director of Science at the Centers for Disease Control and Prevention, United States of America. All study participants provided written informed consent.

Results

Six out of nine provinces achieved above 80% of the desired sample size in the PMTCT survey. One province (Limpopo- LP) had 73% sample size realisation and two provinces (Eastern Cape -EC and Northern Cape-NC) had sample size realisation below 70%. 10820 mothers/caregivers who brought infants to sample clinics for six weeks immunisation services were approached and screened for eligibility. Ninety nine percent (10735) of total screened mother/caregiver infant pairs were eligible and

agreed for interview, of which 94% provided blood sample for infant HIV testing. In total 10182 interview and blood sample data was available for both HIV-exposed and -unexposed infants. For this study 3085 HIV-exposed infants who had both EIA and PCR test result were included in the analysis (fig 8).

Mothers of HIV-positive and HIV-exposed uninfected infants had similar maternal age, and education in both provinces that achieved universal coverage and provinces that did not achieve universal coverage (table 5). SES in provinces that achieved universal coverage was slightly higher than the provinces that did not achieve universal coverage; and within provinces that achieved universal coverage, SES of HIV-infected infants was slightly lower. In both provincial categories, more than a quarter of mothers of HIV-exposed infants reported their pregnancy was a first pregnancy compared to below a quarter of mothers of HIV-exposed uninfected infants who reported their pregnancy as first pregnancy. Planned pregnancies were higher in provinces that did not achieve the universal coverage target compared to provinces that achieved the universal PMTCT coverage target. Low birth weight (<2.5kg) among HIV-infected infants was higher (25%) among provinces that did not achieve universal coverage compared to provinces that achieved universal coverage (19%).

Provincial coverage of PMTCT services and transmission rates

PMTCT service coverage

Three provinces achieved the target for universal access (≥80%) to antiretroviral regimens (maternal and infant ARV prophylaxis/HAART) by 2010. The other six provinces achieved below 80% total ARV regimens coverage (table 6).

A prominent difference between the provinces that achieved the universal access target and the provinces that did not achieve the universal access target was that whilst the three provinces that achieved the universal access target had >90%

coverage for HIV status knowledge and ≥80% coverage for CD4 count and total ARV regimens, the other six provinces that did not achieve the universal access target had below 90% coverage for HIV status knowledge and below 80% coverage for CD4 count and total ARV regimens coverage. The average total ARV regimens (maternal and infant ARV prophylaxis/HAART) coverage in the three provinces that achieved the universal access target was 84% (range: 80%-88% ; 95% CI: 81% – 86%) as compared to 69% (range: 65%-77%; 66% -71%) total ARV regimens coverage in the remaining six provinces. Similarly average CD4 count coverage in the three provinces was substantially higher (83%; ranging 80%-89%; 95% CI: 80% - 86%) compared to the remaining six provinces (62%; ranging 54%-69%; 95% CI: 59% - 65%) (table 6).

Transmission rates

The average perinatal transmission rate in the three provinces that achieved the universal access target for antiretroviral regimen coverage was 2.8% (95% CI: 2.0%-3.6%) compared to 4.9% (95% CI: 3.8%-6.0%) in the remaining six provinces that did not achieve the universal access target (table 6).

Transmission rates in the three provinces that achieved universal (80%) coverage

Among the three provinces that achieved universal coverage, two provinces had below 3% (2.5% and 2.9%) transmission rate and one province had above 3% (3.9%) transmission rate. Among these three provinces, HAART coverage was relatively higher (65%) in the province (Gauteng -GP) with the lowest (2.5%) transmission rate, whilst the province (Western Cape -WC) with the highest transmission rate (3.9%) had the lowest HAART coverage (59%) of the three provinces (table 6).

Transmission rates in the six provinces that did not achieve universal (80%) coverage

Among the six provinces that achieved below 80% total ARV regimen coverage, three provinces had transmission rate above 5%, one province had transmission rate above 4% (4.4%) and two provinces had below 4% transmission rate.

The province (North West - NW) which had 4.4% transmission rate had the highest HIV status knowledge (87%), and total ARV regimens coverage (77%) of the six provinces.

Of the provinces with below 4% transmission rate, one province (NC) had poor sample size realisation, hence we could not confirm whether the estimated transmission rate (1.4%) for this province was a true estimate.

The other province (LP) which had below 4% transmission rate had the lowest ARV regimen coverage (65%) and the lowest CD4 count coverage (54%) of the nine provinces, but the province also had low (3.6%) transmission rate. We did not see any association between the PMTCT cascade coverage and transmission rate in this province. The province had below 80% (73%) sample size realisation.

Free State (FS) also had the second highest ARV regimen coverage compared to the six provinces that did not achieve the universal access target but this province has the highest transmission rate (5.9%). Most socio-demographic, maternal and infant history indicators were similar between LP, FS and the rest of the 4 provinces in this group.

Multivariate analysis

In a multivariate analysis (table 7), after adjusting for other covariates, provinces that had below 80% ARV coverage had significantly higher transmission risk [OR1.7, 95%CI 1.2 -2.6] compared to provinces that achieved ≥80% ARV coverage.

Among other factors found influential in multivariate analysis, transmission rate among mother-infant pairs who received both maternal and infant ARVs was lower by 56% compared to infants who received no or incomplete (mother only or infant only ARVs) ARVs. Any breastfeeding (from eight days recall data) was associated with 1.8 times higher risk of HIV transmission compared to not breastfeeding. At health facility level, facilities that have two or less than two health care personnel

who provide VCT service had 2.2 times higher transmission occurrences compared to facilities that have more than two health care personnel providing VCT service. Uptake of maternal and infant ARV regimen in facilities that have two or less than two health care personnel for VCT was lower by 20% from the national uptake of maternal and infant ARV. Low birth weight was significantly associated with transmission in both the univariate and multivariate analysis (AOR 1.8, 95% CI 1.1 - 2.9).

Other socio-demographic indictors and antenatal and postnatal histories did not have statistically significant influence on transmission.

Discussion

In recent years South Africa has shown significant progress in implementing effective interventions that are designed to reduce mother-to-child-transmission rates to below elimination thresholds. This survey shows while the efforts to implement effective interventions has resulted in declining national transmission rate trends, these gains are not necessarily uniform across provinces. According to our survey, there are substantial transmission differences across provinces (ranging 1.4%-5.9%). Reports from other studies also show similar variations in transmission rates within subpopulations in South Africa.[9] National level estimates often mask geographical and subpopulation differences in HIV transmission rates. Thus in assessing PMTCT programmes progress, subpopulation level inequalities should be recognised.[9]

Our study findings show that provincial level transmission rate differences are explained by differences in uptake of ARV regimens and PMTCT cascade services. Three provinces achieved universal (80%) ARV regimen coverage. PMTCT services coverage (i.e. HIV status knowledge, coverage of CD4 count and ARV regimen coverage) varied widely between the three provinces that achieved universal coverage and provinces that did not achieve universal coverage. Provinces that achieved universal coverage had lower transmission rates compared to provinces that

did not achieve universal coverage. The average transmission rate in the three provinces that achieved universal coverage was close to the global target at 2.8% compared to 4.9% in the six provinces that did not achieve universal coverage. After adjusting for multilevel covariates, the transmission rate in low (<80%) ARV regimen coverage provinces was higher by 70% [AOR 1.7, 95%CI 1.2 -2.6] compared to the transmission rate in the provinces that achieved ≥80% ARV regimen coverage.

This study shows that significantly lower transmission rates (2.8%) can be achieved by increasing PMTCT uptake rates to 80% and above across subpopulations. Two of the three provinces (GP and KZN) that achieved the 80% universal coverage target had below 3% transmission rate. Whilst the third province (WC) in this group had above 3% transmission rate, this may be explained by the somewhat lower (59%) HAART coverage in the province.

In the other six provinces ARV regimen coverage was below 80%. Consequently, three of the provinces with below 80% ARV regimen coverage had above 5% transmission rate. Of the six provinces, one province (NW) that achieved below 80% ARV regimen coverage had 4.4% transmission rate - this relatively lower transmission rate compared to the other provinces in the group may be explained by the province's higher ARV regimen (77%) and HIV status knowledge coverage (87%).

In the remaining two provinces of the six provinces with ARV regimen coverage below 80%: (i) one province (NC) had low transmission rate (1.4%), but the transmission rate of this province could not be confirmed as a true estimate due to poor sample size realisation in the province (<70%), (ii) LP had low transmission rate (3.6%) and low ARV regimen coverage (65%) compared to the other five provinces in this group, whilst FS had the second highest ARV regimen (76%) coverage of the six provinces but had the highest transmission rate (5.9%). We did not see any association, in a univariate analysis, between PMTCT cascade coverage and MTCT

in the three provinces mentioned above. This lack of association could be due to factors that are not considered in the study (e.g. adherence to treatment, duration and type of treatment were not considered in measuring ARV regimen coverage) or due to sample size inadequacy (two of the province had a relatively lower -<75% - sample size realisation). For this reason, in the three provinces where clear association was not established, we recommend results from repeat surveys to be monitored to establish the trend in both the coverage of PMTCT cascade services and transmission rate.

None of the provinces achieved the UNAIDS 90% effective ARV regimen target. The maximum total ARV coverage achieved was 88% in KZN. In the three provinces HAART coverage for women with CD4 ≤350 was assessed, the coverage of HAART was below 70% in all three provinces. Despite this relatively lower antiretroviral regimens coverage, two provinces achieved transmission rate below 3% close to the eMTCT targets. These results are somewhat in contrast with the findings of a recent modelling study by Ciaranello et al. that emphasises the need to achieve near to 100% effective ARV regimen coverage in order to approach the MTCT elimination targets.[5] According to Ciaranello and colleagues, with 95% uptake of WHO Option A treatment guideline, 4-8 weeks transmission rates could only be lowered to 4.1%. In contrast to Ciaranello and colleagues' findings, our study shows, in all provinces that achieved 80% ARV regimen coverage, transmission rate was below 4%.

PMTCT services coverage (i.e. HIV status knowledge, coverage of CD4 count and ARV regimen coverage) varied widely between the three provinces that achieved universal coverage and the remaining six provinces that did not achieve universal coverage. Given the observed strong association between PMTCT cascade coverage and transmission rates, this study recommends attention to be given to provinces that have reported high transmission rates and low PMTCT cascade coverage. One of the predictors of transmission rate in this study was shortage of human resources. In the study facilities with two or less than two health care personnel providing voluntary counselling and testing (VCT) had higher (AOR 2.2, 95% CI 1.1-4.3) transmission

risk compared to facilities that had more than two health care personnel that provide VCT service. Sufficient and equitable distribution of human resources is an important influential factor in the provision of PMTCT services.

Our findings on human resources are substantiated by a report from Day and Gray (2008) and reports from provincial departments.[10-12] According to Day and Gray (2008), three of the six provinces identified in this study as low performing provinces (>5% transmission rate provinces) have the lowest number of professional nurses for their population level compared to the rest of the six provinces; whilst availability of human resource and non-governmental supporting organizations (NGOs) in the three well performing provinces is reported to be higher compared to the remaining six-provinces. The 2009 provincial report from one of the low performing provinces also reported chronic human resource shortages as the key challenge of the health service. The report stated most clinics in the province are overcrowded and patients are often returned home due to long queues.[12]

In addition, strategies tailored to specific problems of the provinces are required in order to meet the unique challenges that each specific province is confronted with. Some of these challenges may include, distance to health facilities, inadequate ARV sites, inequity in allocation of PHC expenditure, and lack of a strong monitoring system.[10,12] Further in-depth research is required to better understand this and other operational, structural and social challenges of PMTCT programmes in provinces identified as low performing provinces.

Comparison of provincial ARV coverage with provincial maternal mortality ratio (MMR) showed no trend/association between ARV coverage and MMR (table 8).[13] Transmission rate was not also associated with antenatal HIV prevalence (table 9).[14]

The following limitations of this study are recognized. Our sample size is calculated to give a stable transmission rate estimate at provincial level. However, since our sample size achievement in two of the nine provinces was lower (<70%), the

transmission estimates for the two provinces have lower precision. We attempted to validate our data by comparing with district health information system (DHIS) data. However the reports from DHIS data are exaggerated due to double counting and data quality problems. Thus comparison could not be made between DHIS and the PMTCT survey data. We had incomplete CD4 count and treatment duration data, and viral load data was not collected. Lastly, neither our studies nor other modelling studies have factored the influence of adherence to treatment, maternal previous experience of treatment and maternal health condition in assessing the influence of ARV regimens coverage on transmission rate.

In conclusion our study shows that PMTCT services coverage is a significant determinant of geographical variations in MTCT rates. The 2.8% transmission rate reported in provinces that achieved universal coverage suggests achievability of MTCT elimination targets with PMTCT service coverage levels lower than 95%.

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Figure 8: Study profile

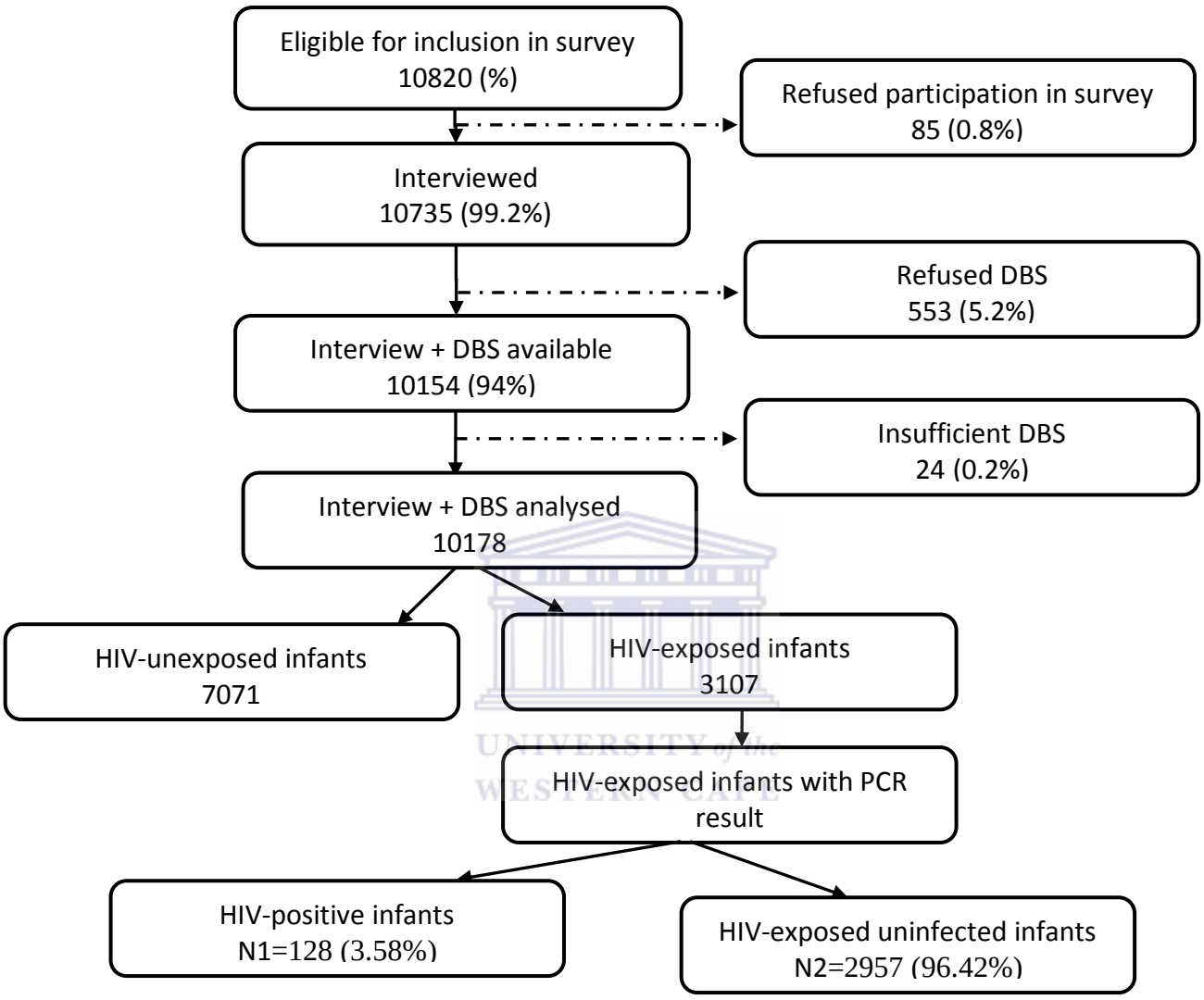

Table 5: Socio-demographic characteristics of the study population by infant HIV infection status and provincial categories

	Provinces achieved universal access [# %)] n1=1349		**Provinces did not achieve universal access [# %)] n1 =1736**		**ZA [# (%)] (n1=3085)**
	HEI infected [# (%)] n1=41	**HEI uninfected [# %)] n1=1308**	**HEI infected [# (%)] n1=87**	**HEI uninfected [# %)] n1=1649**	**HEI (both infected and uninfected)**
Maternal Age					
Mean (Range)	27.7(16-46)	26.3 (17-40)	27.8 (15-46)	27.8 (16-46)	27.7 (15-46)
Maternal Education					
None	0 (0)	100 (2)	2 (2)	62 (4)	89 (2.6)
Grade 1-7	9 (24)	202 (15)	14 (15)	366 (22)	591(18.2)
Grade 8-12	30 (71)	1029 (79)	68 (79)	1165 (71)	2292 (75.8)
Above Grade12	1 (1)	43 (3)	3 (4)	33 (2)	80 (2.7)
No information	1(4)	9(1)	0 (0)	23 (1)	33 (0.81)
Marital status					
Single	33 (80)	1029 (82)	65 (76)	1204 (73)	2331 (78.5)
Married/cohabiting	7 (16)	260 (17)	22 (24)	418 (25)	707 (20.1)
Widowed/Divorced	0 (0)	13 (1)	0 (0)	12 (1)	25 (0.8)
No information	1 (4)	6 (0)	0 (0)	15 (1)	22 (0.6)
Infant Race					
Black	38 (97)	1280 (98)	85 (98)	1607 (98)	3010 (98.6)
Coloured	3 (3)	25 (1)	2 (2)	39 (2)	69(1.3)
White, Indian, other	0 (0)	3 (1)	0 (0	3 (0)	6 (0.1)
SES quintile					
Lowest	7 (21)	200 (15)	23 (27)	401 (27)	631 (19.9)
Lower	10 (22)	246 (19)	18 (23)	358 (23)	632 (20.6)
Average	21 (52)	747 (57)	41 (44)	782 (44)	1591 (51.6)
Above average	3 (5)	115 (9)	5 (6)	108 (6)	231 (7.8)
Number of lifetime pregnancy					
1	12 (30)	269 (20)	24 (27)	370 (24)	675 (21.5)
2	15 (34)	513 (39)	24 (27)	556 (33)	1108(36.6)
3	9 (21)	302 (23)	20 (22)	370 (22)	701 (22.7)
≥ 4	3 (9)	198 (16)	16 (20)	300 (18)	517 (16.8)
missing	2 (6)	26 (2)	3 (4)	53 (3)	84 (2.4)
Planned Pregnancy					
Yes					
No	7 (20)	414 (32)	33 (40)	672 (41)	1126 (35.5)
Missing	31 (72)	858 (65)	50 (56)	912 (55)	1851 (61.4)
	3 (7)	3 (7)	4 (4)	65 (4)	108 (3.1)

Gestational age at 1st ANC					
1st trimester	6 (15)	254 (18)	14 (14)	397 (23)	671 (19.3)
2nd trimester	17 (43)	648 (53)	42 (42)	732 (42)	1439 (48.3)
3rd trimester	5 (15)	157 (13)	8 (9)	183 (11)	353(12.4)
Missing	13 (27)	249 (16)	23 (35)	337 (24)	622 (20.0)
Infant gender					
Male	21 (53)	651 (49)	45 (56)	813 (49)	5222 (50.5)
Female	20 (47)	657 (51)	42 (45)	836 (51)	5135 (49.5)
Infant birth weight					
<2.5kg	7 (19)	219 (17)	26 (25)	284 (17)	536 (16.8)
>=2.5kg	34 (81)	1089 (83)	61 (75)	1365 (83)	2549 (83)

Table 6: Provincial coverage of PMTCT services and transmission rates

	HIV status knowledge	CD4 count [95% CI]	ARV regimen**	HAART coverage	Transmission rate [95% CI]
Provinces achieved the UNGASS target of ≥80% ARV regimen coverage					
GP	92% [89%-94%]	80% [74%-83%]	80% [75%-84%]	65% [62%-69%]	2.5% [1.5-3.6]
KZN	96% [94%-98%]	86% [82%-89%]	88% [84%-90%]	62% [60%-66%	2.9% [1.7-4.0]
WC	95% [88%-98%]	89% [84%-93%]	86% [81%-90%]	59% [52%-63%]	3.9% [1.9-5.8]
Average	**94% [93%-96%]**	**83%** [80%-86%]	**84% [81%-86%**		**2.8%** [2.0-3.6]
Provinces achieved below the UNGASS (<80%) ARV regimen target					
EC	82% [77%-87%]	57% [49%-4%]	66% [60%-72%]	***	5.5% [2.9-8.1]*
FS	87% [84%-90%]	74% [68%-79%]	76% [71%-81%]	***	5.9% [3.8-8.0]
LP	79% [94%-98%]	54% [46%-61%]	65% [59%-70%]	***	3.6% [1.4-5.8]
MP	84% [76%-87%]	63% [57%-68%]	65% [60%-69%]	***	5.7% [4.1-7.3]
NC	87% [76%-93%]	66% [53%-77%]	73% [64%-80%]	***	1.4% [0.1-3.4]*
NW	88% [84%-91%]	69% [64%-74%]	77% [71%-81%]	***	4.4% [2.9-5.9]
Average	**85% [82%-86%]**	**62% [59%-65%]**	**69% [66%-71%**	***	**4.9% [3.8-6.0]**

**** Sample size achievement was low in the two provinces***
***** Receiving maternal HAART or ARV prophylaxis and infant NVP/AZT***
******Response rate for CD4 count number <50% hence HAART coverage is not reported.***

Table 7: Factors explaining transmission differences

Significant Predictors of transmission	Unadjusted ratio [95% CI], p.value	Adjusted Odds ratio [95%CI], p.value
Provinces with ARV regimen coverage below the universal coverage (80%) target	1.8 [1.2-2.6] 0.003	1.7 [1.2 – 2.6 0.011
Facilities that have two or less than two health care personnel doing VCT	2.1 [1.1 -3.8] 0.019	2.2 [1.1 -4.3] 0.024
Low (2.5 kg) birth weight	1.7 [1.1 – 2.9] 0.030	1.8 [1.1-2.9] 0.028
Receiving maternal and infant ARV prophylaxis/HAART	0.3[0.2-0.5] 0.000	0.44[0.27-0.71] 0.001
Any breastfeeding received in the last 8 days	2.2 [1.4-3.4] 0.000	1.8 [1.2 – 2.9] 0.007
Child sick (needing clinic attendance/ hospitalization) since birth	1.1 [0.5-2.2] 0.847	1.3 [0.6 -2.7] 0.510
Gestational age at first antenatal visit (in weeks)	1.0 [1.0-1.1] 0.257	2.0 [1.0 – 1.1] 0.320
Not planned pregnancy	1.2 [0.8-2.0] 0.339	1.3 [0.8 – 2.1] 0.266
Socioeconomic scores	0.9 [0.8-1.0] 0.161	1.0 [0.9-1.3] 0.820
Maternal age (5 years interval)	0.9 [0.8-1.1] 0.431	1.0 [0.8 -1.2] 0.904
Attending facilities with on-site ARV clinic	0.9 [0.6 -1.4] 0.804	0.7 [0.5 – 1.1] 0.139
Attending facilities that have linkage with community	1.0 [0.6 -1.7] 0.840	1.1 [0.6-1.7] 0.829
Mothers who ever heard of PMTCT programme	1.2 [0.6-1.9] 0.813	1.3 [0.6-2.1] 0.629
Education level (4 grades interval)	1.1 [0.7-1.5] 0.777	1.4 [0.8-1.8] 0.335

Table 8: Comparison of ARV regimen coverage with maternal mortality ratio 2008-

Province	**ARV regimen coverage**	**MMR***
KZN	88%	192.3
WC	86%	84.9
GP	80%	147.5
NW	77%	229.5
FS	76%	289.1
NC	73%	249.98
EC	66%	193.3
MP	65%	183.5
LP	65%	164.7

***** National Committee on Confidential Enquiries into MaternalDeaths. Saving Mothers: Fourth Report on the Confidentia Enquiries into Maternal Deaths in South Africa 2005-2007. Pretoria: National Department of Health; 2008.

Table 9: Comparison of provincial transmission rate level with antenatal HIV prevalence

Province	**Transmission rate**	**Antenatal HIV prevalence**
FS	5.9%	29%
MP	5.7%	34%
EC	5.5%	24%
NW	4.4%	30%
WC	3.9%	15%
LP	3.6%	20%
KZN	2.9%	37%
GP	2.5%	31%
NC	1.4%	14%

4.3. Paper 3: Gaps in in approaches for identifying HEI for EID service

Reasons for missed opportunities of early infant HIV testing services at six week immunisation visits: Results of a national situational assessment in South Africa, a high HIV prevalence setting

Running Heading / Short Title: Missed opportunities for early infant HIV testing services

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Abstract

Objectives:

Early infant diagnosis (EID) services are recommended to be offered at six week immunisation visits. Despite the high six week immunisation attendance rate, many sub-Saharan countries have low EID coverage. We explored reasons for missed opportunities of EID services at six week immunisation visits.

Methods:

A national situational assessment was undertaken among randomly selected facilities (n=680) to ascertain procedures for EID. Following this, a cross-sectional survey was conducted in a sub-sample of selected facilities (n=580) to assess the HIV-status of 4-8 weeks old infants receiving six weeks immunisation. Frequency tables were used to describe potential missed opportunities for EID. Logistic regression assessed key factors influencing maternal reporting for EID.

Results:

EID services were available in >95% facilities, and 72% immunisation service points (ISPs). The majority (68%) of ISPs provide EID for infants with reported (by mothers) or documented (on infant's Road to Health Chart - RtHC) HIV-exposure; only 9% ISPs offered provider-initiated counselling and testing (PICT) for undocumented/unknown HIV-exposed infants (HEI). In the cross-sectional survey 32% of infants were HIV-exposed, similar with the infant HIV-exposure rate reported in the 2009 antenatal survey. However, only 35% of known HIV-positive mothers intended to report their HIV-exposure, and only 55% had RtHC that reflect their HIV-status. Poor maternal reporting for EID was associated with feeling discriminated, missing maternal/infant antiretrovirals, and inadequate knowledge about transmission.

Conclusion:

Attendance of six weeks immunisation is high among HEI. Missed opportunities for EID were attributed to poor documentation of HIV-status on RtHC, inadequate

maternal knowledge and fear of discrimination to disclose HIV-status, and the lack of PICT service to undocumented/unknown HEI.

Key Words: EID service, PICT, Targeted testing, universal testing, missed opportunities

Background

HIV is a significant contributor to child morbidity and mortality in sub-Saharan countries.[1,2] HIV progresses more rapidly in children, especially in infants who acquired the infection in utero.[3,4] Early initiation of systematic antiretroviral treatment (ART) substantially reduces the risk of death and disease progression and is standard of care in South Africa.[3,5] Without treatment 48% of perinatally infected and 22% of infants infected through breastfeeding die before their first birthday.[6] HIV-exposed uninfected infants also have higher risk of morbidity and mortality than HIV-unexposed infants.[7]

Identifying HIV-exposed infants is the first critical step in the provision of EID services and linkage to care. In many developing countries, including South Africa, despite substantial improvement in antenatal testing, and maternal enrolment into prevention of mother-to-child transmission (PMTCT) programmes, identifying HIV-exposed infants after birth for early testing and follow-up services has proven to be challenging.[8-10]

Following the introduction of HIV DNA PCR (deoxyribose nucleic acid polymerase chain reaction) testing on dried blood spots (DBS), which simplified the collection and transportation of infant blood samples, many sub-Saharan countries have made significant progress in scaling-up EID services to lower level health care facilities.[11] EID services are recommended to be offered at six week immunisation visits. Many sub-Saharan countries have high coverage rates for six week immunisations. This however has not yet translated into high early infant diagnosis rates for HEI.[11,12] In 2010 globally less than one-third (28%) of HEI received testing by the age of 2 months.[13] In South Africa a review of 2008 and 2010 laboratory data for eight of the provinces (excluding KwaZulu-Natal) indicated 69% and 45% of HEI, respectively, missed opportunities for testing by the age of 2 months.[12]

The 2010 World Health Organization (WHO) guidance on EID recommends that the exposure status of all infants should be determined at the six weeks postnatal visit or earlier, and that all HIV-exposed infants should receive a virological test at six weeks.[14] Currently countries are at various stages of adopting this guideline. At the time of this study, South Africa (SA) was transitioning from the 2008 to the 2010 national EID guideline. The 2008 and 2010 guidelines recommended that infant HIV-exposure status be determined by checking documentation on RtHC or through maternal reporting of HIV-status (referred as targeted testing).[15] The 2010 guideline further stipulated that if infant HIV-exposure status is undocumented/unknown, provider-initiated-counselling and maternal HIV testing should be offered, with same-day infant PCR testing for HIV-exposed infants.[16] If mother refuses or is unavailable for HIV testing an infant rapid test to assess exposure is recommended with same-day PCR testing for HEI. At the time of this study most facilities implemented the previous (2008) EID guideline.

Few studies have gathered national data to assess programs for identifying HIV-exposed and infected infants.[11,17] Several challenges to implementing EID services (including structural challenges, geographical accessibility, maternal knowledge, and psycho-social barriers) have been reported in these studies.[11,17-21] However no study has explored the impact of approaches used at facility level for identifying HIV-exposed and infected infants. This study combined facility and individual-level data collected from across the nine provinces of South Africa to explore how HIV-exposed infants are identified and diagnosed at immunisation service points and report missed opportunities (for EID) occurring due to gaps in approaches used for identifying HEI from six week immunisation visit.

Methods

Study design

A cross-sectional facility-level situational assessment of EID services was conducted from January-May 2010. Between two and nine months later, a cross-sectional

PMTCT survey was conducted among caregiver-infant pairs attending a sub-sample of facilities for their six weeks immunisation.

Facility Sampling

Three thousand three hundred ninety (3390) community health centres and clinics were eligible for inclusion in the sampling frame.[22] These facilities were stratified into four groups: small (<130 annual Diphtheria-Tetanus-Pertussis-1 (DTP1) coverage), medium (130-300 annual DTP1 coverage), large (≥300 annual DTP1 coverage) with below the 2009 national average antenatal HIV prevalence (<29%) and large with above the 2009 national average antenatal HIV prevalence (≥29%). Immunisation coverage was based on the 2007 district health information system (DHIS) data.

The following parameters were taken into account to determine the sample size of medium and large facilities: the 2009 antenatal HIV prevalence data, transmission rate estimates from two KwaZulu-Natal (KZN) surveys, and the coverage of ARV prophylaxis in each province from DHIS report. Sample size was calculated using nQuery Advisor Version 7 software for specified precision levels (±2%) and a design effect of 2. Five hundred eighty (580) facilities were selected from medium and large size facilities using probability proportional to size (PPS) sampling method. The sample size of small facilities was decided based on consideration of the resource allocated for the study. Based on this, 100 facilities (10-20 facilities per province) were selected from small (<130 annual immunisation number) facilities using the PPS sampling method. We took into consideration the logistic and financial resource allocated for the study to decide on. In total 680 facilities were planned for the situational assessment. The cross-sectional PMTCT survey was conducted in a sub-sample of facilities (n=580) selected from medium and large facilities. Small facilities were not included in the cross-sectional PMTCT survey due to logistic feasibility. Detailed description of sampling frame, sampling and sample size is presented elsewhere.[23]

Data Collection Procedures: Situational assessment

Trained field workers (not nurses) used structured questionnaires to conduct face to face interviews with clinic managers and nurses providing immunisation, PMTCT and sick-child services in each selected facility and with district health information officers. Open-ended and close-ended questions were used to collect data on implementation of EID-related policies and procedures, staff attitudes towards EID, and the use of the RtHC at ISPs to identify HEI.

The questionnaire was piloted in two clinics that were not sampled for the main study. Field workers underwent standardised training (four days). The Medical Research Council Ethics Committee approved the final protocol (Ref: EC09-002). Approval was obtained from National and Provincial Departments of Health before commencing the fieldwork. Informed verbal consent was obtained from all respondents.

The PMTCT cross-sectional survey

From June to November 2010, a cross-sectional survey was conducted among mother/caregiver-infant pairs visiting primary healthcare (PHC) facilities for six weeks immunisation. The main objective of the survey was to provide national and provincial level estimates of infant HIV prevalence and vertical HIV transmission. The calculated desired sample size was the collection of interview data and infant blood sample from 12200 mother-infant pairs visiting for six weeks immunisation service.

10820 mother/caregiver-infant pairs visiting six weeks immunisation services were approached by trained nurse data collectors and screened for eligibility. Consenting mothers, with infants aged 4-8 weeks and no emergency illness were enrolled and interviewed face-to-face. Data on reasons for the visit, antenatal and peripartum

PMTCT services received and knowledge about PMTCT were gathered. The road-to-health-card was checked for documentation of maternal and infant status. The questionnaire was translated into all 11 South African official languages and piloted in three languages prior to the survey.

After the interview, pre-test counselling was given to each mother individually, following which mothers were requested for consent to collect a heel prick blood sample from the infant with an option to know the HIV test result of the infant. Mothers who agreed to infant testing were given confidential linked (names were written on lab forms) testing and infant results were returned to mothers through the health facility. Mothers of HIV-exposed infants were referred for HIV testing.

Data Management and Data Analysis

Hard copy questionnaires were used for data collection in the situational assessment. The data was captured in Excel and transferred to STATA SE (version 12, Texas, 77845 USA) for analysis. Descriptive methods (simple frequency tables) were used to analyse the situational assessment data on EID services availability (i.e. EID availability within the health facility and at ISPs), and approaches for identifying HEI for EID services. The cross-sectional survey data were collected on electronic (cell phone) questionnaires and the data was transferred to STATA for analysis. A weighted analysis (weighted for sample size realisation and population live birth) was performed to calculate the proportion of known HIV-positive mothers who brought their child for HIV testing at six weeks immunisation visit, documentation of infant or mother HIV-status (or documentation of maternal/infant prophylaxis) on RtHC among both known HIV-exposed and unexposed infants and acceptance of provider-initiated HIV testing offered as part of the survey.

In the cross-sectional survey, we could not directly measure missed opportunities for EID (in the routine service) as we offered provider-initiated HIV testing to all 4-8weeks old infants visiting six week immunisation services. However, we used the following method to assess potential missed opportunities for EID that could have

occurred in the absence of testing offered in our survey: we assumed that in the absence of the cross-sectional survey, facility policy within the past year would have dictated EID practice. Therefore, HIV-exposed infants who attended health facilities that reportedly use the targeted testing approach (testing documented/reported HEI) for EID would miss opportunities of early (six week) testing unless their HIV-status is documented on the road-to-health-card or their mothers were intending to request for infant testing at 4-8 weeks of infant age. With this assumption, potential missed opportunities for EID were assessed among HEI attending facilities that provided targeted testing.

A logistic model was fitted to examine factors influencing maternal intention to receive EID at six week visit among known HIV-positive mothers. The following variables were considered in a bivariate analysis: maternal age >35 years, maternal age <20 years, education, marital status (being married), socioeconomic score (constructed from availability of the following working items in the house: stove, refrigerator, radio, TV and car), planned pregnancy, number of life time pregnancies, facility delivery, no of postnatal visits, history of child sickness since birth, knowledge about availability of PMTCT service, knowing all three modes of mother-to-child transmission (MTCT), feeling discriminated by the community (for their HIV status), MTCT risk behaviour (missing one or both of maternal and infant ARV regimens), and exclusive formula feeding. In the multivariate analysis: variables that were significant at 10% cut-off point in the bivariate analysis and the following variables reported in the literature as influential factors were considered: formula feeding, maternal education, unplanned pregnancy, and health facility delivery. Variables kept in the final model were either a significant influential predictors (at significance level of 0.05) or had a ≥10% effect on the overall model.

Results

Facility Situational Assessment Profile

Out of the 680 sampled facilities, 625 (92%) were visited for the situational assessment. Fifty-five (8%) of the sampled facilities could not be visited due to time

constraints, temporary closure or reported absence of main staff members needed for the interviews (table10).

The cross-sectional survey study profile

In the national cross-sectional survey, 10820 mothers/caregivers who brought infants to sampled clinics for six weeks immunisation service were approached and screened for eligibility. Ninety nine percent (10735) of screened mother/caregiver infant pairs were eligible and agreed to be interviewed. Ninety-six percent (96%) of participants were mothers; 4% (378) were caregivers. Of the 10735 participants offered PICT, 95% (10178) agreed to confidential linked infant testing, and 32% of infants tested were HIV-exposed.

EID service availability

More than 95% of facilities in the situational assessment reported availability of EID (PCR testing) service within the facility. The majority (72%) of the facilities reportedly provided EID services at ISPs. Five percent (5%) reported that EID services are provided at six week immunisation visits in conjunction with PMTCT/voluntary counselling and testing (VCT) services and 15% reported that ISPs are not involved in the provision of EID services. The rest (8%) did not respond to this question.

Of the facilities that offered EID services at ISPs, 76% reported that offering EID services during routine immunisation visits is feasible.

Testing approach

Our study indicates that more than half (68%) of ISPs provide EID services to infants with reported or documented HIV-exposure (fig 9). Only 9% ISPs reportedly provided PICT for undocumented and unknown HIV-status infants. Nationally 15% of facilities reported that ISPs are not involved in the provision of EID services. The rest 8% did not respond to this question.

Maternal intention and acceptability of provider-initiated counselling and testing

During interviews, mothers were asked to list their reasons for visiting the health facility at the six week immunisation visit: only 35% of self-reported HIV-positive mothers reported that they had intended to request infant HIV testing during the six week immunisation visit (fig10). In a multivariate analysis, mothers who felt discriminated against for their HIV-positive status were less likely to report their HIV-exposure during six week immunisation (AOR:1.8; CI:1.1-2.8). Knowledge of all MTCT modes (AOR:0.5; CI:0.2-0.9), and MTCT risk behaviour (i.e. missing maternal, infant or both ARV regimens - AOR:1.7; CI:1.2-2.5) were also significant predictors of maternal intention for receiving EID service (table 11).

When PICT was offered to all infants during six weeks immunisation visits, 95% of mothers consented to named testing with receipt of results. Almost all (97%) of reported HIV-positive mothers who had no intention to request infant testing agreed to infant antibody testing after provider-initiated testing was offered in our study.

Patient held records

Of 10612 (99%) mother-infant pairs who brought the infant's road-to-health-card, only 34% had a road-to-health-card that indicated maternal/infant HIV-status (fig 11). Among infants born to self-reported HIV-positive mothers, 49% had road-to-health-card with documentation of either a PMTCT code (confidential code indicating maternal HIV-status) or maternal or infant ARV prophylaxis, 6% had maternal HIV test result documented on RtHC, and 45% had no documentation of HIV-status on the RtHC.

Potential missed opportunities in the targeted testing approach

In facilities that reported providing targeted testing, the data (table 12) indicate a substantial number (38%) of HIV-exposed infants would have potentially missed opportunities of early testing as they had neither a documentation of HIV-status on

RtHC nor were their mothers intending to request EID services at the six weeks immunisation visit. Since our study offered PICT to identify all exposed infants and offer EID for all exposed infant at ISPs, none of the infants actually missed HIV testing.

Discussion

We found that, EID services are available in>95% of PHC facilities in South Africa, with 72% of facilities offering EID services at ISPs. Despite this progress in delivering decentralised EID services, our study indicates substantial missed opportunities for EID occur at six week visits, posing significant challenges for early initiation of treatment.

The HIV-exposure prevalence (32%) at six week immunisation visits reported in our study was similar with the HIV prevalence (29%) reported for pregnant women in the 2009 antenatal survey, which shows the high attendance of six week immunisations by HEI in the age 4-8 weeks old. However, our assessment of infant HIV testing services at ISPs identified several gaps related to the approaches used for identifying HIV-exposed infants from six weeks immunisation visits. The majority (68%) of facilities offered targeted testing which relies on maternal reporting or documentation (on RtHC) of HIV-exposure. Despite this, both the RtHC and maternal reporting were poorly utilised for conveying the HIV-exposure status of infants to health workers responsible for EID. Thus, facilities that use targeted approaches potentially missed opportunities of early testing on significant numbers (38%) of HEI.

Close to half (45%) of self-reported HIV-positive mothers, had an RtHC that has no documentation of HIV-status. Poor communication between antenatal, delivery and postnatal facilities and lack of good information systems have been reported as main barriers for continuity of postnatal PMTCT services in developing countries.[9,24] Several efforts in sub-Saharan countries to improve the utilisation of patient-held-

cards for documenting HIV-status had varying outcome.[25-27] In South Africa, the RtHC coding system, MTCT stickers, stamps and the new RTHbooklet were introduced at various stages of the implementation of the PMTCT programme. Health care providers seldom used the coding system, as it required complex and time consuming decoding.[27,28] At the time of the PMTCT survey the new RtHbooklet, revised to include maternal and infant HIV information was being implemented (April 2010). Whilst meticulous documentation of HIV-status using this new RtHbooklet might improve identification of HEI, the reliance on RtHC to identify HEIs has several limitations, including the dependence on mothers to bring the RtHC at all postnatal visits, and the inability to track infants who drop out at six week visit.[29] This sole dependence on patient held cards and the lack of an internal mechanism for exchange of client records between antenatal and postnatal facilities could also result in lack of clear accountability for tracing loss to follow-up infants during early postnatal period and contribute to high early postnatal attrition rate.[30]

A number of pilot studies in less developed countries indicate the introduction of technology such as web-based medical recording system (EMR) could be more effective for identifying and tracking HIV-exposed infants.[31,32] The use of EMR could enable tracking of the six week check-up due date of PMTCT mothers at postnatal units, thus facilitating early identification of dropouts at postnatal visits. However, web-based medical recording systems are rarely available in developing countries due to the cost and infrastructural requirement of setting-up this technology.

Maternal reporting for six weeks infant HIV testing service was also low in this study. Only 35% of known HIV-positive mothers reported they intended to disclose their HIV-status to the immunisation nurse. Knowledge of the mode of mother-to-child transmission, missing one or both of maternal and infant ARV regimens, and feeling discriminated were significant influential predictors of maternal intention for disclosure of HIV-status. Our study findings are supported by several studies that indicate PMTCT knowledge, adherence to treatment, and discrimination as main

determinants of uptake of EID.[20,21,33] A study in rural Kenya that assessed reasons for dropout from EID services indicates most mothers are unsure of the number, exact time points or type of tests to be done for EID services,[33] which suggests that lack of awareness about EID service could be one of the reasons why mothers do not report for testing. Reports from other similar studies conducted in rural areas of sub-Saharan countries indicate lack of privacy at immunisation rooms, and fear of stigma and discrimination as main barriers for maternal disclosure of HIV-status at immunisation visits.[34,35]

The 2010 WHO EID guideline recommends to improve early identification of undocumented and unknown HIV-exposed infants through the use of PICT. South Africa adopted this new EID guideline in 2010, in the same year as this study was conducted. This EID guideline recommends that all infants at six week visit with undocumented/unknown HIV-status be offered maternal or infant rapid screening. The latest revision (2013) to this guideline in South Africa further recommends to offer PICT for HIV-negative mothers.[36] These guidelines are introduced in absence of studies that adequately assess the capacity of immunisation facilities to absorb new services introduced as part of the new EID guidelines. We estimate at least three out of five children (66%) that present to immunisation facilities present without a documentation of HIV-status on the RtHC, therefore the number of infants that require screening test is expected to substantially increase with the introduction of the new guidelines. In order to ensure full transition to the new guidelines, the resource need (staffing, budget and supplies) of the introduction of the new guidelines should be monitored closely. Clear policy guidelines are also needed in the use of lay counsellors and community health workers for performing infant HIV testing.

Similarly, the suitability of the setup of immunisation units for implementing the new guidelines should be assessed. Assessing (asking) maternal antenatal HIV testing histories in immunisation rooms with inadequate privacy may result in false reporting, high refusal rate, and tendency to avoid immunisation services due to fear

of stigma.[26,37] South Africa is a better resourced country compared to other African countries but insufficient space and inadequate privacy at immunisation visits are reported as one of the challenges for providing infant HIV testing services in some areas of the country.[38]

In conclusion, these findings show that improving the EID service uptake requires efforts to improve the identification of HIV-exposed infants at six week visits. The current targeted testing approach is leading to a significant number of missed opportunities for early infant diagnosis. The high attendance of six week immunisations by HEI aged 4-8weeks indicate the presence of a potential for attaining high coverage of EID services at immunisation visits. Missed opportunities for EID were attributed to poor documentation of HIV-status on RtHC, inadequate maternal knowledge and fear of discrimination to disclose HIV-status, and the lack of PICT service to undocumented/unknown HEI. Hence improvement is needed in the following areas: documentation of HIV-status on RtHC, educating mothers about infant testing, reduction of stigma and discrimination through community level educational campaigns, improving privacy at immunisation facilities, and implementing the new EID guideline recommending PICT for undocumented/unknown HEI.

The results from this study are based on reports from service providers and caregivers. However we have triangulated service providers' data with caregiver reports to crosscheck consistency and validity of responses. In this study we were not able to directly measure the link between approaches for identifying HIV-exposed infants for EID service and uptake of EID service as the study offered PICT to all infants, hence preventing us from measuring uptake of EID service in the routine system. Thus far the only data source for routine EID uptake rate is the national health laboratory data. We recommend future studies to consider monitoring the uptake of routine EID services and continuity of care, particularly to assess the impact of the new guidelines recommending increased maternal screening and the new RtHC.

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Table 10: Sampled Facilities for the situational assessment in Total and By Province

Province	Total PHCs + CHCs (DHIS 2007)	No sampled (% provincial PHC+CHC)	No. visited (% sampled in province)	Facility stratum		
				Small No (column %)	Medium No (column %)	Large No (column %)
EC	714	87 (12%)	87 (100%)	10 (10%)	38 (17%)	39 (13%)
FS	266	83 (31%)	73 (88%)	13 (14%)	28 (12%)	32 (11%)
GP	340	76 (22%)	76 (100%)	16 (17%)	14 (6%)	46 (15%)
KZN	562	74 (13%)	71 (96%)	10 (10%)	23 (10%)	38 (13%)
LP	438	84 (19%)	56 (67%)	10 (10%)	23 (10%)	23 (8%)
MP	267	87 (33%)	87 (100%)	12 (13%)	25 (11%)	50 (17%)
NC	138	43(31%)	42 (98%)	10 (10%)	24 (11%)	8 (3%)
NW	338	79 (23%)	74 (94%)	7 (7%)	34 (15%)	33 (11%)
WC	327	67 (20%)	59 (88%)	8 (8%)	18 (8%)	33 (11%)
Total	3390	680 (20%)	625 (92%)	96 (100%)	227 (100%)	302 (100%)

Table 11: Predictors of intention to receive EID service among HIV positive mothers who know their HIV status

Significant predictor factors explaining poor maternal reporting for infant HIV testing at six week immunisation visit among self-reported HIV positive mothers	Unadjusted odds ratio	Adjusted Odds ratio [95%CI], p.value
Maternal age below 20 years	1.5 [1.1-2.1] 0.012	1.3 [0.9-1.9] 0.130
Mothers who felt discrimination by the community	**1.9 [1.2 – 3.0] 0.009**	**1.8 [1.1-2.9] 0.025**
Socioeconomic status score*(continuous)	0.9 [0.9-0.99] 0.035	0.9 [0.9 -1.0] 0.139
Maternal education (four categories)*	0.9 [0.7-1.1] 0.321	0.9 [0.7- 1.2] 0.475
Unplanned pregnancy	1.1 [0.9-1.4] 0.351	1.0 [0.8 - 1.3] 0.722
Missing one or both of maternal and infant ARV regimens	**1.8 [1.3 -2.6] 0.001**	**1.7 [1.2- 2.5] 0.004**
Exclusive formula feeding vs any breast feeding	0.9 [0.7-1.2] 0.442	1.0 [0.8- 1.2] 0.742
Knowledge of all MTCT mode	**0.5 [0.3 -0.97]**	**0.5 [0.2-0.9]**

	0.041	**0.032**
Knowledge about availability of PMTCT programme	1.5 [1.0 – 2.4] 0.060	1.4 [0.8-2.2] 0.205

a. Additionally Sick child, facility delivery, postnatal visit and number of pregnancy(classification of 4: 1 pregnancy, 2 pregnancies, 3 pregnancies, 4 and above pregnancies) *were considered in the logistic regression but were not influential (had <0.10 effect).*
**Education categories: None, Grade 1-7,Grade 8-12, Above Grade12*

Table 12: Potential missed opportunities for EID among infants who attended facilities that use the targeted approach*

Documentation of HIV status on RTHC and mothers intention - among infants attended facilities that use the Targeted approach)*	**No (%)of HEI**
Infant who attended facilities that use the targeted approach who would have **potentially accessed HIV testing**: - HIV-exposure status documented on RtHC and/or mothers intentionally brought child for EID	1815 (62%)
Potential missed opportunities among infants who attended facilities that use the targeted approach: - Infants HIV-exposure status not documented on RtHC and mothers had no intention to request EID	**1041 (38%)**
Total HIV exposed infants who attended facilities that use the targeted approach	2856 (100%)

*Targeted approach refers to the offer of testing to infants who have documentation of HIV exposure on RtHC or whose mothers request HIV testing

Figure 9: Coverage of testing per the WHO 2010 EID guideline and targeted infant HIV testing at six week immunisation service points (per immunisation nurses report

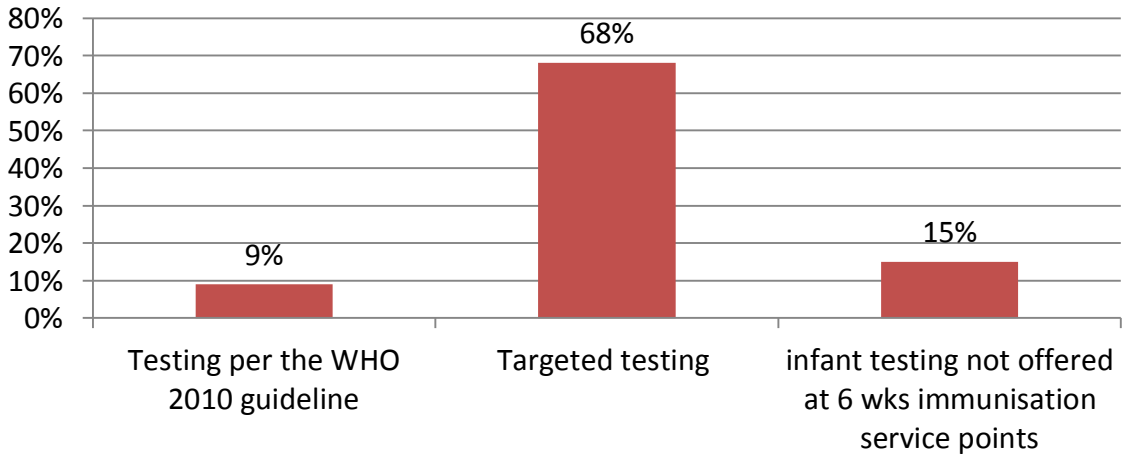


Figure 10: the increase in identification of HIV-exposed infants born to women aware of their HIV positive status, achieved by offering provider initiated testing versus relying on a maternal request for EID

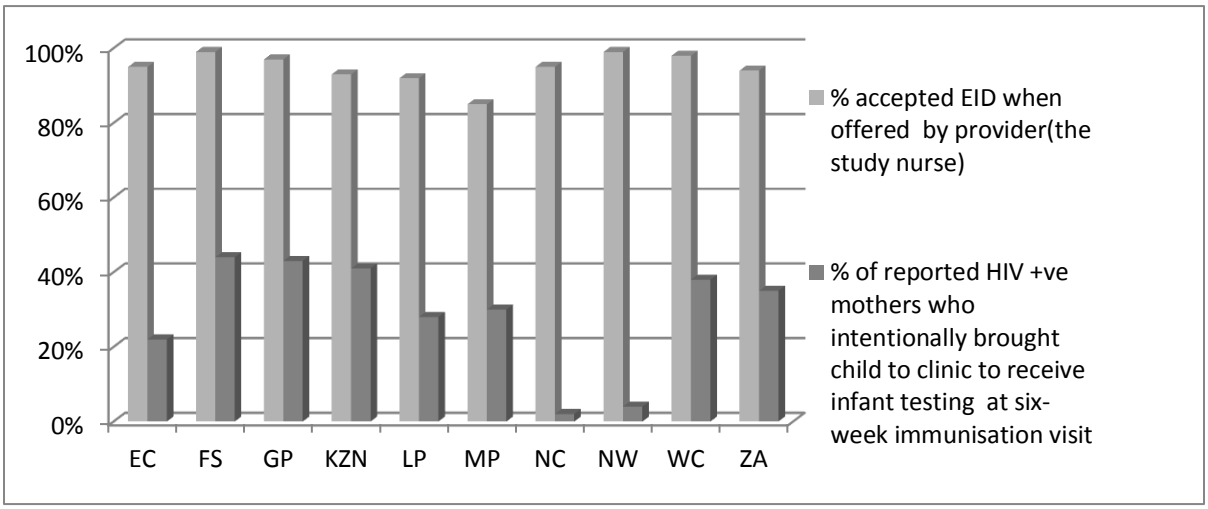
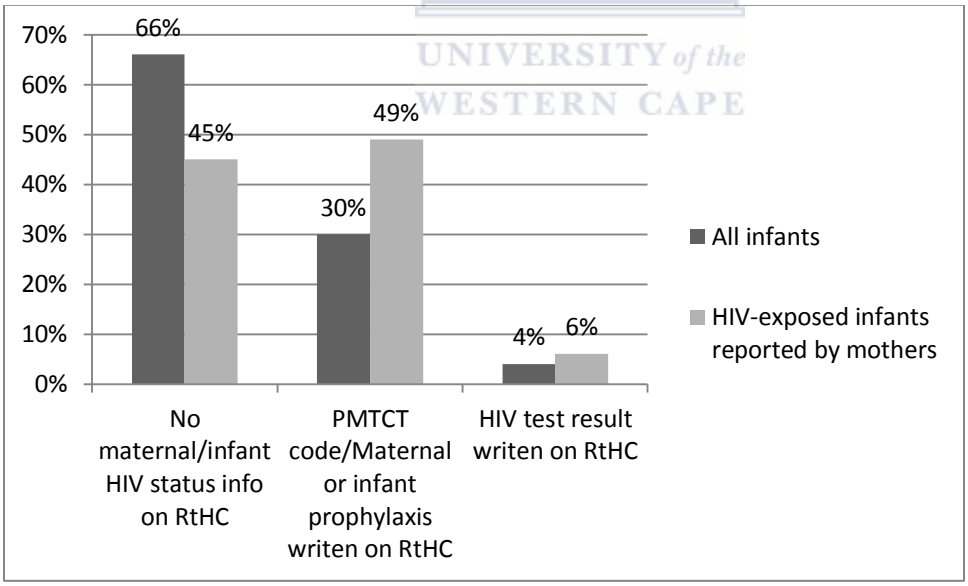


Figure 11: Recording on RtHC for maternal/infant HIV status identification



Chapter 5: CONCLUSION AND RECOMMENDATIONS

5.1. Conclusion

This study provides the first systematically collected national baseline data on coverage of the South African antenatal and early postnatal PMTCT services. Our findings show that 78% of all (known and unknown) HIV-exposed infants in South Africa received both maternal and infant ARVs in 2010. Contrary to our study findings, the coverage figures reported in the routine programme (DHIS) data indicates achievement of >95% ARV regimen coverage in 2010, reporting South Africa as one of the few African countries (Botswana, Swaziland and South Africa) that achieved both the UNGASS (80%) and UNAIDS (90%) ARV regimen coverage targets.[3] However, according to our findings, South Africa is on track to meet the UNGASS (80%) antiretroviral coverage target, but has not yet achieved the UNAIDS 90% ARV regimen coverage target. Several studies have shown the limitations of routine programme data. Incompleteness and inaccuracy of reports and use of denominators limited to known HIV-positive mothers are some of the limitations of the DHIS data that could lead to the overestimation of the coverage of PMTCT services. These quality gaps in DHIS data are well-known, but due to lack of alternative data, DHIS data have been used as a primary source of data to monitor PMTCT programmes performance. This study provides global partners with more reliable data to track progress towards the achievement of international targets.

Although close to 80% (78%) of mother-infant pairs received both maternal and infant ARV regimens, our coverage indicator did not assess duration and appropriateness of maternal and infant treatments. The optimal indicator for assessing PMTCT programmes performance is the coverage of *effective* ARV regimen which documents the percentage of mothers who receive appropriate type of regimen (for e.g. HAART if eligible) for the full duration of the treatment period per recommendations in the guidelines. In order to calculate effective ARV regimen coverage, information on maternal CD4 count numbers (to establish eligibility of

women for HAART) and duration of treatment is required. The assessment of effective ARV regimen coverage was not possible in this study due to significant number of missing data on both CD4 count and duration of treatment. This was the first national survey globally to apply a cross-sectional survey design and retrospective caregiver interview methods to collect PMTCT services coverage data. Response rates for CD4 count number and duration of treatment were low due to the relatively long recall period. In consecutive surveys, adding a record review component in the survey could improve the collection of detail information needed for quantifying coverage of effective ARV regimen.

We estimated the coverage of ARV regimen from the total known and unknown HIV-positive mothers that are target populations for the PMTCT programme. This assessment was possible due to the study design that enabled the collection of data from both known and unknown HIV-positive mothers at six weeks immunisation service points. The high (>95%) attendance rates of DTP1 immunisation services enabled us to give results that closely represent the population under study[122] Unlike cross-sectional six weeks surveys, routine programme data and other cohort study designs do not allow the assessment of missed opportunities among unknown and newly seroconverted HIV-positive mothers, as these methods mainly target mothers enrolled in the PMTCT programmes. Our estimates do not represent infants who died before six weeks of age, infants who attend six weeks immunisations after eight weeks of age and infants who attend private facilities, hospitals and small (<130 annual immunisation) and mobile PHCs.

Overall, according to this data South Africa is well on track to achieve the 80% universal access target. However, substantial effort would be required in order to increase the coverage of effective ARV regimens to above 90%.

Geographical differences in uptake of PMTCT cascade services

Uptake of the PMTCT cascade services was widely different across provinces. Whilst three provinces, which are relatively better off in resource allocation, achieved the

UNGASS universal access target (≥ 80%), the remaining six provinces had an average ARV regimen coverage of 69% (ranging 65-76%). Variations in uptake of the PMTCT cascade services were directly related to variations in mother-to-child transmission rates. The difference in PMTCT programme performance resulted in significant geographical differences in transmission rates.

This study identified shortage of human resources as a significant contributor of low uptake of the PMTCT cascade services and higher transmission rates. Provinces with higher transmission rates were characterized by a shortage of human resources for PMTCT services and a considerably lower PMTCT service uptake. External provincial reports from three of the six low (PMTCT coverage <80%) performing provinces indicated shortage of human resource as the major barrier for provision of good quality HIV/AIDS and other basic services in these provinces.[152-154] Innovative strategies to attract professional health workers to rural and resource poorer settings and task shifting should be used to improve equity in distribution of human resources between better off and resource poorer settings. Budget allocation for provinces should consider these challenges in attracting human resources to resource poorer settings and rural sites. Other challenges such as distance to health facilities, inadequate ARV sites, inequity in allocation of PHC expenditure and NGOs support, and lack of strong monitoring system should also be addressed in order to improve PMTCT services coverage.

The impact of universal access on transmission rate

Universal access (≥80% coverage) to antiretroviral regimens had significant impact on transmission rate. Provinces that achieved below 80% ARV regimen coverage had significantly higher (AOR: 1.7) transmission rates than provinces that achieved 80% and above ARV regimen coverage. In six of the nine provinces a general trend of an increase in transmission rate was observed with a decrease in PMTCT cascade coverage. Three of the nine provinces (of which two had <75% sample size achievement) did not exhibit this trend, however this could be due to the lack of

detail information on other determinant factors (e.g. on adherence to treatment, duration of treatment and type of regimen) or in the two provinces that achieved below 75% sample size, inadequacy of sample size may have decreased precision of estimates. Therefore we recommend the transmission rate and PMTCT cascade coverage in the three provinces be monitored at continuous basis to further strengthen the evidence.

Mathematical modelling estimates predict that 95%-100% effective coverage of PMTCT cascade services is required in order to approach the 2% perinatal and 5% postnatal (18-months) MTCT elimination targets.[41] In contrast, results from our study showed with 80-88% maternal and infant ARV regimen coverage, perinatal transmission rates could be reduced to below 3%. The accurateness of results from modelling studies is dependent on the quality of parameters and assumptions they are based on. PMTCT modelling is often done using parameters from clinical trials and routine programme data. Since routine programme report could overestimate the coverage of ARV regimens, and transmission rates achieved in clinical trials are sometimes lower than transmission rates that can be achieved in real life settings, results from modelling studies may underestimate the impact of PMTCT services coverage. From the findings of this study we argue that lower (<3%) transmission rates can be achieved with ARV regimen coverage levels between 80% and 90%.

However, this argument should be strengthened through repeat surveys. Neither the models nor our study considered type of maternal ARV regimen, duration of ARV regimen and adherence to treatment in measuring the impact of PMTCT cascade coverage on transmission rates. In our study even if we assume highest adherence and effective and long course ARV regimens were received, achieving transmission rate of < 3% with 80-88% effective ARV regimen coverage is still a significant reduction in transmission rate compared to the reports from models that show achievement of 4.1% transmission rates with >95% effective ARV regimen coverage.

Dropout points along the PMTCT cascade

According to our findings South Africa has substantially improved the uptake of the PMTCT programme at antenatal visits, with almost all (97.7%) pregnant mothers having received antenatal HIV testing and significant number (89.6%) of HIV-positive mothers being aware of their HIV-positive status. However, gradual loss to follow-up that occur between CD4 count testing, and referral to ART clinics substantially reduce uptake of effective ARV regimen.

Dropout at CD4 count and ART initiation

Even though 78% of HIV-exposed mother-infant pairs received both maternal and infant ARV regimen, the HAART eligibility of 22.6% of HIV-positive mothers' was not assessed using CD4 count. In addition, of those mothers with CD4 count data, significant number (10%) of mothers identified as HAART eligible (CD4 count <350 cells/µl) did not receive HAART due to dropout at ART referral points. The estimated 10% dropout rate at ART referral point could be an under estimation of dropout at ART referral point as CD4 count data was missing in >50% of the data. Failure to initiate HAART for eligible women results in high risk of mother-to-child HIV transmission and maternal mortality. The main reasons for the identified gaps in assessing eligibility and initiating HAART could be associated with quality of care, unreliable CD4 count testing service, and poor linkage and tracking system at antenatal service points and ART referral points.

The World Health Organization (WHO) recommends treatment Option B be adopted in countries that experience challenges with centralised CD4 count testing service. An analysis of the cost-effectiveness of the WHO treatment Option A and Option B guidelines show that treatment Option B is more cost-effective than treatment Option A if treatment adherence is ensured.[114,144] Treatment Option B benefits both the mother and the infant: women who are on a HAART regimen have the least risk of perinatal transmission and a greater likelihood of an expanded lifespan and better

quality of life. South Africa recently adopted Option B treatment guideline. With the adoption of treatment Option B, significant gains in reduction of MTCT rates are expected as mothers who need lifelong HAART can receive treatment without any delay. The South African Option B is also launched with a fixed dose combination therapy (a single dose therapy given once a day) which significantly reduces pill burden and increase adherence to treatment.

With the introduction of Option B, the demand for ART will increase. Dropout rates at ART referral points could also pose major challenge unless nurse initiated antiretroviral treatments are (NIMART) introduced at antenatal clinics. Other methods such as verifying with ART clinic staff that referred clients (mothers) honoured their appointments, conducting home visits by community health workers (CHWs), and health staff accompanying mother to the ART clinics are best practices that have been shown to reduce dropout at referral points.

Dropout at EID service and linkage

The study also identified that a substantial number of mother-infant pairs potentially (if universal infant testing was not given in our study) missed opportunities for early infant diagnosis due to gaps in the approaches used for identifying HIV-exposed infants at six weeks visits. The study reports although the majority of facilities reported relying on targeted testing (i.e. testing reported/documented HEI), both the RtHC and maternal reporting are poorly utilised for notifying nurses at six weeks immunisation service points on the HIV-exposure status of infants. The six weeks infant HIV diagnosis service is key for ensuring access to needed health services for both HIV-exposed/infected infants and their mothers.

Limited communication between antenatal, perinatal and postnatal services has been found as the major bottleneck for continuity of postnatal PMTCT services.[149,170] This study indicates whilst the PMTCT programme is linked with immunisation facilities and antenatal services, the lack of linkage (communication) between antenatal,

perinatal and postnatal PMTCT and non-PMTCT maternal and child health services creates substantial missed opportunity to identify and follow-up HIV-exposed and infected infants during the early postnatal period. Efforts need to focus on improving linkage and communication between the three (antenatal, delivery and postnatal) MCWH service points. Rapid scale-up of the new RtHC and monitoring its utilisation for identifying HIV status of infants could improve early identification of infants. Regular meetings between antenatal, perinatal and postnatal facilities should be held to discuss on expected number of deliveries and six weeks immunisation appointments. In addition, postnatal service points should fully integrate postnatal PMTCT follow-up services into immunisation services, including the responsibility of identifying and tracking loss to follow-up mothers with the support of community health workers.

Electronic medical recording system (EMR)

This study highlights that communication gaps and lack of linkage between antenatal, perinatal and postnatal services are major barriers contributing to high missed opportunities at early infant diagnosis service points. Good information management systems are fundamental to improve the linkage between antenatal, perinatal and postnatal service points. In the current service, paper-based recording system is widely used for capturing PMTCT follow-up data. In most facilities the PMTCT record/register is either kept at antenatal facilities or shared between antenatal and postnatal maternal and child health services. In sites where antenatal and postnatal services are not provided in one facility, the postnatal services do not have access to information regarding the expected number of PMTCT mothers that should receive postnatal PMTCT services. Hence, given the fragmented nature of the health care, and the large volume of patients (one in three pregnant mothers) that require PMTCT follow-up and referral services, it will be natural to conclude that linkage and communication cannot be improved by sole reliance on paper-based information system. The health system needs the important support of electronic medical recording technology to simplify tracking of HIV-positive mothers and their infants.

The EMR would enable antenatal, perinatal and postnatal services, as well as ART sites to have electronic information of each HIV-exposed mother-infant pairs enrolled in the PMTCT programme.

In developed countries, information technologies are widely used to simplify the delivery of health service, whilst in developing countries the success stories of EMR are limited to research based sites.[181,182] Most information technology applications have also centred on administrative and financial transactions rather than on delivering clinical care. In some areas of developing countries, the infrastructure (network coverage, capacity including space, furniture, and trained staff) required for setting up the EMR system is non-existent. Given the communication problems that can be rectified by introducing EMR, focusing the government health spending on infrastructural development and introduction of technology at health facilities could be worthwhile and could help achieve the MDG goals for reducing both HIV-related and non HIV-related maternal and infant mortalities.

Secondly, the findings of this study indicate that current early infant diagnosis programmes rely on targeted approach to identify HIV-exposed infants. The targeted approach relies on notification of the HIV-exposure status of infants through maternal report or RtHC documentation. Recent national EID guidelines recommend to use provider-initiated counselling and testing approach at immunisation service points to identify unknown/uncertain HIV status infants and infants of recently sero-converted mothers who missed opportunities of PMTCT services at antenatal visits.

Our study shows that majority (61%) of infants were brought to the health facility with a RtHC that have no HIV identifying information. We also identified maternal reporting for six weeks infant HIV testing was low. Hence, the PICT approach recommended in the EID guidelines should be used as a primary approach in order to identify the majority of unknown/undocumented HIV-exposed infants. Our study findings show that universal maternal or infant HIV testing at six weeks immunisation visit could be a more acceptable and feasible approach to increase the

uptake of early infant diagnosis service. However, there is a lack of research that examines the cost-benefit of the universal testing approach in comparison to the approach recommended in current guidelines. Our result shows that the majority of HIV-positive mothers are not identified at postnatal visits due to gaps in the communication between antenatal, perinatal and postnatal facilities. Hence, the postnatal PMTCT service has to find another way of re-identifying and linking HIV-exposed infants to postnatal services. Regular screenings at six weeks visits using either the PICT or universal testing approach could help identify HIV-exposed and infected infants early, allowing for timely treatment that can significantly reduce infant mortality risks.

5.2. Recommendations

1. Immunisation facilities should be able to have access to information on antenatal PMTCT mothers that should receive EID services after child birth. Given the large volume of PMTCT clients, electronic medical recording system may provide an option to simplify communication of this information between antenatal, delivery and postnatal facilities.
2. Government should spend on infrastructural development (expanding internet access to grassroots level facilities, providing adequate space, furniture, and computers to enable the use of EMR at PHC level) and introduction of technology in order to improve communication and linkage between antenatal and postnatal services using electronic medical recording system.
3. The use of the new RtHC for communicating the HIV status of infants should be monitored
4. Routine offer of provider initiated testing at six weeks could improve EID service coverage.
5. The implementation of new EID guidelines should be monitored at local levels
6. Substantial improvement in effective ARV regimen coverage is expected with the introduction Option B in South Africa. However in order to reduce loss to

follow-up at referral points, nurse initiated ARV treatments should rapidly be expanded to all primary health care facilities.

7. Modelling estimations should be reviewed given the population level reports from our study that indicate ARV regimens lower than 90% can reduce perinatal transmission to below 3%
8. Provincial variations in coverage of the PMTCT cascade services should be narrowed through strengthening the health-system infrastructure. Equitable distribution of human resources could narrow differences in provincial coverage.
9. More in-depth need assessment is needed in each province to address health service challenges specific to each province.
10. In future PMTCT surveys, duration and appropriateness of ARV treatment, and viral load level could be measured in order to assess adherence and coverage of effective ARV treatment.
11. The implementation of this survey required a significant resource (budget, human resource etc) allocation as the study was independently carried out by the MRC research team. This type of survey is a useful tool for on-going surveillance and evaluation of the effectiveness of the PMTCT programme. However, to continue the on-going monitoring in a feasible way, the survey could be integrated into the routine programme, as similar with the antenatal survey, (data on few important biomedical markers could be collected - e.g. HIV exposure, transmission, viral load and biomedical markers for adherence to treatment).

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Appendices

Appendix I: Sample size calculation by province

Antenatal HIV Prevalence 2007	% Antenatal HIV test	% admin of PMTCT to babies	Estimated Coverage (prevalence X %tested X %admin to baby)	Estimated Not Covered	Transmission Rate in exposed assuming SD NVP MTCT=15% & untreated MTCT=29% (Rollins)*	Overall Population Prevalence per 100 kids	Same precision across provinces	Same relative precision across provinces (%)	sample size for 30% relative precision	Sample size for design effect** of 2 & relative precision 30%		Overall Population Prevalence per 100 kids	Varying precision by province	Varying relative precision by province (%)	Sample size using varying precision level without design effect	Sample size using varying precision level with design effect** of 2
National	29	67	47	31.5%	68.5%	24.6%	7.1%	2.1	30	575	1150					
WC*	15	97	75	72.8%	27.3%	13.0%	1.9%	0.6	30	1989	3978	1.9%	1.0	51	716	1400
NC	14	81	70	56.7%	43.3%	21.1%	2.9%	0.9	30	1336	2672	2.9%	1.8	60	350	700
EC	24	73	35	25.6%	74.5%	25.4%	6.1%	1.8	30	680	1360	6.1%	1.8	30	700	1400
FS	29	70	52	36.4%	63.6%	23.9%	6.9%	2.1	30	560	1120	6.9%	2.0	29	617	1300
KZN	37	66	52	34.3%	65.7%	21.4%	7.9%	2.4	30	485	970	7.9%	2.0	25	699	1400
MP	34	56	36	20.2%	79.8%	26.2%	8.9%	2.7	30	428	856	8.9%	2.0	22	779	1600
LP	20	74	54	40.0%	60.0%	23.4%	4.7%	1.4	30	878	1756	4.7%	1.5	32	703	1400
NW	29.9	86	50	43.0%	57.0%	23.0%	6.9%	2.1	30	560	1119	6.9%	2.0	29	601	1200
GP	31	65	27	17.6%	82.5%	26.5%	8.2%	2.5	30	463	926	8.2%	2.0	24	723	1800
Total										**7379**	**14758**					**12200**

ANC Prevalence & Coverage Data from DHIS

*WC & KZN assume full coverage dual therapy - Rollins KZN Study is 7%

** Design Effect = 1+(100-1)*(ICC=.01)=2

SAMPLING – SEE TEXT THAT FOLLOWS

The table below shows the number of facilities needed to be sampled from each province to collect data within 3wks (4 weeks for Northern Cape) duration from each facility.

Note DTP1 = 1st DTP

WESTERN CAPE

Strata	Total Annual DTPDTP#	Percentage	Sample size proportional	Median yearly clinic DTP1 number	Median 3 week clinic DTP1 number	number of facilities need to be visited
Medium size clinics (130-300 annual DTPDTP1#)	15953	17.85%	250	192	11	23
large size (Annual DTPDTP1 #>300) but low prev clinics	62884	70.38%	985	535	31	32
large size (Annual DTPDTP1 #>300) but high prev clinics	10517	11.77%	165	857	49	3
Overall Total	**89354**	100%	**1400**			**58**

EASTERN CAPE

Strata	Total Annual DTP for the province	Percentage	Adjusted Percentage	Sample size proportional	Sample size adjusted proportional	Median yearly clinic DTP1 number	Median 3 week clinic DTP1 number	numl of facili need be visite
Medium size clinics (130-300 annual DTP1#)	41620	36.38%	30%	509	420	186.5	11	**47**
large size (Annual DTP1 #>300) but low prev clinics	41646	36.40%	43%	510	602	459	26	**19**

large size (Annual DTP1 #>300) but high prev clinics	31141	27%	27%	381	378	402	23	16
Over all Total	**114407**	100%	100%	1400	**1400**			**83**

FREE STATE

Strata	**Total Annual DTP for the province**	**Percentage**	**Sample size proportional**	**Median yearly clinic DTP1 number**	**Median 3 week clinic DTP1 number**	**number of facilities need to be visited**
Medium size clinics (130-300 annual DTP1#)	14418	27.34%	355	201	12	31
large size (Annual DTP1 #>300) but high prev clinics	38326	72.66%	945	404	23	41
Over all Total	**52744**	100%	**1300**			**71**

GAUTENG

Strata	**Total Annual DTP for the province**	**Percentage**	**Sample size proportional**	**Median yearly clinic DTP1 number**	**Median 3 week clinic DTP1 number**	**number of facilities need to be visited**
Medium size clinics (130-300 annual DTP1#)	15359	8.95%	161	237.5	14	12
large size (Annual DTP1 #>300) but low prev clinics	33023	19.25 %	347	549	32	11
large size (Annual DTP1 #>300) but high prev clinics	123199	71.80 %	1292	629	36	36
Over all Total	**171581**	100%	**1800**			**58**

KZN

Strata	Total Annual DTP for the province	Percentage	Sample size proportional	Median yearly clinic DTP1 number	Median 3 week clinic DTP1 number	number of facilities need to be visited
Medium size clinics (130-300 annual DTP1#)	40070	20.84%	292	209	12	24
large size (Annual DTP1 #>300) but low prev clinics	6505	3.38%	47	536.5	31	2
large size (Annual DTP1 #>300) but high prev clinics	145661	75.77%	1061	483	28	38
Over all Total	192236	100%	1400			**64**

LIMPOPO

Strata	Total Annual DTP for the province	Percentage	Sample size proportional	Median yearly clinic DTP1 number	Median 3 week clinic DTP1 number	number of facilities need to be visited
Medium size clinics (130-300 annual DTP1#)	41027	33.89%	474	206	12	40
large size (Annual DTP1 #>300) but low prev clinics	80048	66.11%	926	470.5	27	34
large size (Annual DTP1 #>300) but high prev clinics	0	0.00%	0	0	0	
Over all Total	121075	100%	**1400**			**74**

MPUMALANGA

Strata	Total Annual DTP for the province	Percentage	Adjusted percentage	Sample size proportional	Sample size adjusted proportional	Median yearly clinic DTP1 number	Median 3 week clinic DTP1 number	number of facilities need to be visited	number of facilities need to be visited based on adjusted distribution
Medium size clinics (130-300 annual DTP1#)	20858	26.73%	20%	428	320	225	13	33	25
large size (Annual DTP1 #>300) but low prev clinics	0	0.00%	0	0	0		0	0	0
large size (Annual DTP1 #>300) but high prev clinics	57172	73.27%	80%	1172	1280	439	25	46	51
Over all Total	78030	100%		100%	**1600**	1600		**79**	**75**

NORTHERN CAPE

Strata	Total Annual DTP for the province	Percentage	Sample size proportional	Median yearly clinic DTP1 number	Median 4 week clinic DTP1 number	number of facilities need to be visited
Medium size clinics (130-300 annual DTP1#)	7766	51.82%	363	207.5	16	23
large size (Annual DTP1 #>300) but low prev clinics	7221	48.18%	337	400	32	11
large size (Annual DTP1 #>300) but high prev clinics	0	0.00%	0	0	0	0
Over all Total	14987	100%	**700**			**34**

NORTH WEST

Strata	Total Annual DTP for the province	Percentage	Sample size proportional	Median yearly clinic DTP1 number	Median 3 week clinic DTP1 number	number of facilities need to be visited
Medium size clinics (130-300 annual DTP1#)	22925	34.26%	411	204.5	12	**35**
large size (Annual DTP1 #>300) but low prev clinics	24100	36.02%	432	413	24	18
large size (Annual DTP1 #>300) but high prev clinics	19887	29.72%	357	432.5	25	14
Over all Total	66912	100%	**1200**			**67**

Each province was divided into 3 strata:

- Stratum 1 is clinics & CHCs that have annual Dtp1st dose 130-300 based on the 2007 DHIS data
- Stratum 2 are clinics & CHCs with 300 & above Dtp1st dose & HIV prevalence below the national (<29%) rate based on the 2007 DHIS data & 2008 antenatal survey data respectively
- Stratum 3 are clinics & CHCs with 300 & above Dtp1st dose (based on the 2007 DHIS data) & HIV prevalence above the national rate based on the 2007 DHIS data & 2008 antenatal survey data respectively

Provinces that don't have the third stratum WC, Limpopo & NC have no third stratum: that is because there is no district with >29% HIV prevalence & high delivery rate (>300 Immunization) in the province. However, for Western Cape, we had a sub district level data from the ANC survey, which indicated that Khayelitsha sub-district has more than 29% HIV prevalence. So, the third stratum was created from large clinics in Khayelitsha. We were not able to do the same for Limpopo & NC, as we did not have sub-district level HIV prevalence data (from the ANC survey) for the two provinces.

Reduced the sample size for Northern Cape province to 700

Northern Cape had 76 facilities to be sampled, logistically 76 clinics may not be achievable target within the allocated time. So we decided to reduce the no of facilities that need to be visited to 34.

Adjusting weighting for Mpumalanga & Eastern Cape

The number of facilities needed to be sampled for Mpumalanga & Eastern cape was 79 & 83 respectively. In addition, most of the facilities were from medium clinics. As this might be difficult to achieve with available logistics capacity, we have slightly shifted the weighting to the large clinics (see column D) & hence the number of facilities need to be sampled from medium facilities decrease from 47 to 39 for EC & from33 to 25 for Mpumalanga (see column J). This will be logistically feasible.

In Free state, we have only two strata - we grouped the last two strata as one stratum.

The second strata (large & low HIV prevalence clinics) in Free state had only 0.74% weighting which translates to sampling only 1 facility from the second stratum. Since

sampling cannot be done for one facility, the second stratum is combined with the third stratum & thus we have only two strata for Free state.

Appendix II - **Information sheet and consent form and Questionnaires**

A. PMTCT survey consent form

CONSENT TO PARTICIPATE IN RESEARCH

Evaluation of the effectiveness of the national prevention of mother to child transmission programme on infant HIV at 6 weeks postpartum, South Africa

INTRODUCTION

Hello. I am Ms/Mr. …… (field worker name) from the Medical Research Council. We ask if you can take part in a study entitled "Evaluation of the effectiveness of the national prevention of mother to child transmission programme on infant HIV at 6 weeks postpartum". This study is being sponsored by the National Department of Health, the Medical Research Council, the University of Western Cape, UNICEF and the Centers for Disease Control and Prevention of the United States.

WHY AND HOW ARE WE DOING THIS STUDY?

We want to find out how clinics look after pregnant women and small babies. We would like to know about small babies who are 4 to 8 weeks old.
We want to find out what care pregnant women got from the ANC clinic. Did pregnant women get an HIV test? Did pregnant women get care for HIV? Did pregnant women get care to prevent HIV in their baby? This is what we want to know.
We also want to know about your baby or the baby that you look after: What type of birth did he or she have? Did he or she get any care for HIV? What milk or food does the baby get?
We also want to know how many babies do not have HIV. So, we want to take some blood from the baby‟s heel. The heel is the bottom part of the foot. We call this a blood spot test. We will send this blood spot to the lab. A lab is a big place where they will test the blood for HIV. The lab will send the result back to the clinic within 4 weeks. When we test the baby‟s blood we know the baby‟s HIV result. If you come back for the result then the nurse in the clinic tell you the result.
But the mother or you can also go for an HIV test today if you want to know your result now.
We ask these questions and take the blood because we want the clinic to give you better service. We also want you and your baby to get all the care that you need. So if you or your baby tests HIV positive the nurses will make sure you get the right care and medicine.
We do this because we do not want children to get sick or to get HIV or to die from HIV.
The work is called a research study. This study is being done in all provinces of South Africa. We will ask 12 200 caregiver and their babies to take part in this study. If the mothers are not at the clinic then we will ask the person who looks after the baby to take part in the study, with the baby.

BEING PART OF THE STUDY AND STOPPING THE STUDY

If you agree to take part in this study, then we will ask you questions. You do not have to answer the questions. At any time during the questions or before the baby‟s heel is pricked you can stop the study. We will then stop.

The questions and the blood test will be done today in a separate part of the clinic.

If you do not want to take part in this study you will still get the same care in the clinic that you would get if the study was not here.

PRIVACY

Your answers will be marked on a form or put into a cell phone. Your name will not be on the answers. Only a secret code will be linked to your answers. This secret code is called a study ID. This means that no one will know your answers. They will only know if they break the secret code and link it to your name.
All information will be kept private. This means that we will not show anyone else your answers. No one will know what you said as a person.
But we need to take your name on the blood test form so that you can get the test results if you want them.
We will send all the results back to the clinic using the secret code. The clinic nurse who can give you the result will see the result and will be able to give it to you. So she will know your secret code. She will know the test result.
We will not force you to come back to get the HIV result. But getting the result is a good idea because then the mother and baby can get the right care and medicine. If you get the right care you will not get very sick very often. The HIV test result will be at the clinic in 4 to 8 weeks time. Please ask the nurse when you come back to the clinic, if you want the result. We strongly think you should know the result so you and your baby can get the right care. But as we said we will not force you to come back. The clinic staff will keep your results a secret from all other mothers in the clinic. When you come back and ask for the results they will answer your questions and give you the results.

POTENTIAL BENEFITS

There are some good things that you may see now if you take part in the study.
If we see that you have not had an HIV test or do not know your HIV result then we will give you a card and ask you to go for the HIV test.
Knowing if you have HIV is good as then you can get the right care. Taking the right medicine will keep you from getting sick. By being part in this study the mother of the baby can also get to know the baby‟s HIV result. If the mother knows the baby‟s result then the baby can also get the right care. This means that the baby will not get sick very often. If you are HIV positive then this test is the 6 week test that you were told about when you were pregnant. The clinic is not going to do a separate test for your baby.
There are also some other good things for other people who use the clinic. The answers that we get from the 12 200 mothers/babies will help us make things better at the clinics in South Africa.

POTENTIAL HARM

The questions will take about 30 minutes of your time. If you are not the mother we will skip some questions. If we ask questions that are a problem for you, you do not have to answer them.

The blood spot test can cause a little pain to the baby. It may also leave a few blue marks on the baby's foot. These will be gone in about one week.
The good thing about the blood test is that the mother can get to know the baby"s HIV result. This means that she can then get the right care for her baby when she comes back for the result.
As we said your name and answers are kept private. This means that we do not share what you tell us with anyone in the clinic. We will only send the blood result back to the clinic so that you can come back and get it, so that you can help the baby.
Please ask me if you have any problems with the questions, or with the study.

WILL YOU GET ANY PAYMENT FOR BEING IN THE STUDY?

You will not receive any money or food for being part of the study. You do not have to pay to be in the study.

USE OF BLOOD SPOTS

The blood spots will be used to test if the baby has HIV. After the HIV test any blood left over will not have a name or code with it. In future the blood may be used for other studies. These may include studies on HIV medicines. We will not put your name or address or any contact information on the blood sample and there will be no way to know it is from your child. Thus we will not be able to report back any test results to you from the future studies. A research ethics board, which watches over the human safety and rights, must approve any future research study using the blood samples from your child. Your child's blood sample will not be sold.

PEOPLE DOING THE STUDY

If you have any questions or problems about the research study please phone the person in charge of the study. Her name and telephone numbers are:
Dr Ameena Goga Specialist Scientist Health Systems Research Unit, MRC Van Zyl Drive, Parow Western Cape 7535 Tel: +27219380454 Mobile +2782 302 3168
Or
For Ethical or Rights questions contact:
The MRC Ethics Committee with the following address: Prof Danie du Toit, tel. (021) 938 0341; e-mail: adri.labuschagne@mrc.ac.za

CONSENT FORM

Researcher: ……*(Research assistant's name)*
Research conducted by: Medical Research Council and University of the Western Cape and Mr/Ms ……. has explained the research study and I agree to take part.
My questions have been answered.

___ I agree to answer questions
___ I agree to the baby having a heel prick blood spot taken for an HIV test
I understand that I can stop taking part in this study at any time without giving a reason. This will not change the care that I or my family get at this clinic/health centre.

Name (print)……
Signature…… *Date*…….
Thanking you for helping us with our research

B. PMTCT survey Questionnaire

SCREENING QUESTIONNAIRE

Evaluation of the effectiveness of the national prevention of mother to child transmission programme on infant HIV at 6 weeks postpartum, South Africa

Patient identifier

Name of the person collecting data (Interviewer code): [ ] Date of interview: ……../……./…….

Province: _____ District: _____ Facility name: _____

Question	Questions and filters	Coding categories
S.1	Are you bringing this child for emergency medical care or urgent referral to hospital or other health facility?	1=Yes→ **Skip to S.13** 2 = No → **Continue Questionnaire**
S.2	What is your relationship to the child?	1 = Mother → **Skip to S.3** 2 = Father 3 = Grandmother/father 4= Legal guardian (if orphan or abandoned) 5 = Other caregiver
S.3	Where is the mother of the child?	1 = At home/work/other place 2 = No longer alive 99 = Don't know (specify)_____
S.4	Age of MOTHER in YEARS	_____
S.5	What is the **highest** school grade PASSED **by the** MOTHER**?** ***Only one response***	1= None 2= Grades 1-7 3= Grades 8-12 4 = Completed tertiary/technical/university 99 = Don't Know
S.6	Marital status of MOTHER ***Only one response***	1= Single 2 = Married 3 = Co-habiting 4 = Widowed 5 = Divorced/Separated 99 = Don't Know
S.7	Child's population group ***Only one response***	1= Black 2=White 3=Coloured 4=Indian 5=Other

S.8	Is your child a boy or a girl?	1=Male 2=Female
S.9	How old is the child in weeks?	_____ **If less than 4 or more than 8 weeks entered → Skip to S.13**
S.10	Why did you bring this child to the clinic today ***Tick all that apply***	1 = Immunisation 2= HIV PCR 3 = Other reasons, please specify _____
S.11	Did your child receive the 1st DTPimmunization **prior** to this visit? ***Check RTH card to confirm***	1=Yes → **Skip to S.13** 2= No
S.12	Do you want the child to receive the 1st DTP immunization today/Did your child receive the 1st DTP immunization during today's visit?	1=Yes → ***Skip to Instruction Field A*** 2= No → ***Skip to Instruction Field A*** 99=Don't know → ***Check RTH Card or Query Clinic staff & click RETURN to select yes /no.***

S.13a	**Is this child eligible for study participation** • **Is age 4 to 8 weeks old** • **Has received or will receive DPT1 immunisation at this clinic visit**	**1=Eligible→ Continue to Information sheet & consent procedure** **2=Not Eligible → Discontinue interview and thank the caregiver**
S.13b	**Are you sure you want to terminate the survey, please confirm** **Say thank you to caregiver**	**1 = Yes confirmed not eligible** **2= No want to go back**

If the child is eligible to participate in the survey, please discuss with the caregiver information provided in the information sheet and complete consent process

S.14a	**Does the mother/caregiver give written consent to participate in study**	**1=Yes→ Continue to questionnaire → *Skip to 1.1*** **2=No → Discontinue interview and thank the caregiver**
S.14b	**Are you sure you want to terminate the survey, please confirm** **Say thank you to caregiver**	**1 = Yes confirmed caregiver did not give consent** **2= No want to go back**

Say thank you to all caregiver of infants who do not meet eligibility criteria

Evaluation of the effectiveness of the national prevention of mother to child transmission programme on infant HIV at 6 weeks postpartum, South Africa

SECTION I: SOCIO-DEMOGRAPHICS

Question	Questions and filters	Coding categories
1.1	What is the **MAIN** material that the house the child lives in built with? ***Only one response***	1=Brick/Cement Block 2=Informal material/corrugated iron/wood 3=Traditional material/mud 4=Other, specify
1.2	What is the **MAIN** source of water used **for** drinking in the child's home? ***Only one response***	1 = Piped in house or in yard 2 = Not piped in house or in yard
1.3	What type of toilet do you use at the child's home? ***Only one response***	1 = Flush toilet 2 = Pit latrine (incl. Ventilated pit latrine) 3 = None 4 = Other (specify)
1.4	What is the **MAIN** fuel used for **cooking in the child's house**? ***Only one response***	1 = Electricity / gas / paraffin 2= other (specify)
1.5	Does the MOTHER receive money from any of the following sources? ***Tick all that apply***	1=Own Employment 2=Child Support Grant 3=Disability Grant 4=Partner/husband/ex-husband 5=Other family member 6=Other 7=doesn't receive any money99=Don't Know
1.6	In the last year (2009) was there a time when you and your family ran out of food and had to ask for help ***Only one response***	1= Yes 2 = No 99 = Don't Know
1.7	Does the household where the child lives have any of the following items (working items only)? ***Tick all that apply***	1=Refrigerator 2=Radio 3=Television 4=Stove (any type, incl primus) 5=Telephone/Cell phone 6=Car

SECTION II: INFANT & POSTNATAL VISITS
(Ask Mother/Caregiver & Check Road to Health Card)

2.1.	*Does the child have a RTHC – ask to see the card*	1=Yes 2=No
2.2.	*Does the child have a new RTHC (road to health booklet)*	1=Yes 2=No
2.3.	Birth weight *(Write 99.99 if Don't Know/Not Documented)*	____ • ____KG 99= Don't Know/Not Documented
2.4.	*Gestational age at birth (from RTHC)*	_____ in wks 99=Not Documented/No RTHC
2.5.	*Has the child been weighed already ?* *(confirm from the RTHC)*	1= Yes 2= Not yet -> ***Skip to 2.7***
2.6.	*Current weight (weight during this visit from RTHC)*	____ • ____KG
2.7.	*Number of postnatal visit since after birth to check maternal & infant health (Write 99 if Not Documented/Don't know)*	_____number of visits
2.8.	*Did the child receive BCG Immunization at birth*	1=Yes 2=Not Documented/No RTHC
2.9.	*Is there a PMTCT code or an HIV test result to indicate maternal HIV result on the RTHC*	1=Yes PMTCT code 2=Yes HIV test result 3=No ➔ ***Skip to 2.11*** 99=Don't Know/No RTHC ➔ ***Skip to 2.11***
2.10.	*Please write the HIV test results as it appears on the card (write code or test result)*	_____
2.11.	*Is there any documentation of maternal PMTCT prophylaxis on the RTHC*	1 = Yes 2 = No 99 = No RTHC
2.12.	*Is there any documentation of infant PMTCT prophylaxis on the RTHC*	1 = Yes 2 = No 99 = No RTHC
2.13.	*Is the mother's (syphilis) serology recorded on the RTHC (RPR on new RTHC)*	1 = Yes 2 = No 99 = No RTHC
2.14.	Type of delivery (from RTHC or mother)	1 = Vaginal delivery 2 = Caesarean section 99=Don't Know/No RTHC

2.15.	Has the child been sick requiring a sick child clinic visit or hospitalisation since birth for treatment? ***Ask the woman***	1=Yes 2=No 99=Don't Know

SECTION III: KNOWLEDGE ABOUT MTCT

3.1.	Can a baby get HIV from the mother if the mother is infected with HIV?	1 = Yes 2 = No ➔ ***Skip to 3.3*** 99 =Don't Know
3.2.	How? *Probe after each answer (e.g. any other way)* ***Tick all that apply***	1= Breastfeeding 2= During pregnancy 3= During childbirth 5= Other 99= Don't Know
3.3.	Have you ever heard of the PMTCT programme?	1 = Yes 2 = No

SECTION IV: INFANT HEALTH and FEEDING PRACTICES

4.1.	Do **YOU PERSONALLY** normally feed and change the baby during the day?	1 = Yes 2 = No ➔ ***Skip to 5.1***
4.2.	From the time you woke up yesterday morning, till you woke-up this morning, have you given the following to the baby	Ask each item and tick yes or no
	1. [ ] Yes [ ] No Breast milk 2. [ ] Yes [ ] No Infant formula 3. [ ] Yes [ ] No Fresh Cow's milk, tea with milk, weak porridge 3. [ ] Yes [ ] No Water only, water with sugar/glucose, fruit juice, tea without milk, rice water 4. [ ] Yes [ ] No Solid food (e.g. yoghurt, cheese, cereals, porridge, bread, fermented porridge, fruits/vegetables, meat/fish/chicken, eggs) 5. [ ] Yes [ ] No Traditional Herbs and/or Traditional Medicines, Non-prescribed over the counter medicines e.g. Gripe water, Panado 6. [ ] Yes [ ] No Prescribed medicine 7. [ ] Yes [ ] No Other, specify _____	
4.3.	Now I am going to ask you if you gave the following items to the baby at all in the last week ending yesterday morning.	**Ask each item and tick yes or no**

	1. [ ] Yes [ ] No Breast milk 2. [ ] Yes [ ] No Infant formula 3. [ ] Yes [ ] No Fresh Cow's milk, tea with milk, weak porridge 3. [ ] Yes [ ] No Water only, water with sugar/glucose, fruit juice, tea without milk, rice water 4. [ ] Yes [ ] No Solid food (e.g. yoghurt, cheese, cereals, porridge, bread, fermented porridge, fruits/vegetables, meat/fish/chicken, eggs) 5. [ ] Yes [ ] No Traditional Herbs and/or Traditional Medicines, Non-prescribed over the counter medicines e.g. Gripe water, Panado 6. [ ] Yes [ ] No Prescribed medicine 7. [ ] Yes [ ] No Other, specify _____

SECTION V: OBSTETRIC HISTORY, ANTENATAL & DELIVERY

5.i	*FROM THE SCREENING QUESTIONAIRE* *What is the relationship of the person being interviewed with the baby? (do not ask question again – use as skip if not mother)*	1 = Child's mother 2 = Not child's mother ➔ ***Skip to 8.1***
5.1.	*How many live-children do you have including this child*	_____number of live children
5.2.	*How many times have you had been pregnant*	_____ number of times mother has been pregnant
5.3.	*Was this pregnancy planned?*	1=Yes 2=No 99=Don't know
5.4.	*How many weeks pregnant were you in your first ANC visit during this last pregnancy*	_____in weeks 99=Don't know
5.5.	*Number of ANC visits made during this last pregnancy*	_____ times 99=Don't know
5.6.	*Did you have had Syphilis test done during the last pregnancy*	1 = Yes 2 = No 99 = Don't know
5.7.	Were you screened for TB during this pregnancy?	1 = Yes 2 = No 99 = Don't know
5.8.	During pregnancy did you ever discuss with anyone at the clinic what the best way for you to feed your baby is? <u>*Only one response*</u>	1=Yes 2=No 99=Don't Know

5.9.	Where was the child born? ***Only one response***	1=Hospital 2=Clinic 3=Home or other
5.10.	Who attended the birth of the child? ***Only one response***	1=Doctor 2=Nurse/Midwife/Other Health Care Worker 3=Traditional Birth Attendant or other
5.11.	Did you receive services or support from any of the following during your pregnancy, delivery or postpartum? *Tick all that apply*	1=Community Health Worker 2=Traditional Birth Attendant 3=Traditional Healer 4=Mothers Support Group

SECTION VI: HIV TESTING

HIV TESTING		
6.1.	During your last pregnancy, were you tested for HIV infection?	1 = Yes ➔ ***Skip to 6.3*** 2 = No 3 = Chooses not to answer - ➔ ***Skip to 6.3*** 99 = Don't Know ➔ ***Skip to 6.3***
6.2.	Why you were not tested for HIV during your last pregnancy?	1 = Never offered 2 = Did not want to test 3 = No reason offered 4 = Other (specify)
6.3.	Have you ever tested for HIV infection prior to the last pregnancy?	1 = Yes 2 = No ➔ ***Skip to 8.1*** 3 = Chooses not to answer ➔ ***Skip to 7.1*** 99 = Don't know ➔ ***Skip to 7.1***
6.4.	Did you get the result of the test / most recent test?	1 = Yes ➔ ***Skip to 6.6*** 2 = No 3 = Chooses not to answer ➔ ***Skip to 6.6***
6.5.	Why did you not get the HIV test result?	1 = Not available ➔ ***Skip to 8.1*** 2 = Did not want the result ➔ ***Skip to 8.1*** 3 = Other (specify) and ➔ ***Skip to 8.1***
6.6.	What was the latest HIV result?	1 = Infected / HIV positive 2 = Not infected/HIV negative ➔ ***Skip to 8.1*** 3 = Chooses not to answer

SECTION VII: PMTCT

	PMTCT ***(For this section refer to examples of medications to assist with ID of drugs taken)***	
7.1.	Did you receive AZT during your pregnancy with your last child? [Explanation: *AZT = a tablet you take every day on its own during pregnancy, starting from 14 weeks – show a picture of AZT]*	1 = Yes 2 = No ➔ ***Skip to 7.3*** 3 = Chooses not to answer ➔ ***Skip to 7.3*** 99 = Don't Know ➔ ***Skip to 7.3***
7.2.	For how long did you take the AZT before your last child was born?	_____ WEEKS
7.3.	Did you take any medicines to prevent transmission of HIV to your infant when you went into labour?	1 = Yes 2 = No ➔ ***Skip to 7.5*** 3 = Chooses not to answer 99 = Don't Know
7.4.	What medicines did you receive when you were in labour? *[Explanation of Drugs: See the relevant card with descriptions of each possible]*	1 = Nevirapine 2 = AZT 3 = TDF/FTC 4 = Other, Specify 5 = Chooses not to answer 99 = Don't Know
7.5.	Did you receive TDF/FTC after delivery *[Explanation of drug: sometimes refered to as Travada, one tablet after delivery – see card descriptions]*	1 = Yes 2 = No 3 = Chooses not to answer 99 = Don't know
7.6.	Was your last child given Nevirapine after delivery? [Explanation: *Nevirapine for the child is a syrup given to the baby within 72 hours of delivery to prevent mother to child transmission.]*	1 = Yes 2 = No ➔ ***Skip to 7.8*** 3 = Chooses not to answer ➔ ***Skip to 7.8*** 99 = Don't know ➔ ***Skip to 7.8***
7.7.	How many days was last child given NVP *(write 99 if don't know; if child is still on Nevirapine write 98)*	_____ days
7.8.	Did your last child get AZT? [Explanation: *AZT for the child is a syrup given with a syringe twice a day to prevent mother to child transmission]*	1 = Yes 2 = No ➔ ***Skip to 7.10*** 3 = Chooses not to answer ➔ ***Skip to 7.10*** 4 = Do not know ➔ ***Skip to 7.10***
7.9.	How many days was your last child given AZT? *(write 99 if Don't Know)*	_____ days
7.10.	*Have you told anyone about your HIV status?*	1=Yes 2=No
7.11.	*In general, have you felt discriminated against (treated badly) by your community due to your HIV status?*	1=Yes 2=No 99=Don't Know

7.12.	*Is the baby getting any formula milk?*	1=Yes 2=No ➔ ***Skip to 7.16***
7.13.	*Where do you get the formula*	1=Purchase 2=Receive from clinic 3= Other(specify) 99= Don't Know
7.14.	*Did you ever run out of formula*	1=Yes 2=No 99=Don't Know
7.15.	*If yes, what did you feed the baby when you did not have the formula*	1=breast milk 2=glucose water 3=water 4=other (specify)
	CD4	
7.16.	Have you had a blood test for a CD4 count?	1 = Yes 2 = No ➔ ***Skip to 7.18*** 3 = Chooses not to answer ➔ ***Skip to 7.18*** 99 = Do not know ➔ ***Skip to 7.18***
7.17.	What was the last CD4 result?	/_____/CD count
7.18.	Have you been referred to the ART clinic?	1 = Yes 2 = No 3 = Chooses not to answer 99 = Don't Know
7.19.	Have you visited the ART clinic?	1 = Yes 2 = No 3 = Chooses not to answer 99 = Don't Know
7.20.	Are you on HAART? [*Explanation: HAART is when the mother is on three ARV drugs*]	1 = Yes 2 = No ➔ ***Skip to 8.1*** 3 = Chooses not to answer ➔ ***Skip to 8.1*** 99 = Don't Know ➔ ***Skip to 8.1***
7.21.	How long ago did you start taking HAART?	1= Before Pregnancy with this infant 2 = During Pregnancy with this infant 3= After Delivery of this infant

SECTION VIII: BLOOD SPECIMENS

8.1.	Blood sample taken	1=Yes ➔ ***Skip to 8.5*** 2=Refused ➔ ***Skip to 8.3***
8.2.	If you are not willing to have your baby tested for PCR test can you tell me why not?	1 = No Reason ➔ ***Go to 8.3***2 = Lack of Time ➔ ***Skip to Stop1*** 3 = Need permission from another person ➔ ***Skip to Stop1*** 4 = Do not want to give name for the test ➔ ***Go to 8.3*** 5 = Other (specify) _____ ➔ ***Skip to Stop1***
8.3	Would you accept testing using only a laboratory ID number and not a name?	1=Yes ➔ ***Go to 8.4*** 2=Refused ➔ ***Skip to Stop1***
8.4	Blood sample taken – study ID used	1=Yes ➔ ***Go to 8.5*** 2=Refused ➔ *Skip to Stop1*
8.5	Cell Phone number belongs to	1=Mother ➔ ***Go to 8.6*** 2=Legal guardian/father (only if no mother is available) ➔ ***Go to 8.6*** 3=Do not have cell phone - ➔ ***write down address on follow-up letter envelope, click NEXT to continue*** ➔ ***Skip to 8.7***
8.6	Cell Phone Number	0##-###-####
8.7	Blood Sample Lab Form Bar Code	_____ ➔*Go to Stop2*

C. Situational analysis consent form and questionnaire

Information sheet and Consent Form for HEALTH FACILITIES SERVICE REVIEW

National Situational assessment

Hello. I am Mr./Ms. _____from Medical Research Council. The National Department of Health has asked the Medical Research Council & the University of the Western Cape to conduct a national PMTCT survey in all the nine provinces of South Africa. Your facility might be one of the facilities selected for this survey.
Before this national survey is conducted, information about how your facility functions and how it offers PMTCT and child-health care is needed. During the national survey we plan to visit the immunization clinic of each facility for about 3-4 weeks. During this time interviews will be conducted with mothers/caregivers at 6 weeks immunization visits. Blood specimens will also be collected from infants at 6 weeks of age. The result of the test will be returned to the facility so that mothers can get their infants HIV status result.
The National Department of Health has informed all Heads of Health that researchers from the Medical Research Council will be visiting primary health care clinics and community health centers to conduct a situational analysis and gather baseline information relevant for the planning of the PMTCT survey (show letter written by National Department of Health). Permission to conduct this situational analysis has been received from the Medical Research Council ethics committee (show letter). Today we are here to conduct this situational analysis: we would like to find out about the most suitable means of transport needed to access your facility; the availability of local / suitable field workers for data collection; your PMTCT and EPI services; your immunisation days; the equipment, supplies, communication and transport systems that exist for DBS PCR testing and the services that your clinic offers for HIV counseling and testing and for adult and paediatric antiretroviral treatment.

The questions will take about 30-45 minutes of your time. The study will pose no risk to you or to your facility. You & your facility will not be identified by name or address in any of the reports we plan to write. Key findings will be reported in aggregate form only. You may refuse to answer some questions and you may withdraw from the interview at any point. Your withdrawal will not have any negative effects on your work. You will not personally benefit from this study, but the information collected will be used to strengthen the existing PCR testing & referral system of health facilities.

If you have any questions or concerns about the research or about your welfare as a research subject, please feel free to contact the principal investigator:

Dr Ameena E Goga
Paediatrician and Specialist Scientist
Health Systems Research Unit

Medical Research Council
1 Soutpansberg Road, Pretoria, 0001
Tel: +2712 3398531 / +2782 302 3168
Or
The MRC Ethics Committee with the following address: Prof Danie du Toit, tel. (021) 938 0341; e-mail: adri.labuschagne@mrc.ac.za

Would you be willing to assist us by answering some of our questions? *(Please ask the respondent to read and sign the consent form if his/her answer is yes)*.
We hope that this situational analysis will help us as we plan for this national survey that the Department of Health has asked for.

CONSENT FORM

Researcher: ……*(Field worker name)*
Facility name*:* ……

Research conducted by: Medical Research Council and University of the Western Cape and
Mr/Ms …… has explained the study and has shown me all permission letters. My questions have been answered and I agree to take part in this study.

Name (print)……
Designation in facility……..

Signature……
Date…….

Filed workers signature (as a witness)…….. *Date* ……

Thanking you for helping us with our research.

Situational Analysis questionnaire

Interviewer read out: Thank you for agreeing to answer our questions. The questionnaire is divided into four sections. The first section assesses general postnatal PMTCT information. You can answer some or all of the questions in this section or you can refer us to a person who can best answer the relevant questions. The second section is particularly for you (the clinic manager). The third section has questions for the key nurse who coordinates or provides EPI / immunization services in the clinic & the fourth section is for the key nurse who provides IMCI or sick babies service.

Section I – Basic postnatal PMTCT information

Note to the field worker: *start the interview with the clinic manager, however the clinic manager may answer all questions in section 1 or may refer you to one of the IMCI nurse, immunization nurse, PMTCT nurse or VCT nurse. Please note the name of the person who you are referred to (i.e. write 'EPI nurse' if you were referred to EPI nurse) next to the relevant question so that you remember the person you need to interview after the clinic managers interview.*

A. Assessment of the existing system for identifying HIV infected & exposed infants

1. Does your clinic offer HIV testing for infants during 6 weeks immunization visit?

   1= Yes

   2 = No ➔ ***if no skip to q2***

1.1. *If yes,* which of the following algorithms/protocols do you use to identify HIV exposed or infected infants during 6 weeks immunization visit: ***PROMPT RESPONDENTS & CIRCLE ALL THAT APPLY***

1= All mothers bringing their infants for 6 weeks immunization visit get offered a DNA PCR test on their infant

2= All mothers bringing their infants for a 6wks immunization visit get offered a rapid HIV test on their own blood & if they are HIV positive (from the rapid test) their infants will be offered DNA PCR test

3= Infants born to mothers who report themselves as HIV positive get offered a DNA PCR test during 6wks immunization visit

4= Infants born to HIV positive mothers as recorded on the RTHC get offered a DNA PCR test during 6wks immunization visit

5= Infants born to HIV positive mothers as recorded on the register get offered a DNA PCR test during 6wks immunization visit

6= Mothers who ask for HIV tests during 6 weeks immunization visit get offered an HIV test on themselves followed by a DNA PCR test on their infant if they are positive

7= Mothers who ask specifically for an infant HIV test get offered an HIV test on their infants during 6 weeks immunization visit

8= Other

8.1= If yes to other, specify _____

1.2.Do you provide PCR testing for infants that comes with a caregiver (eg. grandmothers etc) without the mother present

1=Yes

2= No

2. Do you offer HIV testing to infants at visits other than 6 weeks immunization visit

1= Yes

2= No ➔ ***if no skip to q 3***

➔ ***if no to both q1 & q2 skip to q13***

2.1. *If yes,* other than 6 week visit, can you tell us on which other visits or at what stages of the infants life HIV testing is provided ***PROMPT RESPONDENTS & CIRCLE ALL THAT APPLY***

1= All sick children suspected for HIV exposure from clinical symptoms will be offered HIV test at any age if they were not tested before

2= All HIV exposed babies visiting the sick baby clinic will be given HIV test if were not tested before

3= If a child is born from a known HIV positive mother a PCR test will be given after cessation of breastfeeding

4= If a child is born from a known HIV positive mother a PCR test will be given at 9 months

5= If a child is born from a known HIV positive mother a rapid test will be given at 18 months

6= Other

6.1. =If yes to other, specify _____

3. Do you have Standard Operating Procedures that you follow to do (i.e to collect, dry & pack blood specimens) PCR specimens?

   1=Yes

   2= No

4. In which one of the following services/clinics do you offer HIV testing to identify HIV exposed/infected infants? ***PROMPT RESPONDENTS & CIRCLE ALL THAT APPLY***

   1= HIV testing is offered & performed at the PMTCT clinic

   2= HIV testing is offered & performed at the immunization clinic

   3= HIV testing is offered & performed at the IMCI/sick baby clinic

   4=Immunization clinic offers HIV testing to mother infant pairs & refers those who agree to test to the PMTCT clinic

   5= Immunization clinic offers HIV testing to mother infant pairs & refers those who agree to test to the VCT clinic

   6= IMCI/sick baby clinic offers HIV testing to mother infant pairs & refers those who agree to test to the PMTCT clinic

   7= IMCI/sick baby clinic offers HIV testing to mother infant pairs & refers those who agree to test to the VCT clinic

   8= Other

   8.1= Specify other

B. Sending DBS for lab testing

5. If your facility offers PCR testing, where (to which lab) do you send the DBS/whole blood specimens for testing? Specify the name & address of the laboratory where the blood specimens are sent.

Name

Physical Address & telephone number

6. Is there a transport system that takes these PCR specimens to the laboratory?

1= Yes

2= No ➔ ***if No skip to q9***

6.1. *If yes,* please tell us what transportation system is used:

1= Routine provincial system

2= Routine NHLS system

3= Routine private courier

4= if routine private courier, provide contact details

Name

Telephone number

5= Other:

5.1= If other, specify/provide contact details:

Name

Address

7. How frequently are these infant PCR specimens sent to laboratory for PCR testing?

ONLY ONE RESPONSE

1= Daily

2= on certain standardised day/days of the week

3= Once a week (no standardised day i.e. adhoc whenever there are enough specimens to send)

4= Adhoc basis – sometimes once a week, sometimes fortnightly

5= not sent to the lab

6= other

6.1= if other specify

7.1. If lab specimens are sent on certain standardised day/days of the week, specify which day/days of the week _____ and time of the day (i.e. mornings/afternoons) _____ the DBS/whole blood specimens are sent to the lab

8. Is this transportation system reliable

1= Yes it is reliable ➔ ***if Yes skip to q10***

2=Not reliable

8.1. *If the transportation is not reliable*, describe the problems that you have been having with the transportation system

9. If there is no transportation system , ask how PCR specimens reach to the laboratory

10. Where do you store infant PCR specimens in the facility until they are collected

1= Consulting room in which they were taken

2= Facility pharmacy

3= Clinic Manager's office

4= Facility's staff tea room

5= Facility fridge

6= Other

6.1= if other specify

11. What is the average turnaround time for PCR test result – i.e. the number of weeks from the day the specimen has been taken from the infant to the day that the facility receives the result?

12. When do mothers usually receive their infants PCR test result if the blood specimen was collected at the 6 week immunization visit. ***ONLY ONE RESPONSE***

1= usually at 10 weeks

2= usually at 14 weeks

3= other

4= if other specify _____

To the field worker: if answered yes to q1 or q2 skip to q15

13. If PCR testing service is not given in this facility, are there <u>any other blood specimens</u> (eg. CD4 count) that you send to the lab?

1= Yes

2= No ➔ ***if No skip to q15***

13.1. If yes, specify Name & address of the lab that you use for these other specimens

Name

Physical Address & telephone number

13.2. *If yes*, please tell us what transportation system is used:

1= Routine provincial system

2= Routine NHLS system

3= Routine private courier

4= *if routine private courier*, provide contact details

Name

Contact number

5= Other:

5.1= *If other*, specify/provide contact details:

Name

Address

14. If yes how frequently are these other blood specimens (eg. CD4 count) sent to the laboratory? ***ONLY ONE RESPONSE***

    1= Daily

    2= on certain standardised day/days of the week

    3= Once a week (no standardised day i.e. adhoc whenever there are enough specimens to send)

    4= Adhoc basis – sometimes once a week, sometimes fortnightly

    5= not sent to the lab

    6= other

    6.1= if other specify

14.1. If these other blood specimens (eg. CD4 count etc) are sent on certain standardised day/days of the week, specify which day/days of the week _____ & time of the day (mornings/afternoons) _____ they are sent to the NHLS lab

C. Pretest counseling, providing test result & post-test counseling

15. Who provides pretest counseling <u>for infant</u> HIV testing ***CIRCLE ALL THAT APPLY***

    1= VCT Counsellor (nurse)

    2= VCT lay counsellor

    3= EPI clinic Nurse

    4= Nurse – IMCI trained

    5= Nurse – not IMCI trained

    6= None (eg. PCR testing not done and results not given) ➔ ***if None skip to q19***

    7= Other

    7.1= if other, specify

16. Who provides <u>PCR test result</u> of the baby to the mother ***CIRCLE ALL THAT APPLY***

    1= VCT Counsellor (nurse)

    2= VCT lay counsellor

    3= EPI clinic Nurse

    4= Nurse – IMCI trained

    5= Nurse – not IMCI trained

    6= None (eg. PCR testing not done and results not given)

    7= Other

    7.1= if other, specify

17. Does the same person who gives PCR test result provide post-test counseling for infant HIV testing?

1= Yes -> ***if yes skip to q19***

2= No

18. If no, who provides posttest counseling for infant HIV testing ***CIRCLE ALL THAT APPLY***

1= VCT Counsellor (nurse)

2= VCT lay counsellor

3= EPI clinic Nurse

4= Nurse – IMCI trained

5= Nurse – not IMCI trained

6= None (eg. PCR testing not done and results not given)

7= Other

7.1= if other, specify

19. Who provides posttest counseling for mothers that received testing on themselves ***CIRCLE ALL THAT APPLY***

1= VCT Counsellor (nurse)

2= VCT lay counsellor

3= EPI clinic Nurse

4= Nurse – IMCI trained

5= Nurse – not IMCI trained

6= None (eg. rapid HIV testing not done and results not given) -> ***if none skip to q21***

7= Other

7.1= if other, specify

20. Who provides pretest counseling for mothers that receive HIV testing ***CIRCLE ALL THAT APPLY***

1= VCT Counsellor (nurse)

2= VCT lay counsellor

3= EPI clinic Nurse

4= Nurse – IMCI trained

5= Nurse – not IMCI trained

6= None (eg. rapid HIV testing not done and results not given)

7= Other

7.1= if other, specify

21. Where do mothers receive their infants PCR test results / post-test counselling: ***PROMPT***

    1= in a separate room allocated for VCT

    2= in a separate routine consulting room

    3= in any available private space in the clinic

    4= in any available public space in the clinic

    5= Outside the clinic – under a tree or in a private space outdoors

    6= Others

    6.1= if other specify

22. If there is a separate room available for post-test counseling, write down the directions to the room or the room name or number of the place where mothers receive PCR test results / post-test counseling.

23. If HIV testing is not done in this facility or if there is no separate room available for post-test counselling, write down the full address of the nearest facility where infants can be referred for receiving PCR test results & post-test counseling

    Name

    Address

D. Supplies ***(Skip this section if no PCR testing service is given from q1 & q 2)***

24. Do you have PCR test kits in stock today (field worker should ask to see the kits)?

    1 = Yes 2= No ***-> if no skip to q26***

25. ***For the field worker to see***: are all within the expiry date (ask to see the kits)?

    1 = Yes 2= No

26. Does the clinic have stock-cards (or a similar system) to track supplies of PCR test kits

    1 = Yes 2= No

27. How frequently do you order PCR kits ***ONLY ONE RESPONSE***

    1= Daily

    2= Weekly - on a set day of the week

    3= Weekly – adhoc days

    4= Monthly

    5= Other

    5.1= if other, specify

28. Who is responsible for keeping track of PCR stock?

    1= EPI nurse

    2= IMCI nurse

    3= VCT nurse

    4= other

    4.1 if other, specify

29. Has there been any day in the last month when the clinic ran out of PCR stock?

    1= Yes, 2= No ***-> if no skip to q30***

29.1. *If yes*, for how long _____

E. Mother baby follow-up system - registers & cards

30. Is there any clinic-held recording system or register that tracks postnatal PMTCT follow-up of mother infant pairs?

1=Yes

2=No -> ***if no skip to q36***

30.1. If yes, in which unit(s) of the facility is this register(s) kept (ask to see & confirm).

PROMPT RESPONDENT & CIRCLE ALL THAT APPLY

1= At separate PMTCT clinic

2= At immunization clinic

3= At IMCI/sick baby clinic

4= At VCT clinic

5= Have one register for each of IMCI & immunization clinic

6= Have one register for each of IMCI, immunization & PMTCT clinic

7= kept in a room with multiple services (i.e PMTCT, IMCI, immunization given in same room)

8= Other

8.1= if other Specify

30.2.If yes, which of the following is captured in this register(s) (ask to see & confirm):

TICK ALL THAT APPLY

- ☐ Maternal testing
- ☐ Maternal HIV status
- ☐ Infant PCR testing done at 6wks
- ☐ Infant PCR testing done at any age
- ☐ Infants HIV status
- ☐ Infant CD4 count
- ☐ Mothers CD4 count
- ☐ Infant referral for ARV
- ☐ Mother referral for ARV
- ☐ Infant & mother referral for support & care
- ☐ Infant postnatal prophylaxis
- ☐ Infant Cotrimoxazole (bactrim)
- ☐ Infant feeding

To the interviewer: ***write "no record" if there was no record for some of the questions***

31. According to this record(s), between September 1 & Nov 30, 2009, how many infants were tested for HIV at 6 weeks (DNA PCR)

31.1. Of these infants tested for HIV at 6 weeks using DNA PCR how many were HIV positive (If this is not recorded, please write not recorded)

32. According to this record(s) , between September 1 & Nov 30, 2009, how many infants were tested for HIV using PCR *in total (regardless of age)*

32.1. Of these infants (tested at any age) how many were HIV positive

33. How many were routinely given Cotrimoxazole (bactrim) at 6 weeks as part of a PMTCT intervention_____

34. According to this records, between September 1 & Nov 30, 2009, how many of the HIV positive infants were referred for ARV treatment _____

35. According to this record between September 1 & Nov 30, 2009 how many mothers were known HIV positive (both newly diagnosed & already known)_____

35.1. How many of these HIV positive mothers were given CD4 Count after giving birth _____

35.2. Of those whose CD4 count was done, how many were documented as having a CD4 cell count <200__

35.3.How many of the mothers with <200 CD4 count were referred for ARV service

____

36. Is there any patient-held system that facilitates linkages between maternal antenatal and postnatal care e.g. postnatal card/RHTC?

1=Yes

2=No -> **if no skip to q37**

36.1. If yes, specify which card is used ***CIRCLE ALL THAT APPLY***

1= postnatal card

2= RHTC

3= Antenatal card

4= Other

4.1= if other, specify

36.2.*If RTHC is used*, which RTHC is currently used in the clinic?

1= The new RHTC booklet

2= The old RTHC with the coding system

3= The RTHC with stamp

4= The old RTHC with no coding system and no stamp

5= Other

5.1= if other specify

37. Is there a PMTCT clinic in your facility?

1= Yes

2=No -> ***if no skip to q38***

37.1. *If yes*, which day(s) of the week does the PMTCT clinic run? ***CIRCLE ALL THAT APPLY***

1= Monday 4=Thursday

2= Tuesday 5= Friday

3= Wednesday 6= Everyday

38. Do infants born to PMTCT mothers receive immunizations at certain specific day/days of the week?

1= Yes

2= No-> ***if no skip to q39***

38.1.If yes, on which day/ days of the week do they receive immunization service

CIRCLE ALL THAT APPLY

1= Monday	4=Thursday
2= Tuesday	5= Friday
3= Wednesday	6= Everyday

39. Which of the following medical records do you use to capture patient level data

CIRCLE ALL THAT APPLY

1= electronic medical records (EMR)

2= Paper based ***-> if paper based skip to q40***

3= both electronic & paper based

4= Other

4.1= *If other*, specify

39.1.Which electronic medical records do you use

40. Do you capture your PMTCT data on an electronic database

1= Yes

2= No -> ***skip to q42***

41. If yes, please specify what system/database you use

F. Referrals

42. Do you normally routinely ask all mothers at 6 weeks visit whether they had HIV test (& received their result) during their last pregnancy

1=Yes

2=No

43. If yes, do you refer or provide VCT for mothers who haven't been tested during pregnancy

1=Yes

2=No

44. Do you normally ask HIV positive mothers (as identified by the RTHC or mothers report) when her last CD4 count was done after delivery

1=Yes

2=No -> ***if no skip to q46***

45. If yes, do you routinely identify & provide CD4 count test for mothers who haven't had a CD4 count since giving birth

1=Yes

2=No

46. Can you please tell us the name & address of the clinic/facility where blood is taken /drawn for CD4 count test

Name

Address

47. If you provide CD4 count test, what is the average turnaround time for a return of maternal CD4 cell count result i.e. the number of weeks from the day the specimen has been taken from the mother to the day that the facility receives the results?

48. Do you refer HIV positive infants (as identified by the RTHC or mothers report) for CD4 count 1=Yes

2=No

49. Do you refer HIV positive infants to ARV clinics?

1=Yes

2=No

50. Is there an ARV clinic (for children) in this facility?

1 = Yes

2= No **-> *if no skip to q52***

51. *If yes,* write down the room number or describe how to get to the room where the ARV clinic runs

_____

_____

52. If there is no ARV clinic in this facility then write down the name and address of the facility to which children are usually referred (more than one clinic can be stated)

Name

Address

53. Is there a specific person that you refer them to? 1=Yes 2= No

If yes, who ?

Person's name:

53.1. Do you telephone and make an appointment for the infant or do you simply refer with a letter (no appointment)

1= Referral letter written and appointment made

2= No referral letter written but appointment made

3= Referral letter written but no appointment made

4= Other

53.2. Is there a follow-up mechanism in your clinic to monitor how many referred children actually went to the ARV clinic?

1= Yes

2= No

53.3. Do you know whether there is a follow-up mechanism in the ARV clinic to track attendance of children and follow-up of non-attendees?

1= Yes

2= No

3= Don't know

54. Which day(s) of the week does the paediatric ARV clinic run?

1= Monday	4= Thursday	7= Don't know
2= Tuesday	5= Friday	8= Other
3= Wednesday	6= Everyday	8.1. = if other specify

55. Do you refer HIV positive mothers to ARV clinics?

1=Yes

2=No

56. Is there adult ARV clinic in this facility?

1=Yes

2=No ***-> if no skip to q58***

57. If yes, write down the room number or describe how to get to the room where the ARV clinic runs

_____

_____

_____

_____

58. If there is no ARV clinic in this facility then write down the name and address of the facility to which mothers are usually referred (more than one clinic can be stated)

Name

Address (street name & room no)

59. Is there a specific person that you refer them to? 1= Yes 2= No

If yes, who?

Person's name:

60. Which day(s) of the week does the adult ARV clinic run? ***CIRCLE ALL THAT APPLY***

1= Monday	4=Thursday	7= Other
2= Tuesday	5= Friday	7.1= If other specify
3= Wednesday	6= Everyday	8= Don't know

61. Do you refer HIV positive mothers to community based support & care services?

1=Yes

2=No

62. Do you have referral forms/letters to refer (ask to see & confirm):

62.1. Infants to ARV clinics: 1= Yes 2= No

62.2. Mothers to ARV clinics: 1= Yes 2= No

62.3. Infants to community based support & care services: 1= Yes 2= No

62.4. Mothers to community based support & care services; 1= Yes 2= No

63. ***For the interviewer***: Which of the following clinic staff participated in the interview **CIRCLE *ALL THAT APPLY***

1= PMTCT nurse

2= Immunization nurse

3= IMCI/sick baby nurse

4= VCT nurse

5= clinic manager

6= Other

6.1= if other, specify

Section II - Interview with clinic manager

A. Training need assessment

1. We would like to know more about the number of staff members in this facility,

	Total number in facility	PCR		VCT			How to immunize children		Routine child health services		ARV services	
		Do / provide service	Trained in SOP for PCR	Do Counseling	Do VCT	Formally trained in VCT	Do	Trained in how to provide EPI services	See sick children	Trained in IMCI	Do	Trained in ARV initiation or monitoring
Professional nurses												
Staff nurses												
Enrolled nurse assistant												
Lay counselors												
Doctors												
Other (specify)												

what they have been trained in and what services they provide. ***Instruction to interviewer: if a service is not provided or no-one has been trained please write zero***

2. Of those staffs who provide EPI service, how many have been formally trained in how to do infant PCR testing?
3. What have been the barriers to training on infant PCR? ***CIRCLE ALL THAT APPLY***

   1= No time for training – clinic too busy

   2= No money for training

   3= Other

   3.1.If other specify

4. If some staff members have been trained, have you experienced any barriers to offering PCR tests at EPI clinics?

   1=Yes

   2=No -> ***if no skip to q 6***

5. If yes, what are these barriers? ***CIRCLE ALL THAT APPLY***

   1= Mothers resistant to HIV testing/ Mothers fear of disclosing status

   2= No time at EPI clinics

   3= No supplies for PCR testing

   4= Person other than mother brings infant to the clinic

   5= Staff shortages

   6= Too few staff trained

   7= No one trained on pre & post counseling

   7.1.Other

6. Of those staff who provide IMCI/sick babies, how many have been formally trained in how to do infant PCR testing? (give a definite number)

7. If some staff members have been trained, have you experienced any barriers to offering PCR tests at sick child clinics? 1= Yes 2= No ***-> if no skip to q9***

8. If yes, what are these barriers? ***CIRCLE ALL THAT APPLY***
   1= Mothers resistant to HIV testing
   2= No time at sick child clinics
   3= No supplies for PCR testing
   4= Person other than mother brings infant to the clinic
   5= Staff shortages
   6= Too few staff trained
   7= No one trained on pre & post counseling
   8= Other
   7.1. If other specify

9. Please tell us if you have used any of the following to improve your PMTCT services?

9.1. Task shifting 1= Yes 2= No

9.1.1. If yes, please explain what you have done

9.2. Re-organising the clinic flow 1= Yes 2= No

9.2.1. If yes please explain what you have done

9.3. Mothers to mothers groups 1= Yes 2= No

9.4. Lay counselors 1= Yes 2= No

9.4.1. If yes please explain how you use lay counselors in your clinic (circle all that apply)

1= to do counseling

2= do testing for HIV

2= to weigh babies

3= to fill in the PCR form

4= to do infant feeding counseling

5= to clean the clinic

6= to talk to HIV positive mothers

7= other

7.1= if other, specify

B. Attitude

10. In your opinion, who / which service should offer routine infant DNA PCR testing?

CIRCLE ALL THAT APPLY

1= EPI/immunization clinic

2= IMCI/sick baby clinic

3= PMTCT clinics

3= Hospitals only

4= HIV clinics only

5= Other

5.1 = if other specify

11. Can you give us reasons for your answers

12. Would you be willing to send your EPI and IMCI / child health staff on DBS training sometime this year? 1= Yes ***-> if yes skip to 13***

2= No

12.1.If no, please state why

C. Arrangement of logistics for the 6 weeks survey

Interviewer read out: *The following questions are aimed at assisting us with logistical arrangements for the 6 week survey. We would like to make arrangements for a suitable area to conduct the interviews, storage of blood samples and returning of lab results.*

Accommodation

13. Is there accommodation within or nearby the facility (e.g. nursing residence)?

1=Yes

2=No ***-> if no skip to 19***

14. If available, can we use your facility's accommodation during the data collection period?

1=Yes

2=No

3= Don't know

14.1.*If don't know,* can you tell me who I can ask/talk to

15. How many people can be housed in your facility's accommodation
16. Does the room(s) have a bed or beds?

1=Yes if yes how many _____

2=No

17. Does the room(s) has cooking utensils

1=Yes

2=No

18. Do you serve food?

1= Yes if yes how much do you charge per dinner ___

2=No

19. *If accommodation is not available within the facility*, can you please give us your suggestions where field workers can stay during the survey (B&B or private homes) - get the name, address & contact number of this accommodations

20. Do you perhaps know the costs of these B&Bs/private homes

Transport

21. ***For the fieldworker:*** What is the road type that this clinic is on

    1=Tar

    2=Gravel

    3=Sand / dirt

    4=Other

    4.1= If other, specify:

22. What is the suitable Car type for this road

    1=Normal motor vehicle

    2= by 4 SUV, Venture, bakkie, Condor

    3= 4 by 4 SUV, Venture, bakkie, Condor

    4= other

    4.1.= if other, specify

23. Is there a regular Taxi/Bus/train that can be used to get to the facility -> ***if no to all skip to q25***

    Tick all that apply

    ☐ Taxi

    ☐ Bus

    ☐ Train

24. *If yes*, ask how frequently does it run

    24.1. Taxi

    24.2. Bus

    24.3. Train

    24.4.1. Is there a 6am train in the morning?

25. Cost of Taxi from the nearest B&B /local private houses to the facility

26. Cost of Bus from the nearest B&B /local private houses to the facility

27. Cost of Train from the nearest B&B /local private houses to the facility

Other logistics (local field workers, interview space & clinic address)

28. Do you know anyone who has previous field work experience & that lives within the district/sub district?

    1= Yes

    2= No

29. *If yes*, can you give us the contact addresses of this person(s) & encourage them to send their CV to the following address: targetedevalhsur@gmail.com fax: 0219380483 (***instruction to the field worker*****:** *post the field workers advert on the clinics notice board after asking permission of the clinic manager*)

30. We know that space is problem in most facilities but would you be able to allocate a space for us to interview mothers and collect DBS spots from babies when the national survey starts?

    1=Yes

    2=No

31. ***If yes, ask to see this space & note what equipment this space has. Ask if you would be able to get a chair for the mother and a surface that you could use to lay the baby down when doing the DBS testing. (to the field worker: Note that some***

small clinics may not be able to provide you with a room – therefore any quite corner which is not far from the EPI clinic area & a place/or chair to comfortably sit the mother will be enough.)

32. Ask if we can use a corner of any secure room in the clinic for drying blood specimens (write down agreed room for drying specimens). Report if space is a major problem in the clinic.

33. Ask for a secure place to keep the 6 weeks survey PCR specimens until collection time (write down agreed room for storing specimens) Report if space is a major problem in the clinic

34. What is the referral clinics postal address for return of PCR results

Section III – Interview with key person/nurse that coordinates or provides immunization service

Introduce the study to the interviewee using the information sheet & receive signed consent before starting the interview

1. Are immunizations done every day?
   1= Yes
   2= No
2. Is there any particular day / days of the week when more immunizations are done (compared with other days) – ask to see the register & confirm

To the interviewer: Review the immunization register & capture the following data:

3. How many DPT 1 Immunizations were done last week = _____

4. How many DPT 1 Immunizations were done on the month of November 2009 = _____

5. How many DPT1 Immunizations were done from September 1 to November 30, 2009 =_____

6. Do you provide PCR testing when infants come for their 6 week immunization??
   PROMPT
   1= Yes we provide PCR testing <u>at immunization clinic</u>
   2= Yes we provide PCR testing <u>in conjunction with VCT/PMTCT clinics</u>
   3= No **if no Skip to q 8**

7. If yes how do you identify HIV exposed infants at 6weeks? ***CIRCLE ALL THAT APPLY***

   1= give rapid test to all mothers who presents at 6 weeks immunization visit
   2= from register
   3= if mother reported
   4= we ask mothers their status
   5= from the RTHC
   6=Antenatal card
   7= Others
   7.1= If other specify

8. In your opinion, is it a good idea to offer infant DNA PCR testing routinely as part of EPI/immunization services?
   1=Yes -> ***skip to q10***
   2= No

9. If no, please state why:
   1= It is not part of Immunisation nurses responsibilities
   2= There is not time to do this

3= It is a good idea but it is not part of immunization nurses responsibilities or there is no time

4= There is not enough staff to do this

4= Other

4.1=if other, specify

10. If yes, in your opinion is it feasible to offer DNA PCR testing as part of routine EPI services?

    1=Yes

    2= No

    a. *Please explain your answer*

11. Do you normally ask all mothers at 6 weeks visit whether they had HIV test (& received their result) during their last pregnancy

    1=Yes

    2=No

12. If yes, do you refer or provide VCT for mothers who haven't been tested during pregnancy

    1=Yes

    2=No

13. Do you normally routinely ask HIV positive mothers (as identified by the RTHC or mothers report) at 6 weeks visit when her last CD4 count was done

    1=Yes

    2=No

14. If yes, do you routinely identify & provide CD4 count test for mothers who haven't been checked for their CD4 count since giving birth

    1=Yes

    2=No

15. Do you refer HIV positive infants (as identified by the RTHC or mothers report) for CD4 count 1=Yes

2=No

Section IV - IMCI/sick baby head nurse

Introduce the study to the IMCI/sick baby head nurse using the information sheet & receive signed consent before starting the interview

1. Do you offer PCR testing for HIV-exposed infants at sick baby clinic?

1=Yes

2=No

2. If yes how do you identify HIV exposed infants for PCR testing? ***CIRCLE ALL THAT APPLY***

1= Symptoms of infants

2= from clinic register

3= from patient folder

4= from the RTHC

5= from mothers/caregivers report

4= Others

4.1= If other specify

3. Is it a good idea to offer infant DNA PCR testing routinely as part of routine IMCI /sick child services

1=Yes

2= No

4. If it is a good idea, do you think it is feasible to offer DNA PCR testing as part of routine IMCI/ ill child care??

4.1. Please explain your answer

5. Do you normally routinely ask all new mothers whether they had HIV test (& received their result) during their last pregnancy

   1=Yes

   2=No

6. If yes, do you refer or provide VCT for mothers who haven't been tested during pregnancy

   1=Yes

   2=No

7. Do you normally routinely ask HIV positive mothers (as identified by the RTHC/other registers or mothers report) when her last CD4 count was done

   1=Yes

   2=No

8. If yes, do you routinely identify & provide CD4 count test for mothers who haven't been checked for their CD4 count since giving birth

   1=Yes

   2=No

9. Do you refer HIV positive infants (as identified by the RTHC , registers or mothers report) for CD4 count 1=Yes

   2=No

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26 February 2010

Dr A Goga
Health Systems Research Unit
MRC Cape Town

Dear Dr Goga

Protocol ID: EC09-002
Protocol title: Proposal to evaluate the effectiveness and impact of the prevention of mother-to-child transmission (PMTCT) programme, South Africa
Meeting date: 22 February 2010

Thank you for your response to the Committee clarifying the main PI, synchronising the definitions with the National Health Act and clarifying the use of 'want to' in the consent form. The Committee granted approval for the evaluation of the effectiveness of the national Prevention of Mother to Child Transmission (PMTCT) programme on infant HIV at 6 weeks postpartum in South Africa, as well as the information sheet and questionnaire submitted on 18 February 2010.

Wishing you well with your research.

Yours sincerely

PROF. D DU TOIT
CHAIRPERSON: MRC ETHICS COMMITTEE

SOUTH AFRICAN MEDICAL RESEARCH COUNCIL

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28 January 2010

Dr A Goga
Health Systems Research Unit
MRC Cape Town

Dear Dr Goga

Protocol ID: EC09-002
Protocol title: Proposal to evaluate the effectiveness and impact of the prevention of mother-to-child transmission (PMTCT) programme, South Africa
Meeting date: 23 November 2009

Thank you for your response to the Ethics Committee, dated 21 January 2010, regarding the amendment to the study. The Committee granted ethics approval for the final protocol, consent form and tools for situational assessment.

Wishing you well with your research.

Yours sincerely

PROF. D DU TOIT
CHAIRPERSON: MRC ETHICS COMMITTEE