ASSESSING PROGRESS AND BARRIERS TO ELIMINATION OF MOTHER-TO-CHILD TRANSMISSION AND DECREASING HIV-RELATED MATERNAL DEATHS IN THE JOHANNESBURG HEALTH DISTRICT

Coceka Nandipha Mnyani

Student number: 0301506H

A thesis completed by published work, submitted to the School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, in fulfilment of the requirements for the degree Doctor of Philosophy

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DECLARATION

I declare that this thesis is my own work. It is being submitted for the degree of Doctor of Philosophy to the School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa.

This thesis is submitted in the format of published work with a supporting introduction, a literature review and discussion.

This work has not been submitted before for any degree or examination at any other university.

Signature: 

Name: Coceka Nandipha Mnyani

Date: 7th day of June 2018, Johannesburg

DEDICATION

This PhD is dedicated to the memory of my parents – my mother, Britannia Nomangesi Mnyani for always believing in me, and my father, Jongile Fezile Mnyani for teaching me what hard work is all about.

This PhD is also dedicated to the thousands of pregnant women who have crossed my path and entrusted me with their lives and those of their unborn children.

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ABSTRACT

Background

South Africa has the largest HIV epidemic globally, with a prevalence among pregnant women estimated at 30.8% in 2015. Consequent to this high HIV prevalence rate, which has plateaued around 30% over the past decade, South Africa was identified as one of the priority countries for elimination of mother-to-child transmission of HIV (eMTCT) and decreasing HIV-related maternal deaths. The aim of this thesis was to evaluate the evolution of the Soweto PMTCT and antiretroviral therapy (ART) programme, in Johannesburg, one of the largest and oldest in the country with data spanning almost two decades. The evaluation is on the impact of the programme on MTCT rates and HIV-related maternal mortality, in a high HIV prevalence urban setting.

Methods

This thesis includes six studies that chronicle progress and challenges in eMTCT and decreasing HIV-related maternal mortality. The studies address three objectives: (i) to describe progress made in implementation of efficacious PMTCT interventions and ART coverage in HIV-infected pregnant women; (ii) to identify patient-related risk factors for MTCT; and (iii) to assess the impact of evolving HIV management guidelines and increased availability of ART on maternal mortality in HIV-infected women. Three studies address the first objective and include two secondary analyses of routinely collected PMTCT data, and a cross-sectional study to assess quality of care in the Soweto PMTCT programme. The second objective is addressed by two studies, one a case-control study and the other a cross-sectional survey, both identifying patient-related risk factors for MTCT. The third objective is addressed by a 19-year record review assessing trends in maternal deaths in HIV-infected women.

Results

Findings from this thesis show how successful implementation of evolving PMTCT and ART guidelines, in a high HIV prevalence setting, have led to a significant

decrease in the MTCT rate to levels below 2% at early infant diagnosis. There is also a decrease in the maternal mortality ratio (MMR) among HIV-infected women, coinciding with the expansion of the South African ART programme. While reporting on these are public health successes, this thesis also identifies remaining challenges. Through evaluating aspects of the continuum of care along the PMTCT cascade in the studies that make up this thesis, three overarching themes emerge. These are delayed or lack of access to antenatal care, delayed HIV diagnosis and ART initiation among pregnant women, and suboptimal quality of care in PMTCT and ART programmes as reflected in the healthcare workers' and patients' knowledge of PMTCT interventions.

Conclusion

The findings have important implications for policy and practice. Challenges identified in accessing antenatal care, HIV diagnosis and ART initiation among pregnant women and quality of HIV care all intersect and increase the risk of MTCT and maternal mortality in HIV-infected women. These are both patient-related and health system-related. Targeted interventions are needed to build on the gains made.

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Abbreviations

AIDS: acquired immune deficiency syndrome

ART: antiretroviral treatment

ARVs: antiretrovirals

BANC: basic antenatal care

CHBAH: Chris Hani Baragwanath Academic Hospital

CPR: contraceptive prevalence rate

CYP: couple year protection rate

DART: Demonstration of Antiretroviral Treatment programme

DHIS: Demographic Health Information System

EGPAF: Elizabeth Glazer Paediatric AIDS Foundation

EID: early infant diagnosis

eMTCT: elimination of mother-to-child transmission of HIV

HIV: human immunodeficiency virus

HDACC: Health Data Advisory and Coordinating Committee

IHME: Institute of Health Metrics and Evaluation

iMMR: institutional maternal mortality ratio

IPT: isoniazid preventive therapy

MDG: millennium development goal

MMR: maternal mortality ratio

MTCT: mother-to-child transmission of HIV

NCCEMD: National Committee on Confidential Enquiries into Maternal Deaths

NIMART: nurse-initiated and managed antiretroviral therapy

PCR: polymerase chain reaction

PEPFAR: United States President's Emergency Plan for AIDS Relief

PHRU: Perinatal HIV Research Unit

PICT: provider-initiated counselling and testing

PMTCT: prevention of mother-to-child transmission of HIV

SDG: sustainable development goal

TB: tuberculosis

UNAIDS: Joint United Nations Programme on HIV/AIDS

UN MMEIG: United Nations Maternal Mortality Estimation Inter-Agency Group

USAID: US Agency for International Development

VCT: voluntary counselling and testing

WHO: World Health Organization

THESIS OVERVIEW AND STRUCTURE

This thesis was done through the route of thesis with publications and comprises of two parts: (i) an integrating narrative which provides the background, rationale, methodology and findings of the research and (ii) the research papers that form part of this PhD. The research is made up of six related studies, five which address various aspects of prevention of mother-to-child transmission of HIV (PMTCT) and one on HIV-related maternal mortality. The integrating narrative is divided into five chapters:

Chapter one is the background and literature review and is divided into two sections. The first section is on the evolution of PMTCT and antiretroviral treatment (ART) guidelines in resource-constrained settings, including in South Africa. It will also discuss progress made towards elimination of mother-to-child transmission of HIV (eMTCT) and challenges that still exist within PMTCT programmes. The second section of the literature review is on global trends, and trends in South Africa, on maternal deaths. The literature review will focus on maternal deaths in HIV-infected women and how the evolving PMTCT and ART guidelines have impacted on mortality in this group of women.

Chapter two outlines the rationale for the research and the overall aims and objectives of this PhD.

Chapter three gives an overview of the methodology used in the six studies that make up this PhD with a detailed description of the study setting and a summary of the data collection and analysis. Detailed description of the methodology for each study is described in the appended Papers 1-6.

Chapter four provides a synthesis of the key findings from the six studies and how they address the research objectives.

Chapter five discusses the key cross-cutting themes that emerged from the synthesis of all the data from the six studies. The discussion section also highlights the contribution of the research to existing literature, and also the implications of the

research on eMTCT and decreasing HIV-related maternal mortality. Lastly it outlines the research limitations and makes recommendations for future research.

OUTPUTS FROM THE PhD RESEARCH

A. Original papers

1. **Mnyani CN,** McIntyre JA. Challenges to delivering quality care in a prevention of mother-to-child transmission of HIV programme in Soweto. *S Afr J HIV Med* 2013;14(2):64-69.
   Candidate's role: conceptualised the study, supervised the data collection and wrote the manuscript.

2. **Mnyani CN,** Marinda E, Struthers H, Gulley M, Machepa R, McIntyre J. Timing of antenatal care and ART initiation in HIV-infected pregnant women before and after introduction of NIMART. *S Afr J HIV Med* 2014;15(2):55-56.
   Candidate's role: conceptualised the study, supervised the data collection and wrote the manuscript.

3. **Mnyani CN,** Simango A, Murphy J, Chersich M, McIntyre JA. Patient factors to target for elimination of mother-to-child transmission of HIV. *Global Health* 2014;10:36.
   Candidate's role: conceptualised the study, supervised the data collection and wrote the manuscript.

4. **Mnyani CN,** Tait CL, Armstrong J, et al. Infant feeding knowledge, perceptions and practices among women with and without HIV in Johannesburg, South Africa: a survey in healthcare facilities. *Int Breastfeed J* 2017;12:17.
   Candidate's role: conceptualised the study, did the analysis and wrote the manuscript.

5. **Mnyani CN,** Buchmann EJ, Chersich MF, Frank KA, McIntyre JA. Trends in maternal deaths in HIV-infected women, on a background of changing HIV management guidelines in South Africa: 1997 to 2015. *J Int AIDS Soc* 2017; 20:e25022.
   Candidate's role: conceptualised the study, involved in data collection and wrote the manuscript.

6. **Mnyani CN,** Tait CL, Peters RPH, et al. Implementation of a successful PMTCT programme in a high HIV prevalence setting: 2002-2015. (Manuscript to be submitted for publication)
   Candidate's role: conceptualised the study, did the data analysis and wrote the manuscript.

B. Presentations

- Oral presentation at CROI, Boston, 2014
- Oral presentation at Wits Research day, September 2014
- Oral presentation at Wits Research Day, September 2016
- Oral presentation at the Public Health Association of South Africa (PHASA) Conference, September 2016
- Invited speaker IAS, Paris, 2017

C. Awards

- Carnegie Clinician Scientist PhD Fellowship for 2016
- Travel award from the School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, for the 2016 PHASA Conference in East London, South Africa

CHAPTER 1: BACKGROUND AND LITERATURE REVIEW

1.1 PMTCT BACKGROUND AND LITERATURE REVIEW

This section will discuss progress made towards elimination of mother-to-child transmission of HIV (eMTCT), in the context of evolving prevention of MTCT (PMTCT) and antiretroviral therapy (ART) guidelines. It will also discuss rationale behind the guideline changes and challenges that still exist within PMTCT programmes in resource-limited settings.

1.1.1 The road to elimination of mother-to-child transmission of HIV

In 2011, UNAIDS, the Joint United Nations Programme on HIV/AIDS, launched the Global Plan for elimination of mother-to-child transmission of HIV (eMTCT) by 2015, and keeping HIV-infected mothers alive.[1] The first goal of the Global Plan was for a 90% reduction in new paediatric HIV infections by 2015, and the target was to reduce the MTCT rate to 5% or less among breastfeeding women, and to 2% or less among non-breastfeeding women.[1] The second goal was to decrease HIV-related maternal deaths by 50%, by 2015. There were 22• priority countries identified in the Global Plan and together accounted for 90% of the global number of women living with HIV in 2009. The priority countries included 21 countries in sub-Saharan Africa, and India.

Since the launch of the Global Plan, great strides have been made towards eMTCT, including in South Africa.[2] According to the 2016 UNAIDS report on the 21 priority countries in sub-Saharan Africa, 1.2 million new paediatric HIV infections were averted between 2009 and 2015.[2] This translates to a 60% reduction in paediatric infections, and although this falls short of the 90% target, it has been hailed as 'one of the greatest public health achievements of recent times'.[2] Data were not available for India hence the UNAIDS report is on 21 countries. South Africa is one of seven priority countries that reduced new paediatric HIV infections by more than 70%, with an estimated 84% reduction between 2009 and 2015. The other

• Angola, Botswana, Burundi, Cameroon, Chad, Côte d'Ivoire, Democratic Republic of the Congo, Ethiopia, Ghana, India, Kenya, Lesotho, Malawi, Mozambique, Namibia, Nigeria, South Africa, Uganda, United Republic of Tanzania, Swaziland, Zambia and Zimbabwe

countries that had a more than 70% reduction in new infections were Uganda (86%), Burundi (84%), Swaziland (80%), Namibia (79%), Mozambique (75%) and Malawi (71%). Four of these countries – South Africa, Uganda, Swaziland and Namibia – achieved the Global Plan milestone of an MTCT rate of less than 5%.[2]

These significant gains in PMTCT have been largely due to the increased availability of efficacious antiretrovirals and scale-up of antiretroviral therapy (ART) programmes.[2] In the 21 priority countries, the proportion of HIV-infected pregnant women who received antiretrovirals for PMTCT increased from 36% in 2009 to 80% in 2015, with 93% of the women receiving lifelong ART in 2015. PMTCT and ART guidelines in resource-limited settings have been guided by the World Health Organization (WHO) recommendations and guidelines which have evolved significantly over the past decade – Table 1.1.

1.1.2 Evolution of the World Health Organization PMTCT and ART recommendations and guidelines for resource-limited settings

The first WHO document on interventions for PMTCT in low resource settings were the technical notes published in 2001, following a meeting in 2000 organised on behalf of the United Nations Interagency Task Team on mother-to-child transmission of HIV infection.[3] The document provided evidence and recommendations on various antiretroviral regimens for PMTCT started either early or late in pregnancy, or given intrapartum. The regimens for preventing perinatal transmission were zidovudine either alone or in combination with lamivudine, or intrapartum single-dose nevirapine – Table 1.1.[3] In the early years the main determinant for the choice of antiretrovirals for PMTCT in resource-limited settings was cost, as the cost of providing complex antiretroviral regimens was prohibitive at the time. While the efficacy of more complex regimens with antepartum, intrapartum and postpartum components was recognised to be higher, single-dose nevirapine was more practical for low resource settings. At the time, complex antenatal and intrapartum regimens, and combination antiretrovirals were already in use for PMTCT in resource-rich settings. In the 2001 technical notes, a recommendation was also made for a three-pronged strategy for PMTCT and it comprised the following: “primary prevention of HIV among parents-to-be; prevention of unwanted pregnancies among HIV-infected women; and prevention

of HIV transmission from HIV-infected women to their infants through the provision of antiretroviral drugs to HIV-infected pregnant women and their infants, safe delivery practices, and counselling and support for safer infant feeding practices".[3] The strategy would further be developed into the four prongs of PMTCT, and these will be discussed in detail in Section 1.1.4.

The subsequent WHO guideline, published in 2004, reiterated the efficacy or more complex antiretroviral regimens (Table 1.1), but acknowledged that where these were not feasible or acceptable maternal and infant single-dose nevirapine remained an alternative.[4] Cost and weak health systems that were seen to be unable to manage implementation of more complex antiretroviral regimens for PMTCT necessitated that simpler regimens were used in low resource settings. The 2004 guideline acknowledged the importance of lifelong antiretroviral treatment for maternal health. In the previous year, 2003, WHO released guidelines for life-long antiretroviral treatment for children, adolescents and adults living with HIV in resource-limited settings.[5] The eligibility criteria were based on the WHO clinical stage and a CD4 count where available – Table 1.1.

As the guidelines evolved and there was more experience with implementation of PMTCT programmes programmatic evidence showed that it was possible to implement effective large-scale programmes even in resource-limited setting. The 2006 WHO guidelines called for a public health approach for increasing access to PMTCT services.[6] In the document, it was said that "the main purpose of adopting a public health approach is to ensure access to high-quality services at the population level, while striking a balance between the best proven standard of care and what is feasible on a large scale in resource-constrained settings".[6] In order to optimise the effectiveness of PMTCT programmes, all four components of the WHO comprehensive strategic approach to the prevention of HIV infection in infants and young children, first introduced in 2001, had to be implemented. The strategic approach would also make headway towards elimination of HIV infection in infants and young children. A fourth component, care, treatment and support for mothers living with HIV, their children and families, was added to the original strategic approach.[6]

Table 1.1: WHO PMTCT and ART recommendations for resource-limited settings, 2001-2016 [3–10]

	2001	2004	2006	2010	2013	2016
PMTCT **Maternal antiretroviral regimens**	Long-course (from 14 weeks gestation) or short-course (from 28-36 weeks) ZDV as monotherapy or with 3TC and intrapartum single-dose NVP; or single-dose NVP	Antenatal (from 28 weeks) and intrapartum ZDV with or without 3TC and intrapartum single-dose NVP; or ZDV and 3TC from 36 weeks, continued intrapartum and 1 week postpartum	ZDV starting at 28 weeks gestation and intrapartum single-dose NVP. Intrapartum ZDV and 3TC, and 7 days of ZDV and 3TC if the mother receives intrapartum single-dose NVP	ARV prophylaxis starting at 14 weeks: **Option A:** antenatal ZDV, with intrapartum NVP, ZDV and 3TC, and ZDV and 3TC for 7 days postpartum. **Option B:** triple therapy during pregnancy and breastfeeding	**Option B** **Option B+:** Lifelong triple antiretrovirals for all pregnant and breastfeeding women, regardless of WHO stage and CD4 count	Lifelong ART for all pregnant and breastfeeding women
Infant antiretrovirals	ZDV for 3 days to 6 weeks; or ZDV and 3TC for 1 week; or single-dose NVP	Single-dose NVP and ZDV for 1 week; or ZDV alone or with 3TC for 1 week; or single-dose NVP	ZDV for 1 week or 4 weeks if the mother received less than 4 weeks of ZDV during pregnancy	**Daily NVP or twice-daily ZDV for 4-6 weeks, irrespective of infant feeding method	6 weeks NVP if breastfed. With replacement feeding, 4-6 weeks of NVP or ZDV	Same as in 2013. #Infants at high risk for MTCT: ZDV and NVP for 6 weeks, extended to 12 weeks if breastfed
ART eligibility (lifelong treatment)	_____	*WHO stage 4 irrespective of CD4 count; or WHO stage 3 with CD4 <250; or WHO stage 1 and 2 with CD4 <200	Same as in the 2004 guidelines	CD4 counts ≤350 irrespective of WHO stage; WHO 3 or 4, irrespective of CD4 count	CD4 count ≤500 or WHO stage 3 or 4 disease	Regardless of CD4 count or WHO stage

ZDV=zidovudine; 3TC=lamivudine; NVP=nevirapine; ARV=antiretroviral

*The eligibility criteria were based on the 2003 WHO treatment guidelines; ** Extended NVP prophylaxis for breastfed infants and mothers not eligible for ART

#Infants at high risk for MTCT: less than 4 weeks of maternal ART; viral load >1000 in the 4 weeks before delivery; incident HIV infection during pregnancy and breastfeeding

Up until 2010, antenatal zidovudine and intrapartum single-dose nevirapine remained the recommendation for PMTCT in women who did not need treatment for their own health, in resource-limited settings. In 2010 there were major changes in the WHO guidelines starting with the introduction of two options for prophylaxis in women who did not need treatment for their own health, and an increase in the CD4 threshold for ART initiation in pregnant women.[7] For the first time, there was also a recommendation for antiretroviral prophylaxis during the breastfeeding period, acknowledging the risk of MTCT during this period. The two options for PMTCT were Options A and B, and the CD4 threshold for ART initiation was increased to ≤350 cells/μl irrespective of WHO stage.[7] Option A is antenatal and intrapartum zidovudine, with intrapartum single-dose nevirapine and seven days of postpartum zidovudine and lamivudine, and extended infant nevirapine prophylaxis for the duration of breastfeeding period. Option B is the provision of combination triple therapy for all HIV-infected pregnant women, with withdrawal of treatment postpartum if not breastfeeding, or after cessation of breastfeeding. In both Options, women who were eligible for lifelong ART were started on treatment for their own health and for PMTCT. The decrease in cost of antiretrovirals made it possible to recommend combination regimens for PMTCT even in resource-limited settings. At the time of the release of the 2010 guidelines there was no scientific or programmatic evidence to show that one PMTCT strategy, either Option A or B, was more efficacious than the other. Countries were encouraged to choose a PMTCT option based on local resources and feasibility of implementing either option.

In 2012 WHO released a programmatic update with a recommendation for a single antiretroviral regimen for PMTCT and treatment for HIV-infected pregnant women.[8] While Options A and B were judged at the time to be equally efficacious for prophylaxis, there were concerns that the two options might be confusing and there were challenges with implementation of Option A. The challenges with Option A included the fact that different antiretrovirals had to be used in the antenatal, intrapartum and postpartum periods, and also the need for CD4 count testing which was not always readily available in most resource-limited settings. The 2012 update also introduced a third option, Option B+, which is lifelong ART for all HIV-infected pregnant and postpartum women regardless of the level of immune suppression. The subsequent 2013 guidelines made a recommendation for Option B+ for all HIV-infected pregnant and postpartum women, especially for countries with generalised

epidemics as the option provided a simplified and efficacious regimen with programmatic and operational advantages.[9] Option B+ will be discussed in more detail in Section 1.1.7. The last WHO guideline update was in 2016 and the recommendation is for lifelong ART for all pregnant and breastfeeding women.[10]

1.1.3 Evolution of the South African PMTCT and ART guidelines

The evolution of the South African PMTCT and ART guidelines (Table 1.2) mirrors the evolution of the WHO guidelines.[11–16] The biggest changes in the South African PMTCT guidelines were in the period 2010 to 2015, starting in 2010 with the increase in the CD4 count threshold for ART initiation in pregnant women to ≤350 cells/µl, and the introduction of nurse-initiated and managed ART (NIMART).[14–16] The period also saw withdrawal of free infant formula which was available for HIV-infected women who elected not to breastfeed. As part of the PMTCT programme, a six months' supply of free formula was available until 2011 when South Africa adopted a single policy of supporting breastfeeding for all HIV-infected women.[17] In 2013, Option B was introduced and lastly in 2015 Option B+ was adopted.

Introduction of NIMART in 2010 was part of task-shifting and decentralisation of services where professional nurses, including midwives, could initiate and manage patients on ART.[18] This was an attempt to address delays and limitations with the number of patients started on ART with physician-led programmes. Introduction of NIMART within antenatal clinics became necessary as the proportion of ART-eligible pregnant women increased with guideline changes in 2010 increasing the CD4 threshold for eligibility. Results from the STRETCH (Streamlining Tasks and Roles to Expand Treatment and Care for HIV) trial, a large cluster-randomised trial conducted in South Africa with over 8 000 patients, provided evidence that primary care nurses could safely initiate and manage patients on ART.[19] In the trial, there was no difference in risk of mortality and the proportion of patients that were virally suppressed at 12 months between patients managed by physicians and those managed by nurses. The trial provided no detail on NIMART among pregnant women.

Table 1.2: Evolution of the South African recommendations for PMTCT and treatment for HIV-infected women [11–16]

	2002	2004	2008	2010	2012	2013	2015
PMTCT **Maternal antiretroviral** **regimens**	Intrapartum single-dose NVP	Same as in 2002	**Option A –** ZDV monotherapy from 28 weeks gestation for pregnant women not eligible for lifelong treatment.	Zidovudine monotherapy from 14 weeks. Integration of ART initiation within antenatal clinics (*NIMART)	Withdrawal of free infant formula for HIV-infected women who elected not to breastfeed	Option B – triple therapy for all HIV-infected pregnant women, with postpartum withdrawal of therapy in those not eligible for lifelong treatment	Option B+ – lifelong ART for all HIV-infected pregnant, regardless of level of immune suppression
Infant antiretrovirals	Immediate postpartum single-dose NVP		1 or 4 weeks of ZDV if mother had less than 4 weeks of ZDV	Same as in 2008	-------	Daily NVP for 6 weeks	Daily NVP for 6 weeks, extended for 12 weeks if high risk for MTCT
ART eligibility (lifelong treatment)	-------	Antiretroviral therapy (ART) Eligibility criteria: CD4 <200, or WHO stage 4	Eligibility criteria for ART remains the same	ART eligibility criteria for pregnant women: CD4 ≤350, or WHO stage 3 or 4	-------	CD4 ≤350, or WHO stage 3 or 4	Regardless of CD4 count or WHO stage

ZDV=zidovudine; 3TC=lamivudine; NVP=nevirapine; ARV=antiretroviral

*NIMART= nurse initiated and managed antiretroviral therapy

Challenges with introduction of NIMART within antenatal clinics were highlighted in a review of a donor-funded PMTCT programme in Cape Town, South Africa.[20] Referral of pregnant women to separate ART clinics was associated with failure of linkage to care and delays in starting treatment. In an attempt to address these challenges, a model to integrate ART initiation within midwives' obstetric units was introduced in the Cape Town PMTCT programme. The challenges associated with introduction of NIMART were that ART initiation within the obstetric units was seen as an additional task to perform by overworked staff and midwives were also not skilled to manage both pregnancy and HIV infection. Despite effective ART services led by nurses in nearby ART clinics, it took six years to establish a NIMART programme within the midwives' obstetric units.[20] When the South African guidelines changed in 2010, increasing the proportion of ART-eligible pregnant women with the increase in the CD4 threshold, task shifting and the ability of midwives to prescribe ART became necessary. Midwives were trained in NIMART and a mentorship programme was established. The authors of the paper acknowledge that dedicated staff, government policies, and partnerships between the department of health, academic institutions and non-governmental institutions were all important for the success of the NIMART programme.[20]

The evolution of the WHO and the South African guidelines illustrate the important developments that have occurred in the field of PMTCT. While the greatest achievements have been through the provision of antiretrovirals, the Global Plan goals and targets were built on the WHO four prongs of PMTCT, Figure 1.1.[6] In the first WHO PMTCT recommendations published in 2001, it was recognised that in order to significantly decrease perinatal HIV transmission interventions will have to address various aspects of HIV prevention.[3] These were later developed into the four prongs of PMTCT.[6]

1.1.4 THE FOUR PRONGS OF PMTCT

<u>Prong 1</u> – Primary prevention of HIV infection:

Primary prevention of HIV infection has seen the least progress with only a 5% decrease in new HIV infections among women of reproductive age between 2009

and 2015, falling far short of the Global Plan target of a 50% reduction.[2]

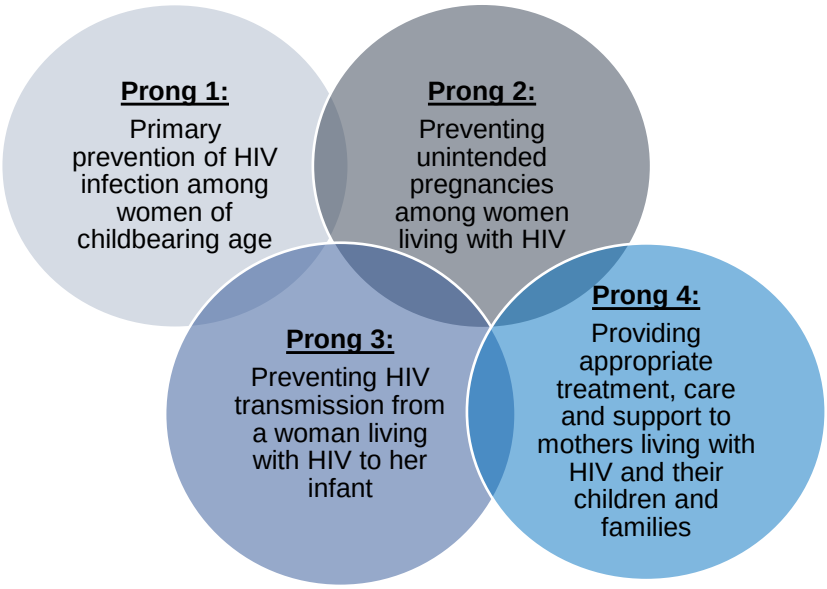


Figure 1.1: The World Health Organization four prongs of prevention of mother-to-child transmission of HIV [6]

According to the 2016 UNAIDS report, South Africa has had the largest number of new HIV infections, with approximately 1.2 million new infections among women of reproductive age between 2009 and 2015.[2] Estimates from the 2012 South African National HIV Prevalence, Incidence and Behaviour Survey (the most recent national incidence survey) are that there was almost double the number of new HIV infections among women of reproductive age, 15-49 years, compared to men in the same age group.[21] The gender-related disparity in HIV incidence was even higher in the 15-24 age group with a four-times greater incidence in women than in men. Age-disparate relationships where the sexual partner is five years older or more, and often associated with transactional sex, is said to be the key driver of the high HIV incidence in girls and women aged 15-24 years.

School attendance has been identified as a protective factor in decreasing HIV incidence in young women.[22] In a large randomized controlled trial done in South Africa with 2 533 participants, young women who attended school less than 80% of

the expected time had an increased risk of HIV acquisition, relative risk 1.88 (95% CI: 1.08, 3.27, p=0.03). Although not statistically significant, dropping out of school was also associated with an increased risk of HIV acquisition, relative risk 1.77 (95% CI 0.95, 3.28, p=0.07). Several prevention strategies targeting adolescents and young women and encouraging them to stay at school and avoid age-disparate relationships have been advocated, but they have yet to show results in South Africa.

<u>Prong 2</u> – Preventing unintended pregnancies among women living with HIV

With prevention of unplanned and unintended pregnancies, indications are that there remains a large unmet need for family planning among all women of reproductive age, including HIV-infected women.[2] Data on unmet need for family planning are however often outdated, based on contraceptive needs of married women and not disaggregated by HIV status.[2] The contraceptive prevalence rate (CPR), which is defined as the proportion of women aged 15 to 49 years who are currently using a contraceptive method, is used to report on contraception use. For South Africa, nationally representative data on contraception use are from the 2003 and 2016 South Africa Demographic and Health Surveys, and the 2012 South African National HIV Prevalence, Incidence and Behaviour survey.[21,23,24] The CPR among married women in South Africa remained unchanged in 2016 at 54% compared to 55% in 1998.[24] Among sexually active unmarried women the CPR declined from 68% in 2003 to 64% in 2016.[24]

Regarding the unmet need for family planning the 2016 Survey defines this as "the proportion of women who are currently fecund and not pregnant who want to postpone or stop childbearing but are not using a contraceptive method, together with the women who report that their current pregnancy or birth in the last 2 years was mistimed or unwanted".[24] The figure was 17% in 1998 and 15% in 2016.[24] In their analysis of the 2012 South African National HIV Prevalence, Incidence and Behaviour Survey, Chersich et al report on a high rate of unwanted and unintended pregnancies.[25] They found that two-thirds of all pregnancies were unintended, and among women who were pregnant at the time of the survey 49% had an unwanted pregnancy.

Another index used for family planning is the couple year protection (CYP) rate, which reflects distribution of contraceptives and is the estimated protection provided by family planning services in a 12-month period. In the 2015 Millennium Development Goal Report, the estimated CYP rate for South Africa increased from 27.6% in 2010 to 52.7% in 2014.[26] While this shows an increase in the distribution of contraceptives, data from national surveys discussed above reflect a high unmet need for contraceptives and also a high rate of unintended pregnancies. The limitation with the national surveys however is that they are cross-sectional and do not reflect on trends.

<u>Prong 3</u> – Prevention of HIV transmission from mothers living with HIV to their infants:

Prevention of HIV transmission from women living with HIV to their infants has largely been the focus of PMTCT programmes and is the area where the greatest success has been achieved, and has been discussed in detail in Section 1.1.1.

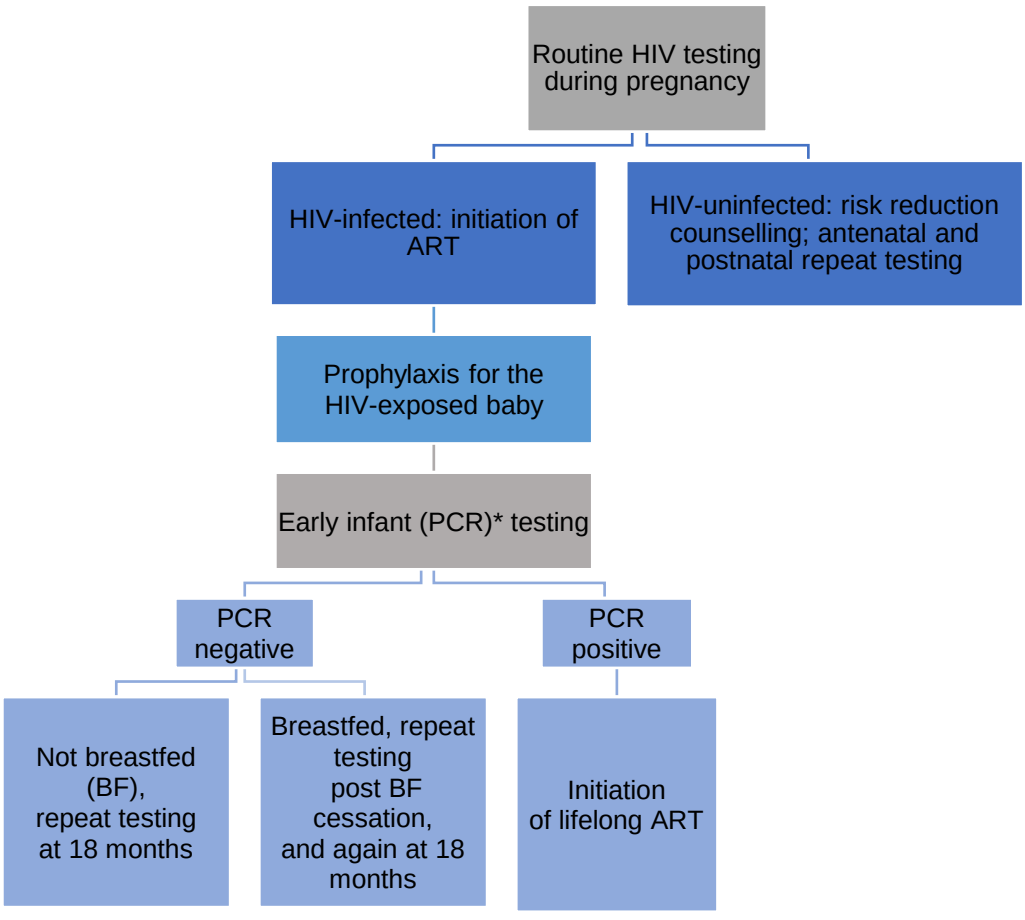
<u>Prong 4</u> – Care, treatment and support for mothers living with HIV, their children and families:

Postpartum retention in care which is part of prong 4 is an area where efforts still need to be intensified.[2] The UNAIDS estimate is that over 50% of new paediatric HIV infections are due to breastfeeding transmission as a result of HIV-infected women not being retained in care and on treatment postpartum.[2] Postpartum retention in care and breastfeeding transmission will be discussed in more detail in Sections 1.1.10 and 1.1.11.

As we celebrate the successes and the enormous gains made in PMTCT programmes in the priority countries including South Africa, it is important to take stock of the gaps that still exist in prevention of HIV transmission to infants.

1.1.5 Challenges that still exist in prevention of mother-to-child transmission of HIV programmes

Availability of antiretrovirals alone does not guarantee a successful PMTCT programme.[27] Several methods have been used in evaluating effectiveness of PMTCT programmes and these include assessing coverage at various steps of the PMTCT cascade; facility- and community-based case finding of HIV-infected infants; prospective cohorts and community-based surveys assessing HIV-free survival.[28] While more representative, community-based case finding and surveys are more complex and expensive to conduct.[28] Hence coverage along the PMTCT cascade (Figure 1.2) and facility-based case finding are often used to assess successes and challenges that still exist in PMTCT programmes.[27,28] While these are convenient and less complex, they rely on accuracy and completeness of routinely collected data.



(PCR=polymerase chain reaction)

Figure 1.2: PMTCT cascade (Adapted from Stringer et al. 2008 and Barker et al. 2011 [27,28])

Several factors influence the risk of MTCT, among them timing of maternal HIV infection, maternal viral load and extent of immunosuppression, initiation of ART and antiretroviral prophylaxis (when prophylaxis was still part of PMTCT guidelines), and infant feeding practices.[29,30] Attrition at any step of the cascade translates to the HIV-infected pregnant woman and HIV-exposed infant not receiving the appropriate care, and hence increasing the risk of HIV transmission.[27]

In a study assessing factors associated with completion of the PMTCT cascade in four countries (Cameroon, Cote d'Ivoire, South Africa and Zambia), just over a third, 36.4%, of HIV-infected women completed the cascade.[31] This was a community-based study where 7 985 mother-infant pairs were enrolled, and women who reported a delivery in the past 24 months were included in the study. Data were collected on details of the last pregnancy and mother-infant pairs were tested for HIV and for HIV-infected women the PMTCT cascade was recreated using information collected during the interviews. A total of 1 014 mothers tested HIV positive and complete data were available for 976 HIV-infected women. Completion of the cascade was defined as attendance of an antenatal clinic at least once, HIV test and receipt of results, and initiation of maternal and infant antiretroviral prophylaxis. Infant testing was not included in the cascade and the MTCT rate was not reported on, both important omissions as the success of any PMTCT programme is based on the MTCT rate. In the study, the biggest fall-off was at receipt of HIV test results – of the 976 women identified as HIV-infected, 87.0% were tested for HIV in the last pregnancy, and only 47.0% received their results. No details were given on whether HIV testing was done using rapid or laboratory-based testing, an important factor in delivery of results.

Factors that were associated with completion of the PMTCT cascade were HIV diagnosis prior to pregnancy, awareness of partner's HIV status, having an HIV-infected partner, and ever use of long-acting contraception, the last factor likely to be a proxy for health-seeking behaviour and access to healthcare.[31] The study has limitations in that it was done in an earlier period of PMTCT interventions, 2007-2009, a factor acknowledged by the authors. The study also does not give details on why there were fall-offs at the various stages of the PMTCT cascade.

In a South African study done in a later time period, 2012 to 2013, where pregnant women who were newly diagnosed as HIV-infected at the first antenatal

visit were followed up for 60 days, there were high rates of loss to follow-up and failure to initiate antiretroviral prophylaxis and treatment.[32] Of the 158 pregnant women diagnosed as HIV-infected, 46.0% were eligible for ART. Only 3.0% of the pregnant ART-eligible women were started on treatment within 30 days of the first antenatal visit, and 21.0% were initiated within 60 days. A third of the women did not return for follow-up within 60 days of the first antenatal visit. The high rate of loss to follow-up and the delays in ART initiation were despite interventions to fast-track ART initiation in pregnant women, including implementation of NIMART and integration of antenatal and ART services. Health system factors – stock-out of HIV test kits, drug stock-outs and staff shortages – contributed to the delays in starting treatment. The study does have limitations in that routine data, which are prone to being incomplete, were used, and the study sample was small at only 158 participants. Patients could have also initiated treatment at other facilities. The authors acknowledge that the study was not designed to identify causes of failure to initiate and adhere to treatment, but rather to assess steps within the PMTCT cascade.[32] Both papers highlight the attrition that occurs at various steps of the PMTCT cascade. The next section of the literature review will discuss the various steps of the PMTCT cascade and factors that contribute to fall-offs at different stages.

1.1.6 HIV diagnosis and initiation of antiretrovirals in pregnant women

Routine HIV testing of all pregnant women at the first antenatal visit, through provider-initiated counselling and testing (PICT), is standard practice and provides an entry point for engagement in care. Pregnant women need to access antenatal care early, and once diagnosed as HIV-infected started on antiretrovirals. For pregnant women to be identified as HIV-infected and started on treatment, they need to access antenatal care. Several factors result in pregnant women not accessing any antenatal care, presenting for care late in pregnancy, or being lost to follow-up. In a meta-synthesis of why pregnant women in low- and middle-income countries do not utilise antenatal services, with four of the studies done in South Africa, the barriers to accessing antenatal care were universal.[33] The main reasons for not accessing any antenatal care or presenting late for care were cultural beliefs, financial considerations, and poor quality of services at antenatal clinics.[33] Cultural beliefs meant that pregnant women delayed pregnancy disclosure, and hence antenatal

clinic attendance, until the pregnancies were advanced because of fears of losing the pregnancies. Cost of transport to the antenatal facilities and fear of losing their employment if they took time off work were also found to be important factors. Even when pregnant women made the effort and managed to access antenatal care, the disappointment with the quality of services offered at the facilities prevented them from continued utilisation of the services. Accessing antenatal care is not only important for HIV diagnosis and ART initiation for PMTCT, but is also an important factor in maternal mortality in HIV-infected women. An in-depth discussion of the role of antenatal care in PMTCT and maternal mortality in HIV-infected women will be included in the discussion, integrating the available literature and findings from the studies that make up this PhD.

Once pregnant women have accessed antenatal care and been found to be HIV-infected, they need to start antiretrovirals for PMTCT and also for their own health. Health system and patient-related factors have both been identified as barriers to accessing care and initiating antiretrovirals among HIV-infected pregnant women. One of the major health system-related barriers to ART initiation among pregnant women was the vertical nature of services, where antenatal care and HIV management were provided at different sites, often in different facilities. This led to fragmentation of care and delays in ART initiation. Integration of antenatal and ART services has been an important intervention in increasing the proportion of pregnant women started on ART.[34,35] In one of the early studies to report on integration of antenatal care and ART initiation, Killam et al found that integration of services doubled the proportion of ART-eligible pregnant women that were started on treatment prior to delivery, AOR 2.01; 95% CI: 1.37, 2.95.[34] This study, done in Zambia in the period 2007-2008, was a stepped-wedge evaluation of integration of ART initiation and antenatal care and involved 1 562 ART-eligible pregnant women.[34] However, even with the integrated model, the overall proportion of pregnant women started on ART was low at 33%. There was no difference in time-to-initiation and gestational age at ART initiation among women started on ART within antenatal clinics, compared to those referred for treatment to ART sites.[34] While the authors provide no explanation on why the percentage initiated on ART was low and the fact that there was no decrease in time-to-initiation in the integrated model, it is likely related to the fact that ART services were only offered once or twice a week in the antenatal clinics that were part of the study.[34]

Similar to the Zambian study, a South African study also done in 2008, found a higher proportion of pregnant women started on ART with integrated services.[35] In the study, there were three models of care for ART initiation: model 1 ('integrated') where ART initiation was done within the antenatal clinic once a week; model 2 ('proximal') where pregnant women were referred for ART initiation to a separate site, but within the same facility; and model 3 ('distal') where the referral was to a separate healthcare facility.[35] There was a significant difference in the percentage of pregnant women initiated in the three models at 55%, 38% and 45% respectively, p=0.003. With referral to separate ART sites, there were delays with ART initiation during pregnancy even if the site was within the same facility and proximal to the antenatal clinic. The other barrier to ART initiation during pregnancy identified in the study was the gestational age at the first antenatal visit. Pregnant women who were started on ART accessed antenatal care at an earlier median gestation compared to those who were not started, 23 weeks vs. 29 weeks, p<0.001.[35] While the results of the study suggest that an integrated model is associated with a higher proportion of pregnant women started on ART, the overall ART initiation rate was low at 46%. The main limitation of the study is that it was a retrospective review of patient records, and data may be incomplete, a fact the authors acknowledge.[35]

There have been various models of integrating PMTCT services into other health services in an attempt to increase the uptake of PMTCT interventions.[36] These models have included integration with maternal, newborn, child health, sexual and reproductive health services and have had mixed results in terms of uptake, effectiveness and efficiency of services.[36] Integration of ART management into maternal and child health services, and task shifting enabling midwives to initiate and manage pregnant women on ART has had the biggest impact in increasing the proportion of pregnant women started on treatment.[36]

Prior to introduction of Option B+, HIV-infected pregnant women were assessed for ART eligibility based on a CD4 count threshold and WHO HIV disease stage, and once found to be eligible underwent a lengthy counselling process in preparation for ART initiation. Several studies from South Africa reported on lengthy delays between assessment for eligibility and initiation of ART among pregnant women, with delays of more than 30 days reported in some studies.[32,37–39] Given that the majority of pregnant women presented for antenatal care late in the second

trimester, or even in the third trimester, a proportion of women delivered without being started on ART. In their study evaluating adherence to recommended PMTCT services, Schnippel et al found that of 72 ART-eligible pregnant women, only two initiated ART within 30 days of their first antenatal visit and 15 within 60 days of the first visit.[32] The median period between the first antenatal visit and ART initiation was 47 days. These delays were despite fast-tracking of pregnant women, availability of NIMART and integration of antenatal care and ART services at the study sites. While the study was not designed to identify causes for the delay in starting ART, the authors mention that there were staff shortages, shortage of HIV test kits and antiretrovirals at the sites, at various points during the study period.[32] The results from this study highlight the fact that despite the best policies programmes are likely to fail if there are inadequate resources to support them.

In a study done in Cape Town, lengthy adherence counselling sessions while delaying starting ART did not improve maternal outcomes.[38] In their study, where the median time between assessment at the ART clinic and starting treatment was 21 days, Myer et al found that the duration of the systemic delays before starting treatment were not associated with improved maternal outcomes. The outcomes of interest were retention in care and virologic suppression up to 12 months after ART initiation. There was no difference in these outcomes among pregnant women who started ART less than 14 days after screening compared to those initiated on treatment after 14 days. In the study, no details are given on why some pregnant women were started on treatment earlier. Also, there are no details on the number of counselling sessions received and how patient readiness to start ART was assessed.[38]

While integration of antenatal and ART services and Option B+ have increased the proportion of pregnant women initiated on ART and eliminated the need for assessment for ART eligibility, timeous initiation of ART still depends on pregnant women presenting early for antenatal care and agreeing to start treatment. The risk of MTCT has been associated with the duration of antenatal ART.[40] In a Zambian study with 1 813 mother-infant pairs, four weeks or less of antenatal ART was associated with a 5.2-fold increased odds of MTCT compared with at least 13 weeks of antenatal ART.[40] In women who had less than 13 weeks of antenatal ART, the risk of MTCT was reduced by 14% with each additional week of ART. There was

no data on maternal viral loads, an important determinant of MTCT risk, and the authors acknowledged this limitation and explain that viral load monitoring was not routinely available in Zambia at the time of the study.[40] Data from resource-rich settings, which have longer experience with using combination ART for PMTCT, also show a significant association between duration of antenatal ART and risk of MTCT.[41] Results from population-based surveillance data from the United Kingdom and Ireland, with over 12 000 singleton pregnancies in HIV-infected women, show that in women starting ART in pregnancy there is a rapid decline in MTCT risk with each additional week of ART, up to 15 weeks of treatment when the risk less than 0.5%.[41] The findings on the association between duration of antenatal ART and risk of MTCT underpin the recommendation for same day initiation of ART in pregnant women diagnosed as HIV-infected.

Early antenatal care also provides an opportunity for pregnant women who initially test negative to be retested for HIV during the course of the pregnancy. The WHO guidelines recommend retesting in the third trimester and again during labour, for all pregnant women who initially test HIV negative.[10] The South African guideline recommendation is for retesting every three months during pregnancy and breastfeeding, and a repeat HIV test intrapartum.[16] The rationale for retesting during pregnancy is that primary HIV infection during pregnancy is associated with high rates of MTCT due to the high viraemia associated with acute HIV infection.[30] High primary HIV infection rates during pregnancy have been reported in high HIV incidence settings, and may contribute to a significant proportion of MTCT, especially where PMTCT programmes are effective in reducing transmission in women with known HIV infection.[42,43] Results from a national PMTCT evaluation study conducted in South Africa between 2011 and 2012 indicate that HIV seroconversion in pregnancy contributes significantly to early MTCT cases diagnosed between four and eight weeks postpartum.[44] In the study involving 9 802 mother/caregiver-infant pairs, there was a 3.3% seroconversion rate during pregnancy and although this group represented 6.7% of all HIV-infected pregnant women, they accounted for 26% of early MTCT cases in the study.[44] The early MTCT risk was also higher for the cases of seroconversion during pregnancy at 10.7% compared to 2.2% for women who were known to be HIV-infected during pregnancy. The women who seroconverted reported fewer antenatal visits and received their last HIV test result at a mean gestational age of 25 weeks. The authors estimated that 50% of the seroconversions

occurred after 32 weeks gestation. The findings from this South African study highlight the contribution of HIV seroconversion during pregnancy to MTCT, in a high HIV prevalence setting. The authors however caution that they could have overestimated the seroconversion rate as they were only able to verify 46% of the cases of self-reported antenatal HIV negative test results with clinic records.[44] However, the 3.3% seroconversion rate reported in the South African PMTCT evaluation study is similar to that reported in an earlier study done in South Africa.[42] In a study done from 2006 to 2007 in three provinces in South Africa, where pregnant women who initially tested HIV negative in early pregnancy were retested at 36 to 40 weeks, the seroconversion rate was 3.0%, similar to the figure from the national evaluation study.[42]

1.1.7 The rationale for Option B+

In 2012, WHO introduced Option B+ as the third option for management of HIV-infected women in resource-limited settings. This was seen as a public health approach as all HIV-infected pregnant and postpartum women would receive the same antiretroviral treatment, regardless of the level of immune suppression.[8] Having all pregnant and postpartum HIV-infected women receive the same antiretroviral regimen meant simplification of the interventions, and hence a public health approach. At the time of introduction of Option B+, the other two options for resource-limited settings were Option A and Option B.[8]

The idea for Option B+ was initiated in the context of the PMTCT programme in Malawi, where health system weaknesses and limitations with technology were a major barrier in CD4 testing to assess for ART eligibility in pregnant women.[45] The other argument for Option B+ was that women in Malawi have high fertility rates and short birth intervals, and that starting treatment for life in all HIV-infected pregnant women would benefit future pregnancies and also protect HIV-uninfected partners.[45] Lifelong treatment would also eliminate the need for starting and stopping treatment associated with PMTCT interventions, and also decrease the risk of disease progression.[45]

When Option B+ was introduced in 2011 in Malawi, no robust data were available to show superiority of triple therapy for PMTCT at high CD4 counts, and

also no data showing benefits of starting lifelong ART at high CD4 counts. Data subsequently became available to support both. Results from PROMISE, a large multinational trial that randomised 3 490 HIV-infected pregnant women with CD4 counts ≥350 cells/µl to receive either zidovudine monotherapy or triple therapy for PMTCT, showed benefits of ART in decreasing MTCT risk even at high CD4 counts.[46] The median CD4 in the participants was 530 cells/µl, and the transmission rate in the ART group was 0.5% compared to 1.8% in the zidovudine monotherapy group, -1.3% points, CI: −2.1 to −0.4.[46] Hence the PROMISE data provides evidence of the benefit of triple therapy for PMTCT even for pregnant women with high CD4 counts.

With regards to starting ART for PMTCT during pregnancy and stopping postpartum, published studies found that treatment interruption was associated with a risk of HIV disease progression.[47,48] Results from a study done in Brazil, where triple therapy started during pregnancy and discontinued postpartum has been standard of care since 2006, found that 24.2% (29/120) of women who had received ART for PMTCT had to be restarted on ART after a mean of 1.5 years postpartum.[47] Of the 29 women restarted on ART, 10 had evidence of HIV disease progression, and in 9/10 the diagnosis of disease progression was based on a drop in CD4 count. A baseline CD4 count <500 cells/µl during pregnancy was the only significant predictor of postpartum HIV disease progression. A total of 19/29 women were restarted on ART for PMTCT for a subsequent pregnancy.[47] Data from a multi-country HIV care programme also showed that an antenatal CD4 count <500 cells/µl was associated with an increased risk of postpartum HIV disease progression in women who discontinued ART for PMTCT after delivery.[49]

An observational study done in Malawi also highlights the issue of a need to restart treatment within a short period postpartum.[48] In the study where HIV-infected women with baseline CD4 counts >350 cells/µl stopped ART six months postpartum, one in five reached a CD4 count threshold of <350 cells/µl by 18 months of stopping ART. A CD4 count of <350 cells/µl was criteria for lifelong treatment at the time of the study. Overall, 30% of women had to restart ART by 18 months, either due to a low CD4 count or a new pregnancy.

The other argument for Option B+ is that even pregnant women with high CD4 counts will be started on treatment early instead of waiting for CD4 counts to drop to

treatment eligibility levels which may occur within a short interval postpartum. Results from a multinational study with sites in Zimbabwe, South Africa, Uganda, and Tanzania showed high rates of postpartum HIV disease progression in women with high CD4 counts that were not started on ART during pregnancy, in accordance with guidelines and standard of care at the time.[50] In 37% of women who had baseline CD4 counts between 400 and 549 cells/µl during pregnancy, and hence not started on treatment, the CD4 count dropped to <350 cells/µl at one year.[50] Evidence from studies involving non-pregnant populations show benefits of starting ART early, at higher CD4 counts. Data from two randomized controlled studies published in 2015, TEMPRANO and START, showed benefits of starting ART early, at CD4 counts >500 cells/µl.[51,52] In both studies, there was a decrease in AIDS- and non-AIDS-related morbidity and mortality in patients started on ART at CD4 counts >500 cells/µl.[51,52] The 2016 WHO guidelines now recommend lifelong ART for all HIV-infected individuals, regardless of level of immune suppression, and South Africa adopted the 'test and treat' guidelines in September 2016.[10,53]

While there has been a significant increase in the proportion of HIV-infected pregnant women initiated on ART through Option B+ with 93% of the women on antiretrovirals in the 21 priority countries on ART in 2015 compared to 73% in 2014, there remain challenges with postpartum follow-up and retention in care.[54]

1.1.8 Postpartum care

Postpartum follow-up is an important component of PMTCT programmes and has received less attention than antenatal care, beyond provision of infant prophylaxis and testing of the HIV-exposed infant.[54] Postpartum care encompasses early infant HIV diagnosis, provision of infant prophylaxis for all HIV-exposed infants, immediate ART initiation in HIV-infected infants, ongoing counselling on safe infant feeding practices, retention in care and adherence to treatment in all HIV-infected mothers on ART, infant testing after cessation of breastfeeding, and retesting and risk reduction counselling for HIV-uninfected mothers. It is also in the postpartum period that HIV-infected mothers and their infants are transitioned into general ART programmes for lifelong care. Infant diagnosis, safe infant feeding practices and

postpartum retention in care will be discussed in turn in the next three sections. ART initiation in HIV-infected infants is beyond the focus and scope of this PhD.

1.1.9 Infant diagnosis

Early infant diagnosis of all HIV-exposed infants ensures prompt diagnosis and initiation of ART in infants found to be HIV-infected. In the CHER (Children with HIV Early Antiretroviral Therapy) trial done in Soweto, South Africa, early HIV diagnosis and early initiation of ART in HIV-infected infants was associated with a 76% decrease in mortality and 75% decrease in HIV disease progression.[55] The CHER trial was a randomized, open label trial where HIV-infected infants at 6-12 weeks of age were assigned to early antiretroviral therapy initiated soon after diagnosis, or deferred treatment until clinical or laboratory criteria for ART were met, according to guidelines at the time.[55] The findings from the CHER trial led to WHO recommendations for immediate ART initiation in HIV-infected infants and children less than two years of age.

Infant testing needs to be at multiple points during the postpartum MTCT risk period in order to identify HIV-infected infants that may be missed by a single test, and to be able to have a final HIV diagnosis.[56] In settings where a single test is done, the 2016 WHO recommendation is for all HIV-exposed infants to have a virological (polymerase chain reaction, PCR) HIV test at 4-6 weeks of age, or soon thereafter.[10] While acknowledging the benefits of doing a birth PCR, and the prompt initiation of infants found to be HIV-infected, in decreasing morbidity and early mortality associated with in utero transmission, the recommendation is for testing at birth to be in addition to testing at 4-6 weeks of age.[10] Testing around 6 weeks of age will identify infants infected in utero and some infected during the intrapartum and immediate postpartum periods.[56] While the 6-week test appears well-timed, coinciding with routine postnatal visits, loss to follow-up occurs in the period between birth and six weeks and cases of in utero transmission may be missed.[56] It may however be early to detect all cases of intrapartum and early breastfeeding transmission in infants receiving antiretroviral prophylaxis who may have low HIV viral loads, hence the recommendation for multiple tests during the at risk postpartum period.[56]

The South African guidelines introduced routine testing at birth in 2015 and recommend testing of HIV-exposed infants at the following intervals: birth, 10 weeks (all HIV-exposed infants), 18 weeks (all infants who receive extended (12 weeks) nevirapine prophylaxis), 6 weeks post cessation of breastfeeding, and the final test at 18 months of age.[16] The reason for the shift in the timing of early infant diagnosis from 4-6 weeks to 10 or 18 weeks is the possibility of false negative or indeterminate results associated with infant nevirapine prophylaxis decreasing the viral load in the HIV-infected infant.[16] A large South African study with over 6 000 neonates tested at birth, and a testing coverage rate of 99%, showed that it is feasible to implement universal screening at birth with early ART initiation in those found to be HIV-infected.[57] A total of 99 out of 6 377 neonates tested were found to be HIV-infected and 95/99 were initiated on ART at a median age of eight days.[57] The authors though acknowledge that their findings may not be generalizable to a routine PMTCT programme setting as their birth testing programme was within a study with additional resources for counselling and tracking of neonates with positive results.[57] The importance of tracking is illustrated by the fact that in the study only 52% of neonates with negative results returned for results.

Coverage of early infant diagnosis at four to eight weeks of life remains low.[2] In 2015, the UNAIDS estimate is that only 51% of the estimated 1.2 million HIV-exposed infants in the 21 priority countries were tested in the first eight weeks of life.[2] Missed opportunities for early infant diagnosis occur throughout the continuum of care, from HIV-infected pregnant women being lost to follow-up during the antenatal period, to failure to identify and test HIV-exposed infants, and failure to deliver results in tested infants.[58] South Africa is one of the few countries that have achieved almost universal coverage of early infant diagnosis, with an estimated 95% of HIV-exposed infants tested in 2015.[2] The other two countries with infant testing coverage rates above 80% are Swaziland (81%) and Lesotho (93%).

There has been less emphasis on infant testing after cessation of breastfeeding, and indications are that late postnatal transmission rates are higher than at early infant diagnosis.[2] While the MTCT rate at early infant diagnosis was estimated to be 4.7% in the 21 priority countries, the transmission rate after cessation of breastfeeding was higher at 8.9%, and the difference was even larger for some countries.[2] In three countries – Cameroon, Democratic Republic of Congo and

Ghana – the transmission rate at the end of breastfeeding is more than double that in the first eight weeks of life.[2]

For South Africa the estimated transmission rate at early infant diagnosis is 1.4% while that at the end of breastfeeding is 2%.[2] Data from South Africa also indicate that while MTCT rates at early infant diagnosis have declined significantly, late postnatal transmission rates are higher than at early infant diagnosis.[59] In the South African PMTCT evaluation study, the cumulative MTCT rate at 18 months in the national cohort was 4.3% compared with the 2.6% transmission rate in infants aged four to eight weeks.[59] The South African data were not disaggregated according to infant feeding option, and the study was done during the transition period from Option A to Option B.[59] Infant feeding practices are the major determinant of late postnatal transmission rates, and it is important to determine the contribution of breastfeeding to MTCT rates.

1.1.10 Infant feeding practices

Safe infant feeding practices are an integral part of PMTCT, and an important part of postpartum care and follow-up. There are several challenges to promoting safe infant feeding practices, with low exclusive breastfeeding rates and mixed feeding the norm in most sub-Saharan countries, including South Africa.[60] In 2010, WHO made a recommendation for a public health approach to infant feeding, with each country advised to promote and support one infant feeding practice for HIV-infected women.[61] Following the recommendation, South Africa in 2011 made a declaration to promote and support breastfeeding for HIV-infected women.[17] Free infant formula which had been available for HIV-infected women who elected not to breastfeed was withdrawn following the declaration.[17] The current South African PMTCT guidelines recommendation is for HIV-infected women to exclusively breastfeed for six months, with introduction of complementary food at six months and continued breastfeeding for 12 months.[16] ART taken by the mother provides prophylaxis for the breastfed infant. The South African guidelines are in line with the 2010 WHO guidelines which stated that 12 months presented the best time for cessation of breastfeeding as the survival benefit associated with breastfeeding

decreases with age, especially after 12 months of life, while the risk of HIV transmission continues with ongoing breastfeeding.[61]

Despite low quality of evidence based on observational studies, WHO in 2016 updated its infant feeding guidelines in the context of HIV infection to recommend that breastfeeding may continue for up to 24 months or longer, with adherence support for lifelong ART for breastfeeding women.[62] The WHO guideline goes on to say that "the recommendation is intended mainly for countries with high HIV prevalence and settings in which diarrhoea, pneumonia and undernutrition are common causes of infant and child mortality".[62] While acknowledging that "breastfeeding has less protective effect against serious morbidity and mortality in the second year of life than in the first 12 months", breastfeeding has nutritional benefits for infants in food insecure countries.[62] There is acknowledgement in the guideline that no comparative data exist on breastfeeding for 24 months, compared to 12 months, in mothers on ART. Data are available from observational studies assessing HIV-free survival at 12 and 18 months, and the pooled estimates were marginally higher for infants whose mothers were receiving lifelong ART compared to those who stopped ART at six months postpartum.[62] Not enough data were available for women on lifelong ART to be able to estimate HIV-free survival at 24 months.[62]

There are several health system challenges with extending breastfeeding duration in HIV-exposed infants to 24 months – follow-up of the mother-infant pair for more than 24 months; provision of co-trimoxazole prophylaxis for 24 months as recommended for all HIV-exposed breastfed infants; ensuring maternal ART adherence and viral suppression throughout the period of breastfeeding; infant HIV retesting after cessation of breastfeeding; and initiation of ART in infants found to be HIV-infected. There are also concerns about extended infant exposure to antiretrovirals through breast milk, but available evidence suggests that extended exposure is not associated with an increased risk of adverse events.[63]

1.1.11 Postpartum retention in care

Postpartum retention in care of mother-infant pairs has been one of the major challenges in PMTCT programmes, and reports from Malawi, the first country to adopt Option B+, highlight high rates of lost-to-follow-up postpartum.[64,65] Estimates

are that 25% to 50% of women on ART at delivery are lost to follow-up postpartum.[66] Similar factors identified as barriers to ART initiation and retention in care during pregnancy also contribute to postpartum loss to follow-up.[67,68] While introduction of Option B+ has led to an increase in the number of HIV-infected pregnant women initiated on ART, and decrease in time-to-initiation, available data show high rates of attrition postpartum.[64,65] In a review of the first three years of Malawi's Option B+ programme, with analysis of facility- and patient-level data of almost 30 000 women, patients who were started on ART under Option B+ had higher rates of loss to follow-up than women who were not pregnant and initiated ART because of a CD4 count <350 cells/μl, or WHO stage 3 or 4 disease.[65] Loss to follow-up was highest in the first year of treatment. Poor adherence, defined as a cumulative medication adherence of less than 85%, younger age, and initiation of ART during breastfeeding were all associated with an increased risk of being lost from care.[65]

In another study done in Malawi comparing service uptake and outcomes along the PMTCT cascade before and after the introduction of Option B+, significantly more pregnant women were enrolled in the PMTCT programme with Option B+ compared to before, 68% vs. 93%, p<0.001.[64] There was however a higher rate of withdrawal from PMTCT services during the antenatal period with Option B+; 5% withdrew with Option B+ compared to 3% prior to the introduction of the programme, p=0.02.[64] There was also a higher rate of loss to follow-up at six months after initiating ART under Option B+, 6% vs. 11%, p=0.02. While a proportion of the cases of loss-to-follow-up occurred in the postnatal period as a third of the women were started on ART in the third trimester, this is not specified in the paper. The rate of loss-to-follow-up was high despite the fact that the women were initiated on treatment within a programme that had facility- and community-based healthcare worker support for HIV-infected women during pregnancy and postpartum.[64]

Results from a qualitative study on barriers and facilitators to uptake and adherence to ART in a Option B+ programme in Malawi show that various factors influence uptake of treatment and retention in care, and may be more salient in women initiating ART in the context of Option B+ than in other ART programmes.[69] The need for more time to decide on starting ART, including consulting with their partners, and feeling healthy were the main reasons pregnant and postpartum women gave for refusing to start ART.[69] Among women who stopped taking ART,

lack of partner support and side effects were the main reasons women defaulted treatment, with side effects cited as the main reason by 50% of the women. Community health worker support, declining health and resolution of side effects led some women who had initially declined or defaulted treatment to start ART. While the study findings cannot be generalised to all settings because of the small sample size, as is the nature of qualitative studies, they provide insight and important lessons for interventions to improve retention in care, as Malawi has the longest experience with Option B+.

Results from an implementation science study describing early experiences with Option B+ in 11 African countries, highlight the importance of counselling and support to increase acceptance of lifelong ART among pregnant women, and hence improve postpartum retention in care.[70] Pregnant women felt overwhelmed by being told that they were HIV-infected and on the same day having to commit to lifelong treatment.[70] There was also the issue of disclosure to partners and families they also had to deal with.[70] While postpartum loss to follow-up is not new or unique to Option B+ programmes, expedited ART initiation and committing to lifelong treatment, especially among women who do not need treatment for their own health, appear to be the major barriers to retention in care.[69,70]

Several interventions have been tried in an attempt to increase postpartum retention in care, but a recent systematic review on interventions to increase postpartum retention in care identified only four studies that were judged to be of high or moderate quality evidence.[66] Of the interventions evaluated, only telephone-based interventions (calls and text messages), appear to improve retention in care in the first three months postpartum.[66] The authors concluded that due to the small number and poor quality of the studies included in the systematic review, they could make no meaningful conclusions for policy implications.[66] Factors that impact on postpartum retention in care are complex, and need multiple interventions throughout the continuum of care, starting in the antenatal period.[66]

WHO recommends periodic retesting of HIV-uninfected women throughout the breastfeeding period, however there is no guidance on the retesting intervals.[10] The South African guidelines are explicit in their recommendations with retesting recommended at the 6-weeks postnatal visit and every three months during breastfeeding.[16]

While great strides have been made towards eMTCT, primarily through scale-up of efficacious antiretroviral regimens for HIV-infected pregnant women, there are many lessons to be learnt from programmatic experience in implementation of PMTCT programmes. This PhD makes an important contribution to the existing literature on PMTCT as it chronicles the evolution of one of the oldest and largest PMTCT programmes in South Africa, starting in the period when only single-dose nevirapine was available for PMTCT, to adoption of Option B+ in 2015. It provides information on performance of the Soweto PMTCT programme through evaluation of 14 years of routinely collected data and original research conducted in the programme. The evaluation chronicles evolution of the PMTCT programme through various steps of the PMTCT cascade, from diagnosis of HIV infection in pregnancy through to postpartum infant testing. The original research highlights important patient-related risk factors for MTCT, and also infant feeding practices among HIV-infected and HIV-uninfected women following changes in South African infant feeding guidelines.

The second part of the background and literature review addresses the second goal of the Global Plan, that of decreasing HIV-related maternal deaths. In the next section I will provide an in-depth discussion of the maternal mortality trends in sub-Saharan Africa and also discuss causes of maternal deaths in HIV-infected women and what the impact of ART has been.

1.2 KEEPING MOTHERS ALIVE: TRENDS IN MATERNAL MORTALITY AMONG HIV-INFECTED WOMEN

In 2015, approximately 830 women died every day from complications related to pregnancy and childbirth, and an estimated 10.7 million maternal deaths occurred globally from 1990 to 2015.[71,72] Maternal mortality is a health indicator that highlights the disparities in access to health, with two-thirds of global maternal deaths occurring in sub-Saharan Africa alone.[71] Maternal deaths are a public health concern and reducing maternal mortality remains a global priority.

This section of the literature review will discuss classification of, and trends in maternal mortality, globally and in South Africa. There will also be an in-depth discussion of maternal mortality in HIV-infected women, including causes of death and the role of ART.

1.2.1 Definition and classification of maternal deaths

The WHO classification of maternal deaths is the most widely used classification system, and it allows for standardisation in reporting of maternal mortality.[73] A maternal death is defined as 'the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to, or aggravated by the pregnancy or its management, but not from accidental or incidental causes'.[73] Deaths that occur more than 42 days, but less than one year after termination of pregnancy are defined as late maternal deaths. Maternal deaths may be either direct or indirect, and direct maternal deaths are those resulting from obstetric complications, and may occur either antenatally, intrapartum, or postpartum. Direct maternal deaths include complications related to hypertensive disorders, obstetric haemorrhage, pregnancy-related infections, early pregnancy losses (abortion, miscarriages and ectopic pregnancies) and other obstetric complications. Indirect maternal deaths refer to deaths due to non-pregnancy related diseases that are either pre-existing or develop during pregnancy, and are aggravated by the physiologic effects of pregnancy. Complications due to diseases and conditions related to the various organ systems that lead to death, including infections and neoplasms that are not a direct result of pregnancy, are classified as causes of indirect maternal deaths. Incidental causes of

death, which are not classified as maternal deaths, are due to external causes such as accidents and assault.[73]

The classification of maternal deaths in HIV-infected women is more complex. According to the WHO classification, direct maternal deaths in HIV-infected women are those that are due to obstetric causes, similar to HIV-uninfected women.[73] AIDS-related indirect maternal deaths are defined as deaths in HIV-infected women that are 'the result of the aggravating effect of pregnancy on HIV' infection, and include infectious and non-infectious causes of death. Deaths that are due to fatal complications of HIV/AIDS are however classified as HIV-related deaths and are not considered maternal deaths as the causes are considered incidental. Conditions listed under this category include HIV wasting syndrome, infectious and parasitic diseases and malignant neoplasms due to HIV/AIDS. In the WHO ICD-10 classification, these are termed 'HIV-related deaths to women during pregnancy, delivery or puerperium'.[73]

While the ICD-10 list of non-obstetric causes of indirect maternal deaths is the same for HIV-infected and –uninfected women, the terminology on the aggravating effect of pregnancy on HIV infection can be confusing and lead to misclassifications.[74,75] It is difficult to determine the aggravating effect of pregnancy on HIV infection and its complications, and there have been several debates on whether pregnancy is associated with HIV disease progression, especially with increased availability of ART.[74,75] The debate on pregnancy and HIV disease progression will be discussed further in the section on mortality in HIV-infected pregnant and postpartum women.

Given the complexities in classification of maternal deaths in HIV-infected women, Rosen et al and Calvert et al have suggested that the focus be on pregnancy-related HIV deaths, which would include all deaths in HIV-infected women during pregnancy, or within 42 days of termination of pregnancy, irrespective of the cause.[73–75] Using the classification of pregnancy-related HIV deaths will include direct obstetric deaths, indirect maternal deaths and also deaths from HIV disease that were incidental to the pregnancy.[74,75] The rationale for using the classification of pregnancy-related HIV deaths is that no distinction needs to be made on whether HIV infection was a cause of an indirect maternal death aggravated by the

pregnancy, or whether it was incidental to the pregnancy, what the ICD-10 classification terms HIV-related deaths.[74,75]

In the following section of the literature review, the classification systems used in the various publications for global, regional and country estimates and the contribution of HIV infection to maternal mortality will be discussed. Global and regional trends in maternal mortality, with a focus on sub-Saharan Africa, will be discussed first, followed by a discussion on maternal mortality trends in South Africa.

1.2.2 Global trends in maternal mortality

In 2000, at the United Nations Millennium Summit, the Millennium Development Goal 5 (MDG 5) target was set to reduce the global maternal mortality ratio (MMR) by 75% from 1990 to 2015, and also to achieve universal access to reproductive healthcare.[76] While the intentions were good in focusing global attention on the burden of maternal mortality and setting a target with a deadline, MDG 5 came under much criticism.[77] The criticism centred on the MMR as a target for improving maternal health given the poor quality of data, and in many instances the complete lack of data, in the countries with the highest rates of maternal mortality.[77] Questions were raised on how progress could be assessed when the baseline data on which progress would be measured were inaccurate.[77] The original MDG 5 goal was also seen as reductionist, focusing on just one figure and ignoring all the complexities and drivers of maternal mortality.[78] A secondary target of universal access to reproductive healthcare was later added in 2007, but the focus was again on numbers.[78] Despite the shortcomings, MDG 5 targets were used worldwide up to 2015 to assess progress made in improving maternal health.

Estimates of global trends in maternal mortality for the 25-year period, 1990 to 2015, come from two sources, the United Nations Maternal Mortality Estimation Inter-Agency Group (UN MMEIG) and the Institute of Health Metrics and Evaluation (IHME). The IHME data on maternal mortality estimates are published as part of the Global Burden of Disease Studies. The IHME is a multinational consortium that collects and analyses data on more than 300 diseases and injuries in 195 countries.[79] There have been debates about the differences in the UN MMEIG and IHME estimates for maternal mortality and how to interpret these differences in

monitoring trends.[80,81] The differences in estimates are due to several factors and include different data sources used, differing methodologies used in processing the data, and also different modelling estimates used for incomplete maternal mortality data.[80,82] Taking into account concerns raised about the varying estimates, and their value in monitoring maternal mortality trends, there has been a concerted effort by the UN MMEIG and the IHME to include country-level data in calculating the estimates.[71,82] Reports from the UN MMEIG and the IHME will be discussed in turn to assess progress made in decreasing maternal mortality, and the merits of each will be discussed.

The 2015 UN MMEIG estimates for 183 countries, for the 25-year period from 1990, report a 44% decline in the global MMR.[71] The decline is from an estimated 385 maternal deaths per 100 000 live births in 1990 to 216 per 100 000 live births in 2015, falling short of the MDG 5 target of a 75% reduction in the global MMR.[71] For sub-Saharan Africa, which accounted for approximately 66% of the global maternal deaths in 2015, the decrease in MMR was 45%, from 987 in 1990 to 546 maternal deaths per 100 000 live births in 2015.[71,82] Globally the UN MMEIG report estimates that nine countries globally achieved the target of decreasing their MMR by at least 75%.[71] The nine countries are Rwanda (the only country from sub-Saharan Africa), Maldives, Bhutan, Cambodia, Cabo Verde, the Islamic Republic of Iran, Timor-Leste, the Lao People's Democratic Republic and Mongolia.[71]

Results from the IHME, the other source of reports on trends in maternal mortality, suggest a lesser decrease in the global MMR.[82] The reports are based on data from 195 countries and include late maternal deaths, up to 1 year postpartum.[82,83] Reports from the IHME are published as Global Burden of Disease Studies. According to the Global Burden of Disease Study 2015, the global MMR decreased by 30% from 1990 to 2015, from a MMR of 282 in 1990 to 196 maternal deaths per 100 000 live births in 2015, reflecting lower estimates for the baseline and the 2015 MMR than the UN MMEIG figures.[82] Estimates of the MMR in sub-Saharan Africa are also lower than those reported by the UN MMEIG, with the decrease in MMR for sub-Saharan Africa estimated to be from 495 in 1990 to 375 maternal deaths per 100 000 live births in 2015, with none of the countries achieving the MDG 5 target.[71,82] The authors of the Global Burden of Disease Study 2015 identified various strategies that could drive success in decreasing maternal mortality. These

are: addressing inequities in access to care; improving the quality of sexual, reproductive and maternal healthcare; strengthening of emergency obstetric care; increasing literacy rates among women and girls; and also conducting maternal death and near-miss audits.[82]

In assessing the drivers of decreasing maternal mortality, the Global Burden of Disease Study 2015 used the sociodemographic index, a composite of income per capita, level of education and total fertility rate.[82] While the sociodemographic index improved in all global regions from 1990 to 2015, trends in the MMR did not reflect improvements in the index universally, in any of the regions.[82] In terms of reproductive healthcare, the study assessed coverage of the following interventions: one antenatal visit, four antenatal visits, delivery in a healthcare facility and availability of skilled birth attendants, and found that countries with the lowest MMR had more than 90% coverage of all four interventions.[82]

The IHME report, published as the Global Burden of Disease Study 2015, appears robust as it is based on 599 data sources compared to 203 used for the UN MMEIG report, but the authors acknowledge that it also has limitations.[82] No directly observed 2015 maternal mortality data were included in the final report, and all the 2015 results were modelled on historical data.[82] While the UN MMEIG and the IHME reports give different figures for the MMR estimates, they are in agreement that there has been a decrease in maternal deaths, albeit lower than the MDG 5 target.

In addition to the MMR being the key indicator for monitoring progress in achieving the MDG 5 target, other indicators include key strategies for reducing maternal morbidity and mortality.[84] These include the proportion of births attended by skilled healthcare workers, antenatal care coverage and addressing the unmet need for contraception.[84] While globally there has been an increase in the proportion of births delivered with skilled attendance, from 59% in 1990 to 71% in 2014, the improvements in sub-Saharan Africa have been modest.[85] For 2014, the MDG 2015 report estimates that only 52% of births in sub-Saharan Africa were attended by a skilled birth attendant.[85] In the same year, only 49% of pregnant women in sub-Saharan Africa received the recommended four antenatal visits.[85] There also remains a huge unmet need for contraception with only 28% of women in sub-Saharan Africa receiving contraception, and this reflects only married women and women in unions.[85]

With the deadline for MDG targets having ended in 2015, the Sustainable Development Goals (SDGs) came into effect in January 2016.[86] The SDGs build on the successes of the MDGs, and targets have been set for the next 15 years.[86] Maternal mortality is addressed in SDG 3 and the target is to reduce the global MMR to less than 70 per 100 000 live births by 2030, with no country having more than double the global average.[86,87] While the setting of a threshold for MMR, instead of a percentage decrease as was set out in MDG 5, has been welcomed, commentaries on the SDGs have given criticisms that health does not play a central role in the new goals.[88,89] The criticism is that only one, SDG 3, of the 17 SDG goals addresses health, compared to the three health-related goals that were part of the eight MDG goals.[88,89] Also, the agenda set out for health is too broad with the goal for SDG 3 being 'to ensure healthy lives and promote wellbeing for all at all ages', and that this may result in less focused attention on the challenges prioritised in the MDGs.[88] Besides the MMR target, the only other target within SDG 3 that addresses maternal mortality directly is that of ensuring universal access to sexual and reproductive health by 2030, and this is not a new target as it was part of MDG 5.[86]

As the global community works towards decreasing maternal mortality, the focus within countries and programmes needs to shift from chasing targets, to understanding the causes and drivers of maternal deaths.

1.2.3 Causes of maternal deaths

The majority of maternal deaths are preventable, with the antenatal and peripartum healthcare interventions to prevent the deaths being well known.[82,85] The key interventions are for all pregnant women to access antenatal care, with a minimum of four antenatal visits, and to have a skilled birth attendant at the time of delivery.[85] Accessing antenatal care allows for timely identification and management of pre-existing conditions and their complications, and also identification of conditions that may arise for the first time during pregnancy. Having a skilled birth attendant decreases the risk of peripartum complications. Much of the information on causes of maternal deaths is based on modelled estimates due to the paucity of maternal mortality data, especially in low-resource settings where the majority of maternal deaths occur. According to the Global Burden of Disease Study 2015, 86% of all

global maternal deaths in 2015 were due to direct obstetric causes, with obstetric haemorrhage and hypertensive disorders of pregnancy the leading causes of maternal deaths.[82] This proportion did not change compared to 1990, where 87% of all maternal deaths were attributed to direct obstetric causes.[82] Regarding the role of HIV infection, estimates from the Global Burden of Disease Study 2015 are that HIV-related indirect maternal deaths accounted for 0.84% of global maternal deaths, and 1.6% of maternal deaths in sub-Saharan Africa, in 2015.[82] In their modelling estimates, the Global Burden of Disease Study group disentangle the HIV-related indirect maternal deaths from the incidental HIV-related deaths as defined in the WHO ICD-10 classification.[83] The authors of the 2015 Study state that a large number of HIV-infected women are dying incidentally during pregnancy or after delivery, and in the modelling of maternal deaths, they estimated the population attributable fraction of maternal mortality to HIV infection.[82] In the modelling estimates for sub-Saharan Africa, there were 133 043 maternal deaths in 2015, and 2 181 (1.6%) HIV-related maternal deaths.[82] If incidental HIV-related deaths during pregnancy and postpartum are added to the HIV-related maternal deaths, the figure is much higher with an estimated 20 180 (15.2%) HIV-infected women in sub-Saharan Africa dying during pregnancy or postpartum.[82]

The UN MMEIG estimate for 2015 of 2% for HIV/AIDS-related indirect maternal deaths in sub-Saharan Africa is similar to the Global Burden of Disease Study 2015 estimate of 1.6%.[71] No estimates of incidental HIV-related deaths are given in the UN MMEIG report. In countries with high HIV prevalence, the contribution of HIV-related indirect maternal deaths is higher, and South Africa is estimated to have had the highest proportion of maternal deaths due to indirect, HIV-related causes in 2015, at 32%.[71] A detailed discussion of maternal mortality in South Africa is given below, in Section 1.2.4.

The 2014 WHO systematic analysis on global causes of maternal deaths is another, but less comprehensive, source of data on leading causes of maternal mortality.[90] The report is an analysis of maternal deaths from 2003 to 2009, and includes data from 115 countries. Sources used include vital registration data, studies published between 2003 and 2012, confidential enquiries, maternal mortality surveys and verbal autopsy data. The authors acknowledge that the datasets used in the report represent only 2.5% of global maternal deaths in the 7-year period.[90] For

the large number of countries without any information on causes of maternal deaths, the authors used modelled estimates. According to the analysis, almost three-quarters (73%) of global maternal deaths were due to direct obstetric causes, with obstetric haemorrhage the leading direct cause of maternal mortality, similar to the finding from the Global Burden of Disease Study 2015 report. Other leading direct causes of maternal mortality were complications related to hypertensive disorders, sepsis and unsafe abortions. Indirect causes were responsible for 27% of global maternal deaths, with 70% of these deaths from pre-existing disorders, including HIV infection. The pattern was the same for sub-Saharan Africa, with 28.6% of maternal deaths due to indirect causes, and 6.4% estimated to be HIV-related indirect maternal deaths.[90] This figure is higher than that reported in the UN MMEIG report and the Global Burden of Disease Study 2015, and may be a result of the different time period that the WHO systematic analysis reports on, as well as different data sources and modelling estimates used.

Despite the limitations of the data sources and modelling methods used in the different reports, direct maternal deaths dominate mortality worldwide, with obstetric haemorrhage and hypertensive disorders of pregnancy the leading causes. The three reports quoted above identified HIV infection as an important cause of indirect maternal deaths, especially in high HIV prevalence settings. All the reports have limitations as they are largely based on estimates because of lack of routinely collected maternal mortality data. As the global community works towards the SDG 3 target of decreasing the global MMR to less than 70 per 100 000 live births by 2030, there is a need for routine collection of good quality maternal mortality data to facilitate implementation of targeted interventions and monitor progress.[91,92] South Africa is one of the few countries in sub-Saharan Africa that has a functioning audit system for maternal deaths, and has tracked the causes of maternal deaths from early in the HIV epidemic.

1.2.4 Maternal mortality trends in South Africa

In 1997, the South African Department of Health established the National Committee on Confidential Enquiries into Maternal Deaths (NCCEMD). The committee is comprised of healthcare professionals experienced in obstetrics,

midwifery and anaesthetics, with representatives from all nine provinces in South Africa.[93] The mandate of the committee is to recommend interventions to decrease maternal mortality, based on the analysis of maternal deaths. The committee releases annual interim reports on maternal deaths in South Africa, and publishes comprehensive reports on national trends in maternal mortality every three years. The enquiries into maternal deaths are facility-based, and hence report only on maternal deaths that occur in hospitals and community health centres. Provincial and national live births provide the denominator for reporting institutional maternal mortality ratios (iMMRs).[93] While the enquiries do not report on maternal deaths that occur in the community, Moodley et al, writing on behalf of the NCCEMD, report that 91% of pregnant women in South Africa give birth in a healthcare facility, hence the enquiry most likely covers the majority of maternal deaths in the country.[93] According to the NCCEMD reports, few maternal deaths occur at home and these are reported in a 'non-systematic and unstructured way'.[94]

According to the UN MMEIG estimates, South Africa made no progress towards achieving the MDG5 target of decreasing the MMR, and actually saw an increase in the MMR, largely due to the HIV epidemic.[71] The HIV prevalence among pregnant women in South Africa increased from less than 1% in 1990 to a peak of 30.2% in 2005, and has plateaued at around 30% since 2006.[95] The UN MMEIG estimate for the MMR, for South Africa in 1990 is 108 per 100 000 live births, while that for 2015 is 138 per 100 000 live births.[71] In the Global Burden of Disease Study 2015, the MMR estimates for South Africa are 154 and 158 per 100 000 live births for 1990 and 2015 respectively.[82] The NCCEMD figures on iMMR trends are only available from 2005, therefore comparisons with other estimates of maternal mortality in South Africa can only be made from then.[93]

There are several challenges with getting accurate estimates of the MMR trends in South Africa, with a reliance on local measurements and international modelling estimates, many of them point estimates.[81,96] The baseline MMR figure used to assess trends in maternal mortality in South Africa is that of 150 per 100 000 live births, and is based on data from the 1998 South Africa Demographic and Health Survey (DHS).[96,97] According to the 2015 South African MDG report, 'the last reliable survey-based estimate of maternal mortality in South Africa was made in the 1998 DHS'.[26] The 1998 Survey MMR estimate is for the period 1992 to 1998 and is based

on ‘reported survivorship of sisters’, the validated sisterhood method.[98] Respondents in the survey who reported that their sisters had died were asked questions to determine whether the deaths could be classified as maternal deaths.[97] The questions included whether the deaths occurred during pregnancy, delivery, or within two months postpartum or termination of a pregnancy, and whether the deaths were due to complications of pregnancy or childbirth.[97] This method of obtaining maternal mortality data has its limitations in that it depends on accuracy of recall of information by relatives, and may be inaccurate, especially if the deaths occurred several years before the survey.

Other sources for MMR estimates for South Africa include vital registration data analysed by Statistics South Africa, and the 2012 Rapid Mortality Surveillance report.[26] MMR estimates from vital registration data are from 2002, hence the 1998 DHS estimates from 1992 are closest to the MDG baseline year of 1990.[26,97] Based on these data sources, the MMR in South Africa increased from a baseline of 150 per 100 000 live births to a peak of 311 per 100 000 live births in 2009.[26] From 2010, the MMR estimates show a progressive decline with the MMR estimated for 2013 at 141 per 100 000 live births, which is the most recent available MMR estimate.[26]

Figures from the NCCEMD reports, on facility-based maternal deaths, also show a peak in the iMMR in 2009 at 189 per 100 000 live births, a much lower figure than that of 311 per 100 000 live births reported from vital registration data.[85,94] Modelling estimates for the South African MMR are generally higher than those from the NCCEMD reports, which underestimate the MMR because they do not include maternal deaths that occur in the community, especially postpartum.[99] As an illustration, the South African Health Data Advisory and Coordinating Committee (HDACC) used the 2008 MMR estimate from vital registration data, and adjusted it for incompleteness of adult death registration data and classification of causes of death.[99] The figure after adjustment was also scaled up by 50% to account for under-notification of maternal deaths, as suggested by international modelling groups.[99] The modelled estimate for MMR for 2008 was then reported as 310 per 100 000 live births, compared to the MMR of 167 per 100 000 estimated from the vital registration data and the NCCEMD report for 2008.[99] It is difficult to determine whether the modelled estimates are a more accurate estimation of the MMR in South Africa than

the figures reported in the NCCEMD, as many assumptions are made in the modelling process.

In their analysis of different data sources used to estimate the MMR for South Africa, Dorrington and Bradshaw (2016) highlight the challenges with getting an accurate estimate of maternal mortality figures, even in South Africa, which has a functioning maternal death auditing system and where 94% adult deaths are said to be registered.[81,100] Figure 1.3 illustrates the different estimates for South Africa for the period 2000 to 2013.[81] While the NCCEMD reports provide trends in iMMR, it may be an underestimation of maternal deaths especially deaths occurring early in pregnancy and also late maternal deaths beyond the first six weeks postpartum. The deaths may be occurring at home, or may be occurring in hospitals, but outside obstetric units.[93]

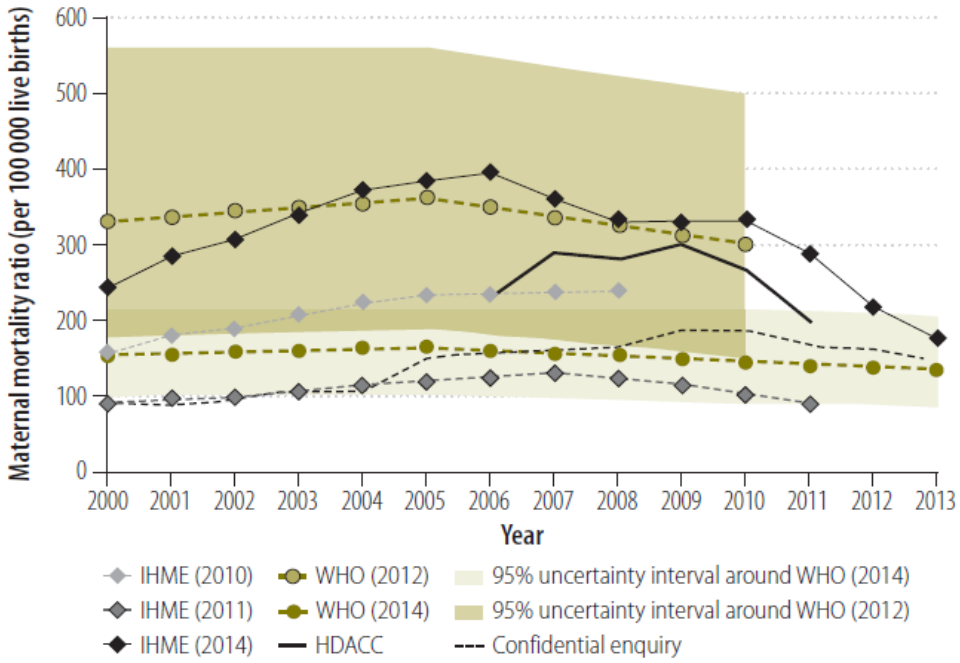


Figure 1.3: Estimates of the maternal mortality ratio for South Africa from several data sources, 2000 to 2013. ***Source: Dorrington and Bradshaw (2016)*** [81]

It is accepted that the NCCEMD reports, being facility based, are likely to underestimate the true MMR for South Africa. Yet, because of consistent data

collection and reporting methods, they remain the best source for monitoring trends in maternal mortality and also causes of maternal deaths in South Africa.[26,96] According to the latest triennial NCCEMD report published in 2014, there has been a decline in the iMMR from 176 in the triennium 2008-2010 to 154 per 100 000 live births in 2011-2013.[94,101] The finding of a reduction in the MMR is supported by vital registration data.[85] The 2015 South African MDG report estimated that the MMR, based on vital registration data, decreased from 270 per 100 000 live births in 2010 to 141 per 100 000 live births in 2013.[26] While the MMR in South Africa is clearly on a downward trend, the number of maternal deaths remains high. According to the NCCEMD report, 4 452 women died during pregnancy and the puerperium in South African healthcare facilities in 2011-2013.[94] Similar to assessing global trends, it is important to understand the causes of maternal deaths in South Africa, to be able to implement interventions to decrease the deaths.

1.2.5 Causes of maternal deaths in South Africa

The leading causes of maternal deaths in South African health institutions have remained the same since the first published report for the triennium 1999-2001, with non-pregnancy related infections, the majority HIV-related, being the leading cause of maternal mortality – Figure 1.4.[94,101–104] In the classification of indirect maternal deaths in HIV-infected women, in the triennial reports, no distinction is made on whether the deaths are aggravated by pregnancy or are incidental. All HIV-related deaths in pregnant or postpartum women (not including direct maternal deaths in HIV infected women) are considered as indirect maternal deaths.

Among the non-pregnancy related infections, TB and respiratory infections have been identified as the most common causes of death.[94] The other leading causes of maternal deaths in South Africa are complications related to hypertensive disorders, obstetric haemorrhage, pregnancy-related sepsis and medical and surgical disorders, and together these five leading causes were responsible for 86% of maternal deaths in the period 2011-2013.[94]

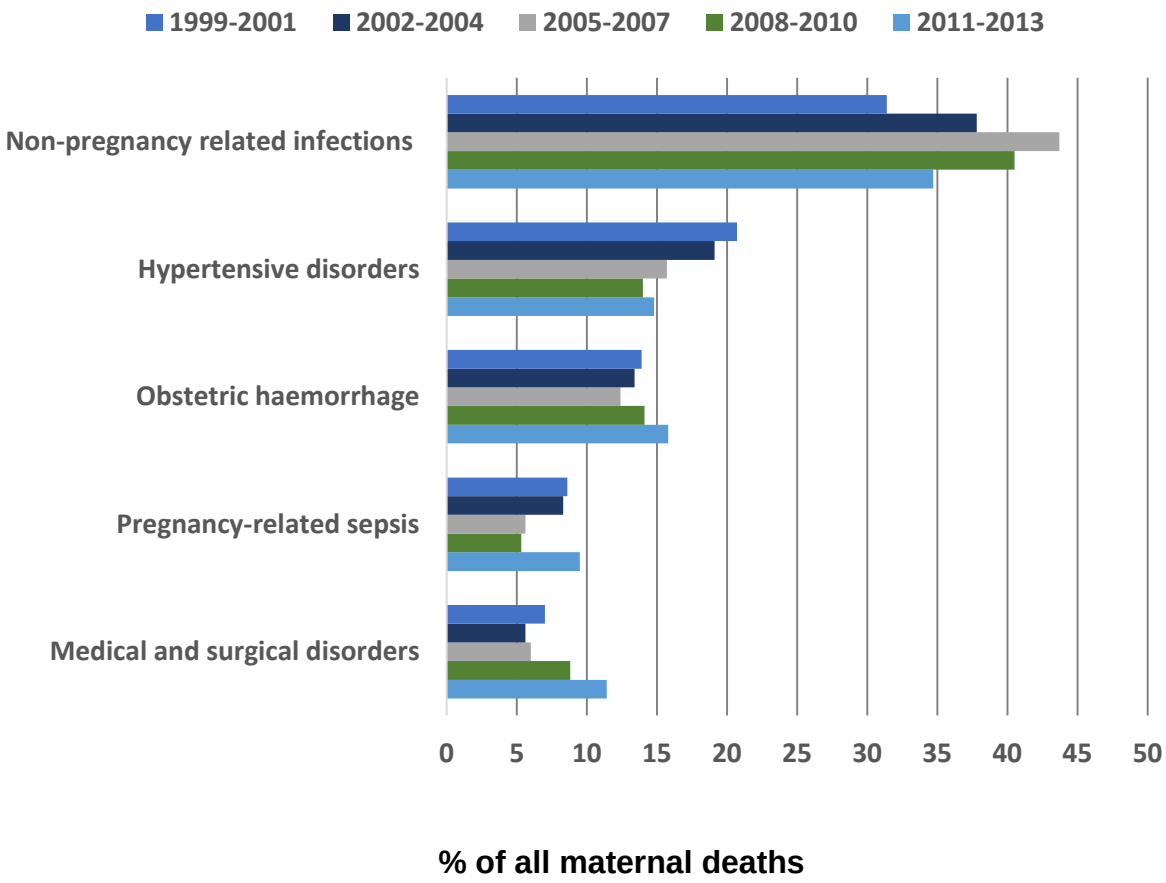


Figure 1.4: Leading causes of maternal deaths in South Africa, 1999-2013 [94,101–104]

Source: Author's own design

The decrease in the iMMR in South Africa is due to a decrease in maternal deaths due to non-pregnancy related infections and complications of hypertensive disorders.[94] The proportion of deaths due to non-pregnancy related infections peaked in 2005-2007 at 43.7% of all maternal deaths, with a subsequent steady decline to 34.7% in 2011-2013 (Figure 1.4). Among the women who died from non-pregnancy related infections, 90% were HIV-infected.[94] The authors of the 2014 report suggest that the decrease in deaths due to these infections is likely to be related to routine HIV testing during pregnancy, and expansion of the ART programme.[94] Of the HIV-infected women who died from non-pregnancy related infections in 2011-2013, 55% were on ART at the time of death, falling to 36% in the 2008-2010.[94] No data are available in the 2014 NCCEMD report on what the unmet need for ART was. CD4 counts were also not available for most cases, but 80% of HIV-infected women who

died of non-pregnancy related infections were classified as having AIDS on clinical assessment.[94]

Similar to global reports, obstetric haemorrhage is one of the leading causes of maternal deaths in South Africa.[94] The last decade has seen an increase in the number of maternal deaths due to obstetric haemorrhage, the majority related to caesarean section.[105] According to the 2001-2013 NCCEMD, 71% of the obstetric haemorrhage-related deaths had avoidable factors.[105] Obstetric haemorrhage-related maternal deaths, together with deaths due to non-pregnancy related infections and complications of hypertensive disorders were the three biggest contributors to preventable maternal deaths, accounting for 65% of avoidable deaths.[94]

Factors identified as contributing to avoidable maternal deaths are: not adhering to standard protocols; sub-standard care related to poor clinical assessment and inappropriate response to abnormalities detected; delays in referral to higher levels of care; and also delays in patients accessing care, including presenting late for antenatal care.[94] While maternal deaths due to non-pregnancy related infections are decreasing in South Africa, they remain an increasingly important cause of avoidable maternal deaths. Of all the maternal deaths due to non-pregnancy related infections in the triennium 2011-2013, 43.3% were considered avoidable.[94] In assessment of medical management of the cases, there were many cases where there was failure to recognise the severity of the illness, with substandard care and failure to make a diagnosis.[94] Some women with HIV-related complications were assessed as having a poor prognosis and management was not aggressive, despite the fact that HIV infection is no longer a terminal illness.[94]

In South Africa and in other high HIV prevalence settings, it is important to understand the patterns of maternal mortality in HIV-infected women, and also to understand the role of ART in reducing HIV-related maternal mortality.

1.2.6 Maternal mortality in HIV-infected women

The HIV epidemic has had an enormous impact on maternal mortality in sub-Saharan Africa, and the 2015 UN MMEIG estimates are that 85% of global HIV-related maternal deaths occurred in sub-Saharan Africa.[71] In 2015, there were five

countries where more than 10% of maternal deaths were estimated to be HIV-related, with the highest figure in South Africa at 32.0%, a figure similar to the 34.7% reported in the 2011-2013 NCCEMD report.[71,94] Other countries with a high percentage of HIV-related maternal deaths reported for 2015 are Swaziland (19%), Botswana (18%), Lesotho (13%) and Mozambique (11%).[71] The 2016 UNAIDS report estimates that there has been a 43% decline in HIV-related deaths in women of reproductive age in the 21 priority countries in sub-Saharan Africa between 2009 and 2015, and the decrease is said to be related to ART scale-up.[2]

There are challenges in determining the impact of HIV infection on maternal mortality because of paucity of data, different data sources used to estimate number of deaths, and misclassification of causes of death in HIV-infected pregnant and postpartum women.[92] Paucity of data and different data sources used has been discussed earlier. Blencowe et al argue that misclassification of causes of maternal deaths may be a result of difficulties with the definitions used for reporting, or may be deliberate for reasons related to blame or stigma, all important factors when determining HIV-related maternal deaths.[92] With misclassification of causes of death, it is likely that the proportion of HIV-related maternal deaths may be underestimated.[75,92]

In their systematic review and meta-analysis of studies from Africa, the United States, Europe, India, and South America, Calvert et al found a 7.74 risk ratio (95% CI: 5.37–11.16) of pregnancy-related deaths in HIV-infected compared to HIV-uninfected women.[75] They estimate that in regions where HIV prevalence among pregnant women is at least 15%, half of all deaths during pregnancy and up to 1 year postpartum are attributable to HIV infection.

1.2.7 Mortality risk among HIV-infected women

Despite the abovementioned challenges with data, several studies from sub-Saharan Africa have consistently shown an excess risk of maternal mortality among HIV-infected women.[106–113] In my literature search of studies on maternal deaths among HIV-infected women in the 21 priority countries in sub-Saharan Africa, I identified 25 publications from 1990, the baseline year for the MDGs, to 2016 where the primary outcome was maternal mortality in HIV-infected women – Table 1.3. Of

the 25 studies, six compared the risk of maternal mortality among HIV-infected women versus HIV-uninfected women, and the risk of mortality was increased from 2- to 7-fold among HIV-infected women.[106–110,112,113] Seventeen of the studies reported on maternal deaths up to 42 days postpartum, while five included late maternal deaths up to one year postpartum.[106–127] Three studies also included deaths beyond the first year postpartum.[128–130]

Twenty-four of the 25 studies were hospital-based or cohort studies within HIV programmes, and one study, done in Mozambique, was a secondary data analysis of two national cross-sectional surveys. Data from the national surveys in Mozambique, representing community-based data, can however not be used to assess trends in maternal deaths in HIV-infected women, as different categorizations for causes of death were used in the two time periods.[123] This again highlights the point made already about the inconsistencies in classification of maternal deaths. Other community-based data are from a secondary analysis of pooled data from six studies in Eastern and Southern Africa by Zaba et al.[131] The studies were designed for HIV surveillance, and data were collected on demographics and pregnancy reports, with analyses done to determine the contribution of HIV infection on mortality. The authors reported on pregnancy-related mortality during pregnancy and in the 42 days postpartum, and did not exclude deaths that were coincidental or incidental. Verbal-autopsy reporting was used to determine circumstances surrounding the death, including information on whether the woman was pregnant or postpartum at the time of death, and whether she was known to be HIV-infected. Based on the analyses, the authors estimate that HIV-infected pregnant and postpartum women have an eight times higher risk of mortality than HIV-uninfected women. With this finding, the estimation is that in sub-Saharan Africa, about 24% of deaths in pregnant or postpartum women are attributable to HIV infection. The limitation of this study is that only half of the pregnant and postpartum women had a known HIV status, and that 61% of the pregnancy-related deaths were determined on verbal autopsy reports alone.[131]

While hospital-based, cohort and community-based studies all have limitations – the first two miss deaths that occur outside of healthcare facilities, while the later rely on verbal autopsy reports that may lead to misclassification of causes of death –

studies consistently show that there is higher risk of maternal mortality among HIV-infected women.

1.2.8 Causes of maternal mortality in HIV-infected women

Infectious causes are said to be the predominant cause of death in HIV-infected women in low-resource settings.[132] In the 25 studies I identified through my literature search (Table 1.3), a significant proportion of women died with an unknown HIV status, and this proportion was higher in the earlier years when universal testing for pregnant and postpartum women was not standard. It is possible that there was an underestimation of indirect, HIV-related causes of maternal deaths.

Indirect maternal deaths

Fourteen of the 25 studies reported on the causes of maternal deaths and the leading causes of indirect death in HIV-infected women were non-pregnancy related infections, mainly TB, pulmonary and extrapulmonary, respiratory infections, and malaria.[107,109–118,121,123,129] TB has long been recognised as one of the leading causes of indirect maternal deaths in high HIV prevalence settings, with a two to three times increased risk of dying in TB/HIV co-infected pregnant women than those with TB alone.[107,114,133–135] Pregnant women have an increased incidence and risk of complications associated with respiratory infections, and these are related to immunologic and physiologic changes associated with pregnancy.[136] These changes include alterations in cell-mediated immunity and decrease in functional residual capacity of the lung. HIV infection, which alters immune function, further increases the incidence and risk of complications from respiratory infections.[136] With malaria, pregnant women have increased susceptibility to infection, and have also been shown to have a three times increased risk of severe infection compared to non-pregnant women.[137] Similar to respiratory infections, by altering immune function, HIV infection increases susceptibility to malaria during pregnancy.[138] In summary, infectious causes of maternal deaths in HIV-infected women have an underlying factor of immune suppression associated with HIV infection. Hence it follows that the risk of mortality from infectious diseases will be higher in HIV-infected pregnant and

postpartum women with advanced immune suppression. As expected, several of the studies reviewed (Table 1.3) reported that in the HIV-infected women who died and were assessed for level of immune suppression, the majority had advanced disease, based on either a CD4 count of <200 cells/μL, or WHO stage 4 disease.[109,111,113,115,117–121,129,127] Anaemia has also been identified as an important underlying risk factor for maternal deaths in HIV-infected women.[111,112,117,119,123,127] The cause of the anaemia is multi-factorial and includes pregnancy itself, HIV infection, malaria and parasitic infections.

In all but one of the 14 studies, the causes of death were determined from patient records. This has obvious limitations in terms of quality and completeness of clinical information. In the one autopsy study, Menendez et al reported on 139 cases of maternal deaths who had autopsies, and 123 were tested for HIV and 65/123 (53%) were found to be HIV-infected.[118] Out of the 139 autopsies, the cause of death could be determined in 131 women and 60% (78/131) of the deaths were due to indirect causes. Among the leading causes of indirect maternal deaths were HIV/AIDS-related diseases, respiratory infections and severe malaria, similar to findings from studies where the cause of death was determined from patient records. The authors used the Centre for Disease Control (CDC) criteria to define the HIV/AIDS-related diseases and these included opportunistic infections and other AIDS-defining conditions, including malignancies. There was no significant difference in the non-HIV related causes of indirect maternal deaths between HIV-infected and –uninfected women. This finding highlights the importance of indirect causes of maternal deaths even for HIV-uninfected women.

Direct maternal deaths

Similar to HIV-uninfected women, puerperal sepsis, complications of hypertensive disorders, and obstetric haemorrhage are the leading causes of direct maternal deaths in HIV-infected women.[107,109,112,115,116,118,123] Data on whether HIV infection increases the risk of these obstetric complications are inconsistent, with the only consensus being on the increased risk of postpartum infectious morbidity with HIV infection.[110,139–143] Studies on infectious morbidity with HIV infection are not limited to puerperal sepsis, but also include fever beyond 24 hours postpartum,

respiratory infections, peritonitis, generalised sepsis, and abdominal and vaginal wound infections.[139–143]

The highest risk of postpartum infectious morbidity in HIV-infected women has been found after emergency caesarean sections, but the risk is also increased with elective (non-emergency) caesarean sections and vaginal deliveries in comparison with HIV-uninfected women.[139–141,143] In a study on puerperal sepsis after caesarean section, done at a tertiary hospital in South Africa, the majority of women that were readmitted with sepsis were HIV-infected and all had had emergency caesarean sections.[144] The numbers in the study were however small and the study was not powered to detect association between risk factors, including HIV infection, and puerperal sepsis. Livingston et al, in a study done in the United States and Puerto Rico with over 2 000 HIV-infected women, assessed complications associated with mode of delivery.[141] They found that the highest rate of all postpartum morbidities – infectious, haemorrhagic, gastrointestinal and thromboembolic events – were in women who had emergency caesarean sections.

While earlier studies, done before the widespread availability of ART, report a higher risk of infections and subsequent complications in women with advanced immune suppression, recent studies report that the rate of complications remains higher in HIV-infected women who have had caesarean sections despite ART use.[141–143,145] In their study, which was done in the US and had a nationwide sample of over a million HIV-infected and –uninfected women, Kourtis et al found that the rate of infectious complications and hospitalization after caesarean section remained higher in HIV-infected women despite use of combination ART.[143] In the study done in the United States and Puerto Rico discussed above, 89% of the women were on combination ART and 84% were virally suppressed.[141] Hence available data suggest that even with widespread availability of ART, the incidence of postpartum infectious morbidity, largely related to caesarean deliveries, remains higher in HIV-infected women.

Routine antibiotic prophylaxis is well established at caesarean section irrespective of HIV infection status. A Cochrane review of 95 studies comparing the use of prophylactic antibiotics at caesarean section vs placebo or no treatment found a 60% to 70% reduction in the incidence of wound infection, endometritis and serious infectious complications.[146] With regard to prophylactic antibiotics at vaginal delivery,

a South African randomized controlled trial found no significant difference in overall sepsis rate in HIV-infected women who delivered vaginally and received a single, intrapartum dose of prophylactic antibiotics and those who did not.[147] The majority of cases of infectious morbidity occurred in the first week postpartum, and there was no difference in the mean CD4 count in women who developed sepsis and those who did not.

Data on the risk of complications of hypertensive disorders in pregnancy, one of the leading direct causes of maternal mortality in HIV-infected women, are inconsistent. The pathophysiology of hypertensive disorders in pregnancy is complex and is thought to have an immunologic basis, and it has been postulated that HIV infection and the use of ART may modify the risk of the disorders through the effect on immune function. Wimalasundera et al found that HIV-infected pregnant women on no antiretroviral therapy and those on zidovudine monotherapy, or zidovudine and lamivudine dual therapy, had a significantly lower incidence of preeclampsia compared to women on triple therapy, odds ratio 15.3 (95% CI 0·9–270), p=0.0087.[148] The authors suggested that the immunosuppressive effect of untreated HIV infection decreases the risk of hypertensive disorders and their complications, and that with triple therapy use and immune reconstitution, the risk increases. Contrary to this suggestion, it has also been postulated that untreated HIV infection could increase the risk of hypertensive disorders of pregnancy due to inflammatory changes associated with HIV infection, and that ART use reverses these changes and thereby decreasing the risk. In their systematic review and meta-analysis, Browne et al found no clear association between hypertensive disorders in pregnancy and their complications, and HIV infection.[149] There was also no difference found in studies done before and after widespread availability of ART. The authors considered that in the 28 studies they reviewed, there was a high risk of bias.[149]

Studies done in South Africa also show inconsistent results.[150–152] In a study done in South Africa, in the pre-ART era, Frank et al found no difference in the rate of pre-eclampsia and eclampsia among HIV-infected women compared to HIV-uninfected women.[150] No details were available on the level of immune suppression in the population as only 0.5% of the HIV-infected women had a known CD4 cell count. In another South African study, done when ART was widely available in public

health facilities, there was a significantly decreased incidence of gestational hypertension and preeclampsia among HIV-infected women compared to – uninfected women, odds ratio 0.59 (95% CI: 0.42, 0.84), p=0.003.[152] CD4 counts were known for 95% of the women, and there was no difference found in women with CD4 counts <350 cells/µl and those with CD4 counts ≥350 cells/µl. There was also no difference between women on triple therapy (ART) and those on zidovudine monotherapy. Contrary to these findings, Tooke et al, in another South African study, found a significant increase in the risk of early onset preeclampsia in women who had more than four weeks of antiretrovirals – triple therapy or zidovudine monotherapy.[151] There was no association between CD4 count levels and the risk of preeclampsia.

The available literature on the association between HIV infection and hypertensive disorders of pregnancy and their complications remain inconsistent. While hypertensive disorders remain one of the leading direct causes of maternal mortality in HIV-infected women, similar to HIV-uninfected women, no clear association is evident between the disorders and HIV infection. It is likely that, apart from bias related to study designs, the inconsistencies may relate to studying different populations with differing HIV and treatment exposures, and baseline risk factors for preeclampsia.

Turning to obstetric haemorrhage as a cause of maternal deaths in HIV-infected women, findings on the association between HIV infection and obstetric haemorrhage are also inconsistent.[153–156] Among participants in a cluster-randomized controlled trial of a non-pneumatic anti-shock garment in Zambia, HIV-infected women who presented with hypovolaemic shock, secondary to obstetric haemorrhage, had increased odds of severe haemorrhage compared to HIV-uninfected women, OR 1.92 (95% CI: 1.05, 3.50), p= 0.03.[153] The study however has limitations as it was not designed to assess an association between HIV infection and obstetric haemorrhage.[153] Despite this limitation, a prospective cohort study done in Uganda, on prevention of postpartum haemorrhage using misoprostol, found similar results to the Zambian study.[154] In the Ugandan study involving 1 188 women, HIV infection was associated with almost double the odds of postpartum haemorrhage – aOR 1.93 (95 % CI: 1.06, 3.50), p=0.004.[154] In both studies, there were no details on the level of immune suppression or whether the women were on ART. Contrary to

the findings from the Ghanaian and Ugandan studies, a cross-sectional study involving four referral hospitals in South Africa, with over 15 000 study participants, found no association between HIV infection and obstetric haemorrhage, OR 0.95 (95% C: 0.72, 1.25).[155] The study did however find that HIV-infected women were more likely to receive blood and blood products than HIV-uninfected women, aOR 1.52 (95% CI, 1.14, 2.03). Half, 50.9%, of the HIV-infected women had CD4 counts <350 cells/µl and 81.2% were on ART.[155] The authors suggest that the higher incidence of blood transfusion among HIV-infected women could be related to higher rates of untreated anaemia, making them less able to tolerate peripartum blood loss.[155]

Hence available data on whether HIV infection increases the risk of hypertensive disorders of pregnancy and obstetric haemorrhage remain inconsistent. While the majority of studies on maternal mortality in HIV-infected women, in sub-Saharan Africa, were done in the pre-ART era, the question is what impact has the widespread availability of ART had on maternal deaths in this group of women.

Table 1.3: Studies on HIV-related maternal mortality in the 21 Global Plan priority countries, 1999-2016

Author and year	Country	Methods	Key findings	Key findings	Comments
Ahmed *et al*. 1999 [114]	Zambia	**Retrospective record review of maternal deaths in a teaching hospital**. Study period: 1996-1997	251 maternal deaths: 106 (42%) were due to direct obstetric causes **145 (58%) were due to indirect causes**. Malaria (30%), TB (25%) and 'unspecified' chronic respiratory tract illnesses (22%) were the top three causes of indirect deaths.	Diagnosis of AIDS, based on clinical criteria, was associated with 92% of cases with TB, and 97% of cases with 'unspecified' chronic respiratory tract illnesses. Overall MMR 921.	Hospital-based data. No details on the unspecified chronic respiratory illnesses. No details on what % were HIV+. Diagnosis of AIDS clinical. Pre-ART.
Sewankambo *et al*. 2000 [106]	Uganda	**Prospective cohort to assess mortality impact of HIV in adults 15-59 years.** Study period: 1994-1997. HIV-associated maternal mortality estimated in 2997 women who were pregnant during the study period.	Highest attributable risk of HIV-associated deaths were observed in persons aged 20-39 years and in women. 7 maternal deaths in 415 HIV-positive mothers; 8 maternal deaths in 2582 HIV-negative mothers	**MMR:** **HIV+ 1687** **HIV- 310** **RR: 5.44 (95% CI: 1.98, 14.93)**	Population HIV prevalence 16%. No details on cause of maternal deaths. Small number of maternal deaths overall. Data from community-based studies. Pre-ART.

HIV+ = HIV-infected; MMR=maternal mortality ratio, maternal deaths per 100 000 live births; OR=odds ration; CI=confidence interval

Author and year	Country	Methods	Key findings	Key findings	Comments
Khan *et al*. 2001 [107]	South Africa	**Retrospective and prospective study to determine impact of TB and HIV on maternal mortality at a tertiary hospital.** Imputations from seroprevalence rates for those with unknown HIV status. Study period: 1996-1998	101 maternal deaths Overall MMR 200 40/101 tested for HIV **30/40 (75%) HIV+** **Calculated MMR** (with imputations): **HIV+ 323** **HIV- 149** RR of death due to HIV 2.2	Leading causes of maternal deaths: puerperal sepsis (34%); hypertensive disorders (25%); TB (15%) – **15 cases of TB – 14 HIV+** HIV+ - 43% of deaths due to direct obstetric causes **HIV+ more likely to be anaemic and unbooked**	60% had an unknown HIV status at time of death. **Included late maternal deaths up to 1 year postpartum.** Pre-ART.
Kruger *et al*. 2003 [115]	South Africa	**Retrospective review of maternal deaths at a tertiary hospital**. Study periods: 1995-1996 (20 deaths) and 2000-2001 (35 deaths). **iMMR:** 183 for 1995-1996; 354 for 2000-2001.	**1995-1996: 4 (20%) HIV+,** 10 HIV unknown. Causes of death: hypertensive disorders (10); haemorrhage (4); pneumonia (1). **2000-2001: 16 HIV+ (42.7%)**, 17 HIV unknown. Causes of death: pneumonia (13 – 10 cases in HIV+); hypertension (6); haemorrhage (5)	**2000-2001:** HIV/AIDS-associated disease was the leading cause of mortality at 42.7%. Pneumonia the leading cause of death. 5/13 cases had TB. 11/16 had CD4 counts – median 34/µL.	High number with unknown HIV status. According to the authors, no evidence in the records that HIV unknown died from HIV-related diseases. Pre-ART.

Author and year	Country	Methods	Key findings	Key findings	Comments
Le Coeur *et al*. 2005 [108]	Congo	**Prospective study on cause of death in women 15-44 yrs.** Post-mortem examination (HIV status and pregnancy), interview of relatives, and record reviews. Study period: 2001	368 deaths analysed – **34 maternal deaths, 7 (20%) HIV+.** Antenatal HIV prevalence – 6%. HIV prevalence among non-pregnant women who died – 78%.	**MMR:** 1842 for HIV+ 478 for HIV- **RR: 3.9; 95% CI: 1.7, 8.8.** Death rate lower in HIV+ pregnant vs. non-pregnant women, RR, 0.2; 95% CI: 0.1, 0.5.	Good birth and death registration system. 'Healthy pregnant woman effect' – women in early stages of HIV infection likely to be pregnant. No details on causes of death, or level of immune suppression. Pre-ART.
Mbizvo *et al*. 2005 [128]	Uganda and Zimbabwe	**Prospective case-control study –** antenatal to two years postpartum. Compared birth outcomes, hospital admissions and mortality in (400) HIV+ and (400) HIV- women.	One death in the antenatal period in a HIV- woman. **6/8 deaths in the 6 weeks postpartum in HIV+ women.** **6 weeks to 2 years after delivery: 51/53 deaths in HIV+ women.**	RR of death in HIV+ vs. HIV-: Uganda: RR = 17.7; 95% CI: 4.3, 73.2; Zimbabwe: RR = 10.0; 95% CI:2.3, 43.1	Looked at deaths up to two years postpartum.

Author and year	Country	Methods	Key findings	Key findings	Comments
Ramogale *et al*. 2007 [116]	South Africa	**Retrospective review of maternal deaths at a tertiary hospital.** Study period: 1998-2004 378 maternal deaths HIV+: 146 HIV-: 50 HIV unknown: 182	**Leading causes of death in HIV+:** WHO stage 4 disease (21%); pneumonia (20%); pregnancy-related sepsis (19%); pulmonary TB (15%) **Peak HIV-associated MMR in 2003 at 553, 164 in 1998**	**Causes of death in HIV- women:** Pregnancy-related sepsis (32%); hypertension (22%) No maternal deaths in HIV- women related to pneumonia or pulmonary TB.	48% of maternal deaths with an unknown HIV status – more than 50% died of pregnancy-related sepsis. Pre-ART.
Chilongozi *et al*. 2008 [117]	Malawi, Tanzania, and Zambia	Part of an **antibiotic trial** to decrease chorioamnionitis-related MTCT (HIVNET 024). Study period: 2001-2003 **2292 HIV+ and 367 HIV- women enrolled in the 2nd trimester until 1 year postpartum.**	42 maternal deaths, all in HIV+ women – 7 antenatal and 35 postpartum. **Anaemia, sepsis, TB and malaria leading (53%) causes of deaths.** Other significant causes: pneumonia, meningitis, AIDS-related complex and Kaposi's.	**CD4 <200 and VL ≥50 000 associated with an increased risk of mortality.**	Pre-ART. Postpartum deaths not divided into early and late. No maternal deaths in HIV- women. Anaemia – role of malaria, intestinal parasites and HIV.

Author and year	Country	Methods	Key findings	Key findings	Comments
Menendez *et al.* 2008 [118]	Mozambique	**Prospective study at a tertiary hospital.** Study period: 2002-2004 179 maternal deaths MMR 847 **139 had autopsies and formed the basis of the analysis.**	123/139 had an HIV test, and 65 (53%) were HIV+ 131/139 cause of death known: 53 (40%) due to obstetric complications with haemorrhage the commonest cause of death.	**78 (60%) due to non-obstetric causes – HIV/AIDS-related complications the commonest cause.** 67/78 died of infectious diseases. Pneumonia, meningitis and severe malaria leading indirect causes of maternal deaths in HIV+ women.	Strength – autopsy diagnosis of cause of death. Pre-ART.
Black *et al*. 2009 [109]	South Africa	**Record review of maternal deaths at a tertiary hospital.** **Study period: 2003-2007** 106 maternal deaths HIV+: 59 HIV-: 17 HIV unknown: 30	**70% of deaths in HIV+ women considered to be HIV-related** **Leading causes of death in HIV+:** TB 36%; pneumonia 20% **MMR:** HIV+: 776 HIV-: 124 HIV unknown: 195	**MMR in HIV+ 6.2-fold higher (95% CI 3.6 –11.4) than in HIV-** **Leading causes of death in HIV- and HIV unknown:** Hypertension – 34% Pregnancy-related sepsis: 15% Cardiac disease: 17%	28% had an unknown HIV status. Only 2/59 on ART despite availability for 4 years during the study period 53/59 HIV+ had a CD4 count; median 72 µ/L (IQR: 29, 194)

Author and year	Country	Methods	Key findings	Key findings	Comments
Marazzi *et al*. 2011 [119]	Mozambique and Malawi	**Retrospective observational cohort study** – mother–infant pairs enrolled in a public health PMTCT programme. 3273 pregnant women Study period: 2005-2009	**MMR was 10-fold lower in women with >90 days of antenatal ART, compared with no ART prior to delivery, p<0.001.** Decrease in MMR directly proportional to duration of ART and present at all CD4 count levels.	Survival benefit of ART seen even at CD4 >350 µ/L. Independent association between baseline CD4, anaemia, BMI, and pre-delivery length of maternal ART with maternal mortality.	No details on the causes of maternal deaths. No adherence data.
van den Akker *et al*. 2011 [110]	Malawi	**Facility-based prospective cohort study.** Assessed association between mortality and non-obstetric infection, HIV prevalence, and ART uptake. Study period: 2007-2009	23 infection-related maternal deaths, 15/23 (65%) non-obstetric; classified as indirect. 15 of the 23 maternal deaths were HIV+. **Pneumonia the most common non-obstetric infection**. All TB cases in HIV+.	**HIV+ 3X likely to die compared to HIV-.** OR 3.1, 95% CI: 1.1, 9.2; p=0.03 Independent association between mortality and HIV+ and not on ART – aOR 3.0, 95% CI: 1.1, 8.6 HIV+ on ART aOR 0.5 95% CI: 0.1, 2.7	ART introduced in 2003 – approx. 80% coverage in 2007. Eligibility then: CD4 <200 µ/L, WHO stage 3 or 4 disease

Author and year	Publication date Country	Methods	Key findings	Key findings	Comments
Liotta *et al*. 2013 [120]	Malawi and Mozambique	**Retrospective observational cohort in established PMTCT programmes.** Median CD4 count at baseline 392 µ/L Study period: 2002 -2010	101 maternal deaths – **87 in women initiating ART for PMTCT, 14 in women initiated on ART pre-pregnancy** **Higher risk of death with shorter duration of antenatal ART** (<30 days OR =2.6 (CI: 1.6, 4.2) p<0.001), and baseline CD4 counts <350 µ/L, OR: 1.9 (CI: 1.3, 2.9) p= 0.001	Long-term mortality – 43 days to 4 years postpartum – 2-fold higher with <30 days of antenatal ART compared to ≥90 days, p<0.0001. **Shorter duration of antenatal ART; baseline CD4; Hb and BMI associated with long-term mortality.**	Pre-pregnancy ART – mortality not increased despite low CD4 counts **No details on causes of deaths.** Long-term deaths determined from home visits. **High rate of LTFU** – 56 women who died in within 42 days postpartum were LTFU.
Matthews *et al*. 2013 [125]	Uganda	Assessed pregnancy-related mortality **(up to 1 year postpartum)** in a cohort of women initiating ART. Study period: 2005-2011 109 self-reported pregnancies out of 354 women.	4 pregnant at ART initiation. **5 pregnancy-related deaths** – 1 during pregnancy and 4 postpartum. Death determined through interviews with relatives and review of clinic records.	Cause of death unknown in 3 cases. 1 had pulmonary TB. 1 probably died from cryptococcal meningitis.	**Very small number of deaths to make any conclusions on pregnancy-related deaths in the 1st year of ART.** Definitive cause of death unknown in 4/5 cases. Pregnancy self-reported.

Author and year	Country	Methods	Key findings	Key findings	Comments
Ngene *et al*. 2013 [126]	South Africa	**Prospective study.** Maternal and fetal outcomes of HIV+ and HIV- women admitted in ICU during pregnancy or up to 42 days postpartum. Followed up to 7 days post ICU discharge or discharge from hospital. Study period: 2010-2011	**84 admissions: 31 (37%) HIV+;** 42 (50%) HIV-; 11 (13%) HIV unknown **HIV+:** 8 (26%) on ART; 25% with CD4 ≤200 µ/L on co-trimoxazole **18 maternal deaths:** 11 (61%) HIV+; 4 (22%) HIV-; 3 (17%) HIV unknown	**Leading indications for ICU admission:** HIV+: respiratory failure (26%); obstetric haemorrhage (26%); sepsis (19%) HIV-: respiratory failure (2%); obstetric haemorrhage (29%); sepsis (2%); seizures (10%)	Majority of maternal deaths in HIV+ women, not statistically significant – small numbers. Small number on ART. No details on causes of death.
Ray *et al*. 2013 [121]	Botswana	**Record review of maternal deaths up to 42 days postpartum.** Study period: 2010 80 deaths notified, MMR – 163 56 case records available for review. **Cause of death identified in 55 cases.**	**36/56 (64%) HIV+; 20/36 (55.6%) on ART** 11 (20%) HIV- 9 (16%) HIV unknown. Direct causes of death– 23/55 (42%): haemorrhage (43%), hypertension (22%), pregnancy-related sepsis (13%).	**Indirect causes of death – 32/55 (58%): 19/32 (59%) attributable to HIV;** 13/32 due to medical and surgical disorders. Of the 19 deaths attributable to HIV, 12 had AIDS.	**58% of maternal deaths due to indirect causes.** No data on duration of ART. High number (24) of missing case records – could have influenced study findings.

Author and year	Country	Methods	Key findings	Key findings	Comments
Shapiro *et al*. 2013 [129]	Botswana	**RCT of maternal ART for PMTCT.** **CD4 ≥200** – ART initiated antenatally through weaning or 6 months postpartum. **Observational arm:** CD4 <200 or AIDS-defining condition – lifelong ART. Study period: 2006 – 2008.	**14 women died up to 24 months postpartum** **1** antenatally, **3** from delivery though 6 months postpartum, and **10** from 6–24 months postpartum. 5 deaths were in the observational arm – all had CD4 counts <250 µ/L	**9 deaths were in the interventional arms and occurred** – 5 deaths in women with CD4 >350. 8/9 **deaths occurred after stopping ART for PMTCT.**	Some of the causes of death – extrapulmonary TB, pulmonary TB, diarrhoea, hepatic/renal failure, PJP, toxoplasmosis, nevirapine toxicity. Small number of maternal deaths.
Westreich *et al*. 2013 [122]	South Africa	**Observational cohort –** retrospective analysis of an electronic patient database, N=7 534 women. **Main exposure –** incident pregnancy after ART initiation. **Main outcome –** death. Study period: 2004-2011	918 (12%) women were ever pregnant, median of 14 months (IQR: 7, 26) after ART initiation. 21/918 (2.3%) women died, median time between start of pregnancy and death was 15 months (IQR: 8, 24).	**Incident pregnancy was not associated with an increased hazard and risk of death in women on ART, HR** 0.67 (95% CI: 0.43, 1.05)**.** Incident pregnancy associated with decreased risk of LTFU, HR= 0.62 (95% CI: 0.51, 0.75).	No details on causes of death in the women who died. Cohort – high retention rates in care. Adherence to treatment assessed as good.

Author and year	Country	Methods	Key findings	Key findings	Comments
Buchmann *et al*. 2014 [111]	South Africa	Record review of maternal deaths in a referral hospital obstetrics unit. Study period: 1997-2012	Top 3 leading causes of death: **1. Non-pregnancy related infections (40%) (92% HIV+, >50% respiratory infections, 68% had anaemia at baseline)** 2. Hypertensive disorders (17%) 3. Obstetric haemorrhage (13%)	46% of maternal deaths due to indirect causes. Decrease in MMR with introduction of ART; 23% on ART. Peak MMR of 139 in 2004 and a decline to 86 in 2011. CD4 counts – majority <200 µ/L.	Record review – possible misdiagnosis and misclassification of causes of death. Increase in HIV prevalence in women who died with increased testing.
Li *et al*. 2014 [127]	Tanzania	**Prospective cohort study** – 64 296 HIV+ women enrolled in a HIV/AIDS care and treatment programme. Study period: 2004-2011 20 996 live births 363 maternal deaths, MMR – 1729	27% on ART overall – 16% started pre-pregnancy. **Advanced immune suppression and anaemia were significantly associated with an increased risk of maternal mortality**	**Pre-pregnancy ART associated with 55% decrease in risk of mortality,** (OR 0.45, 95% CI 0.29–0.70)**.** 34% decrease in risk of death in those on ART at delivery, (OR: 0.66, 95% CI: 0.51, 0.87) risk decreased by 8% with each additional month on ART during pregnancy.	Death information from clinic records and home visits. **No information on causes of death.** 82% decrease in MMR from 2007 to 2011 MMR for HIV+ women estimated to be 5X higher than for HIV- women

Author and year	Country	Methods	Key findings	Key findings	Comments
Bailey *et al*. 2015 [123]	Mozambique	**Secondary data analysis from two national cross-sectional surveys done in 2007 and 2012.** Evaluated changes in iMMR, causes of death, and contribution of HIV, malaria and anaemia to maternal mortality.	Obstetric haemorrhage the leading cause of death in direct causes. **2007** – 10% of deaths due to HIV/AIDS; 9% due to malaria. **2012** – different categorization allowed multiple conditions – **comparisons not possible.**	With indirect causes of death, HIV infection, malaria and anaemia were more prevalent. Also present in women dying of direct causes. Appears to be an increase in deaths due to indirect causes.	**In 2007, large number of maternal deaths that appear as "other" direct and indirect causes.** **2007 – 12 months of data; 3 months for 2012** **No information on ART use.**
Nganira *et al*. 2015 [130]	Tanzania	**Sub-cohort in a PMTCT study** – 84 women with **CD4 ≤200 at enrolment,** continued **on ART for life** and followed up for 24 months after delivery. Median CD4 139 cells/μ/L. Enrolment 2004-2006	**Increase in proportion of women who had a detectable viral load (≥400) at 12 months – 61%, 86% at 24 months postpartum – p=0.000.** Increase in proportion with **immunologic failure** postpartum: 25% at 12 months (p = 0.032) and 41% (p = 0.035) at 24 months.	**High rate of treatment failure and drug resistance** – 56% at 12 months postpartum – despite close monitoring and follow-up, including home visits. **5 deaths postpartum:** 1 at 1 week; the other four died at months 2,5,14 and 24 – **all died of HIV-related complications.**	Probability of virologic and immunologic failure associated with self-reported non-adherence – wide CI. Adherence was taken as not having missed a single dose. Small number of maternal deaths.

LTFU= lost to follow-up – ≥60 days late for scheduled follow-up

Author and year	Country	Methods	Key findings	Key findings	Comments
Auld *et al*. 2016 [124]	Mozambique	**Observational cohort study.** Analysed database of patient-level data. Adults ≥15 years initiated on ART. Study period: 2004-2013; Option B+ introduced in 2013 **Primary outcomes – mortality and LTFU**	**6-month mortality lowest among Option B+ pregnant women** with CD4 >350 cells/μ/L and WHO stage 1 or 2 disease (0.1%), vs. other pregnant ART enrolees (1%), non-pregnant females (3%), and males (5%).	**6-month LTFU highest for Option B+ group (38%),** compared with other pregnant ART enrolees (26%), non-pregnant females (18%), and males (23%). **LTFU** for pregnant women: **aHR:** 1.11, CI: 1.00 to 1.22, p=0.049	High rates of LTFU. No details on causes of death in pregnant women. **Mortality risk for pregnant women: aHR:** 0.81, CI: 0.69 to 0.94, p= 0.007.
Ngonzi *et al*. 2016 [112]	Uganda	**Retrospective unmatched case control study in a referral hospital**. Cases – maternal deaths (139), controls – women admitted to the obstetric ward and survived (417). Study period: 2010-2014	**Causes of mortality** **Direct causes 78%:** puerperal sepsis (31%), PPH (22%), hypertensive disorders (14%), abortion complications (11%). **Indirect causes 22%:** malaria (40%), anaemia (4%), others (9%).	Some of the factors associated with mortality: **HIV infection – aOR 3.6 (CI: 1.9–7.0) p<0.001; lack of antenatal care – aOR 3.6 (CI: 1.9–6.9), p<0.001.**	Hospital-based data. Record review. **HIV prevalence:** cases (35%); controls (16%) Causes of death not disaggregated into HIV+ and HIV-; no details on ART use.

Author and year	Country	Methods	Key findings	Key findings	Comments
Black *et al*. 2016 [113]	South Africa	Audit at a tertiary hospital. Compared causes of death and MMR over 3 periods corresponding to changes in ART policy. Study period: 2003 to 2012	**MMR in HIV+ vs. HIV-** women **decreased from being 7.1X** higher in the pre-ART era **to 3.2X higher** with expanded ART programme. Even with expanded ART (period 3), 33.3% of maternal deaths attributed to HIV.	In period 3, 28.6% of women who died were on ART. Decrease in maternal deaths due to TB, among HIV+ women, over time.	Higher coverage of HIV testing and ART reduced MMR among HIV+ women. MMR among HIV- remained unchanged.

1.2.9 The role of ART in HIV-related maternal mortality

ART for maternal health was not available in state health institutions in sub-Saharan Africa, before 2003. In the early years of the ART roll-out, treatment was usually offered within donor-funded HIV programmes, and much of the published literature on maternal mortality in HIV-infected women from this period is from cohorts within these programmes.[109,110,119,120,122,124,125,129,130,127] In the 25 studies on maternal mortality in HIV-infected women (Table 1.3), where ART was available as part of routine care, the proportion of women that were on treatment at the time of death ranged from 3% to 29%.[109,111,113,121,127,126] In only one study, done in Botswana, was the proportion of women on ART higher at 56%.[121] This illustrates that even when ART programmes had been scaled up, women who died were likely not to have been on treatment, despite advanced immune suppression as mentioned above. Botswana is one of the countries in sub-Saharan Africa that had a rapid evolution of its PMTCT programme, and according to a UNAIDS 2010 report, when the maternal mortality study was done, the estimated that ART coverage among pregnant women was 94%.[157]

Data from five of the 25 studies show a survival benefit of ART for both pregnant and postpartum women, even for those without advanced immune suppression.[110,119,120,124,127] The studies suggest that the effect of ART in decreasing HIV-related maternal mortality is modified by the duration of treatment and also the level of immune suppression at ART initiation.[119,120,127] In a retrospective cohort study of women enrolled in PMTCT programmes in Mozambique and Malawi, Marazzi et al found that maternal mortality up to 42 days postpartum, was 10-fold higher in women who had no ART prior to delivery, compared to those who had 90 days or more of prenatal ART ($p<0.001$).[119] In the same study, even a short duration of prenatal ART was associated with a significant decrease in risk of maternal deaths – there was a 70% decrease in risk of death in women who had more than 30 days of prenatal ART compared with no ART.[119] The benefits of prenatal ART in decreasing the risk of maternal deaths was seen at all CD4 count strata, even at CD4 counts greater than 350 cells/µl. While the results of the study are important, no details were given on the causes of maternal deaths. The study cohort was also in relatively good health, with a median CD4 count of 357 cells/ µL, IQR: 234-518, and the women were enrolled in

a donor-funded HIV programme where they were followed up antenatally and postpartum.[119]

Additional evidence on the benefits of ART initiation in pregnancy at higher CD4 counts comes from another study done in Mozambique.[124] The aim of the study was to assess scale-up of an ART programme in Mozambique from 2004 to 2013, a period that saw several guideline changes with introduction of Option B+ in 2013.[124] There was evidence of a decline in mortality among pregnant women initiated on ART within an Option B+ programme and with CD4 counts above 350 cells/μl, compared to pregnant women initiated on ART outside of an Option B+ programme, non-pregnant women and men.[124] There was however a high rate of loss to follow-up, with 38% of women lost by six months after ART initiation.[124] It is difficult to appreciate the decrease in mortality with such a high rate of loss to follow-up as it is estimated that up to 60% of patients lost to follow-up are likely to have died.[158]

A study by Liotta et al, done in the same PMTCT programmes in Mozambique and Malawi as the study by Marazzi et al discussed above, showed a lower risk of maternal mortality in women initiated on ART pre-pregnancy.[120] In women on pre-pregnancy ART, the mortality rate was 0.7%, while that in women initiated on ART during pregnancy and had a higher baseline CD4 count was 1.1%; the difference was however not statistically significant. There are limitations to this study in that there were no details on the causes of maternal deaths. The authors report that “41 women died in the process of giving birth, presumably of obstetrical complications, while 4 others died due to complications leading to concurrent fetal demise during the labour process”, a statement that does not give insight into the causes of death.[120] There was also a high rate of loss to follow-up, with 56 women who died in the six weeks postpartum period not returning for care in the programmes, and deaths ascertained through home visits.[120]

With ART started before pregnancy, Li et al from Tanzania also found a reduction in risk of maternal mortality compared to pregnant women not on any treatment.[127] In a prospective cohort study done within a large HIV care and treatment programme, pre-pregnancy ART was associated with a 55% reduction in risk of maternal mortality compared to women who were not started on ART. While the study was large, with 363 maternal deaths reported in seven years, no details were given on the duration of pre-pregnancy ART and no details were given on the

causes of death, making it difficult to compare the findings with those from other studies.

ART has also been shown to be associated with a decrease in deaths due to TB in HIV-infected individuals, one of the leading HIV-related causes of maternal mortality.[159] In their audit of maternal deaths in a referral hospital in South Africa, Black et al showed a more than 50% decline in odds of death from TB with expansion of the ART programme.[113]

While available data show a beneficial effect of ART started before pregnancy, or early in pregnancy, questions have been raised about the impact of incident pregnancy on maternal mortality in HIV-infected women on ART.[122,125] This is an important concern because as ART programmes are scaled up, more HIV-infected women will become pregnant already on ART. A South African study looking at the impact of incident pregnancy on maternal mortality, in women already on ART, showed no increased risk of death in women who became pregnant compared to those who did not.[122] In a cohort of 7 534 women, there were 21 deaths (2.3%) in 918 women who had a recognised pregnancy compared to 614 deaths (9.3%) in 6 616 women who did not have a pregnancy. The median time between the start of the pregnancy and death was 15 months (IQR 8, 24). The authors argue that the results do not show a protective effect of pregnancy, but rather illustrate that incident pregnancy is not associated with an increased risk of death in women already on ART.[122] At the time of pregnancy, the median time on ART was 14 months (IQR: 7; 26), and women ≤25 years and those with higher CD4 counts were more likely to be pregnant than older women and those with lower CD4 counts.[122] At follow-up, the majority of women in the cohort (this is not quantified in the paper) were likely to be virally suppressed and also have a CD4 count greater than 200 cells/µl. Hence the women who became pregnant were a young and healthy cohort, who intuitively would have a decreased risk of maternal mortality. One of the limitations of the study is that there were no details on the causes of death.

Some studies have suggested that there is a ‘healthy pregnant women effect’, i.e. HIV-infected women who become pregnant are likely to be in early stages of HIV infection, and hence have a lower risk of death.[108,160] In a study done in the Republic of Congo, in the pre-ART era, Le Coeur et al found the risk of death in HIV-infected pregnant women to be five times lower compared to HIV-infected women that were

not pregnant, RR: 0.2, 95% CI: 0.1, 0.5.[108] No details were given on the causes of death, or the level of immune suppression. In another study, a large community-based study done in rural South Africa, HIV-related mortality in women during the maternal risk period (pregnancy, delivery and puerperium) was lower compared to HIV-infected women of reproductive age that were not pregnant, RR = 0.75; 95% CI = 0.63, 0.89.[160] The authors postulate that HIV-infected women who become pregnant are less likely to have advanced disease and therefore at lesser risk for death, but no details are given in the paper on the level of immune suppression and ART use in the study cohort.[160]

While HIV-infected women who become pregnant are likely to be in the early stages of HIV infection, and there appears to be no increased risk of death associated with incident pregnancy in women on established ART, there is limited information on the impact of incident pregnancy on maternal mortality in the early stages of ART initiation, in women with advanced immune suppression. In their cohort study of women initiating ART in Uganda and assessing pregnancy-related mortality up to one year postpartum, Matthews et al report that there is increased mortality within the first year of ART initiation among pregnant and postpartum women with advanced HIV disease.[125] The authors postulate that this could be an effect of persisting immune suppression, or related to an increased risk of immune reconstitution inflammatory syndromes at ART initiation. While this is a plausible explanation, the numbers in the study are too small, at only five deaths reported during pregnancy and postpartum, to make any definitive conclusions.[125] Data from non-pregnant populations, including women and men, show an increased risk of mortality in the first year of starting ART, in patients with advanced immune suppression, and it is likely that the same effect will be seen in pregnant women.[161,162]

To be able to see substantial and sustained decreases in HIV-related maternal mortality, there needs to be an increase in HIV screening and ART initiation outside of pregnancy, especially for women with advanced immune suppression. Universal access to ART for all pregnant and postpartum women, through either Option B+ or through the Universal Test and Treat strategy, will be the key driver in further decreasing HIV-related maternal mortality. With many sub-Saharan African countries adopting Option B+, a significant proportion of HIV-infected pregnant women will be

started on ART at higher CD4 counts, and the expectation is that this will offset the risk of maternal mortality associated with advanced immune suppression. However, retention in care and adherence to ART remain a major challenge, with high rates of postpartum loss to follow-up reported in established Option B+ programmes.[65,64,163] Retention in care within Option B+ programmes has been discussed in the PMTCT literature review.

Reducing maternal mortality remains a global priority. Monitoring trends in maternal mortality in sub-Saharan Africa, where two-thirds of maternal deaths occur, has been hampered by the lack of comprehensive data on maternal deaths.[71] As a result, there has been a reliance on modelled estimates, which have yielded varied results. Despite this, there appears to be a downward trend in maternal mortality in sub-Saharan Africa. From this literature review, it is evident that HIV-infected pregnant and postpartum women have an excess risk of mortality compared to those who are HIV-uninfected. While the leading cause of indirect maternal death in HIV-infected women is HIV-related disease, the causes of direct maternal deaths remain important targets for intervention. Although the data are inconsistent, some of the leading causes of direct maternal deaths have risk factors directly related to HIV infection. Expansion of ART programmes will undoubtedly have an important impact on decreasing direct and indirect maternal mortality in HIV-infected women.

CHAPTER 2: RATIONALE FOR THE RESEARCH, OVERALL AIM AND OBJECTIVES

This chapter outlines the rationale, overall aim and objectives of my PhD.

2.1 Rationale for the research

There are many lessons to be learnt from programmatic experience in implementation of PMTCT programmes. This PhD makes an important contribution to the existing PMTCT literature as it chronicles the evolution of one of the oldest and largest PMTCT programmes in South Africa, starting in the period when only single-dose nevirapine was available for PMTCT, to adoption of Option B+ in 2015. It provides information on the successful implementation of the Soweto PMTCT programme through evaluation of 14 years of routinely collected data and original research conducted in facilities that form part of the programme. Results from the different studies also highlight challenges that still exist within PMTCT programmes.

While studies have reported on maternal mortality in HIV-infected women, the quality of the evidence is limited by small sample sizes and short review periods. Hence the findings from the study on maternal deaths in HIV-infected women, which is part of this PhD, make an important contribution to current literature. The review of maternal deaths in HIV-infected women covers a 19-year period, much longer than in any of the published studies, and chronicles changes in HIV diagnosis and treatment in pregnant women, and causes of maternal deaths in HIV-infected women. The review reflects on evolving HIV management guidelines, starting prior to availability of ART, through different eligibility criteria, culminating with availability of triple therapy for all HIV-infected pregnant women.

2.2 Research aim

The aim of this PhD was to evaluate the impact, on maternal and child health, of a large PMTCT and ART programme in the Johannesburg Health District, South Africa, and how therapeutic interventions have had an impact on MTCT and maternal mortality. Successes achieved in the programme were evaluated based on progress made in implementation of evolving PMTCT and ART interventions. The evaluation

was also based on progressive reduction in the MTCT risk and changing patterns in maternal deaths in HIV-infected women.

The research projects that contribute to this PhD are unique in that they were conducted in one of the largest and most established PMTCT and ART programmes in South Africa, and provide an opportunity to chronicle the evolution of the South African PMTCT and ART guidelines.

2.3 Research objectives

The conceptual framework, Figure 2.1, illustrates how the research objectives address elimination of MTCT and reduction of maternal mortality.

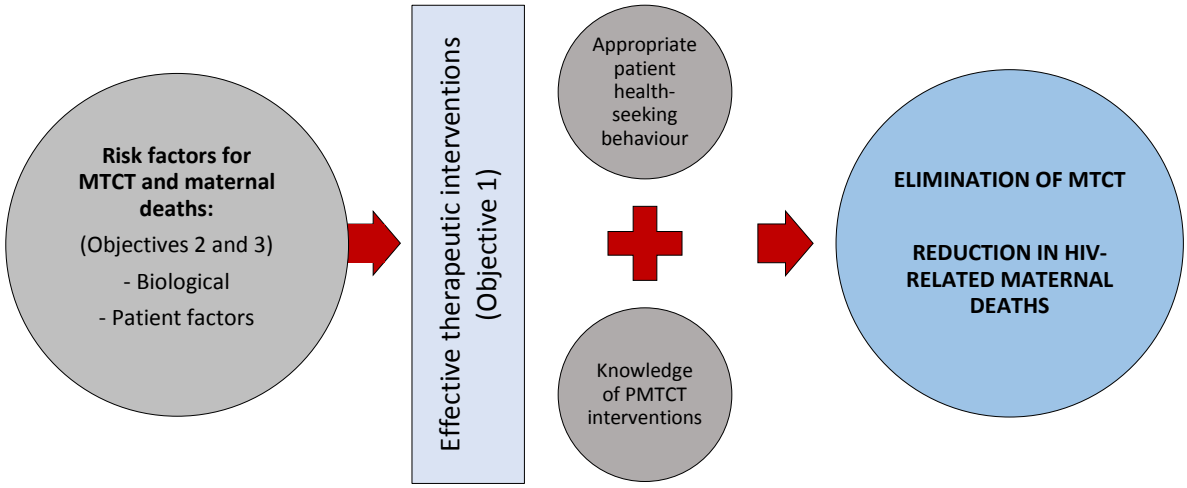


Figure 2.1: Conceptual framework for elimination of MTCT and reducing HIV-related maternal deaths. ***Source: Author's own design***

Objective 1

The first objective was to describe progress made in implementation of efficacious PMTCT interventions and ART coverage in HIV-infected pregnant women, from January 2002 to December 2015. Also, to document advances made towards eMTCT.

Objective 2

The second objective was to identify patient-related risk factors for MTCT, and also to evaluate infant feeding practices among HIV-infected women, an important factor in MTCT.

Objective 3

The third objective was to assess the impact of evolving HIV management guidelines and increased availability of ART on maternal mortality in HIV-infected women.

CHAPTER 3: METHODS

Chapter 3 gives a summary of the methodologies of the six studies that contributed to this PhD. Details of the methodologies for the individual studies are contained in the appended Papers 1-6.

3.1 Study setting

All the studies were conducted in regions D and G of the Johannesburg Health District, in Johannesburg, Gauteng Province, South Africa. The Johannesburg Health District is divided into six regions, A to G – Figure 3.1. The estimated population for the City of Johannesburg, for 2016, is just under five million people at 4 949 347.[164]

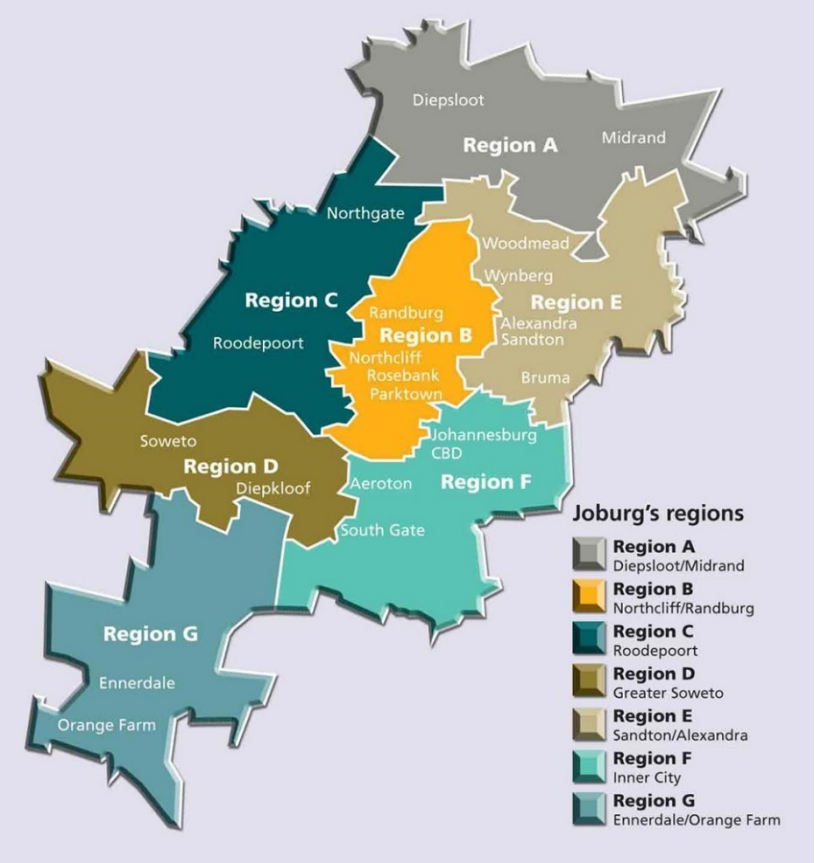


Figure 3.1: A map of the six regions that make up the Johannesburg Health District

Region D is the Greater Soweto, and is the most populous of the six regions and constitutes approximately 26% of the population in the City of Johannesburg.[164,165] Region G is made up of Ennerdale and Orange Farm, and is home to approximately 14% of the population in the City of Johannesburg. Both regions D and G are areas of mixed urban and informal settlements, and the official overall unemployment rate for the City of Johannesburg was 25% in 2011, while that for individuals aged 15-34 years was 32% for the same year.[164]

The HIV prevalence among pregnant women accessing antenatal care in the Gauteng province increased rapidly from less than 1% in 1990 to 23% by 1998, and has plateaued around 30% for the past decade – figures similar to the national prevalence, Figure 3.2.[95,166] The rapid increase in prevalence coincides with a dark period in the South African history marked by denialism about the aetiology of HIV infection and related deaths, and also refusal of the government to provide antiretrovirals.

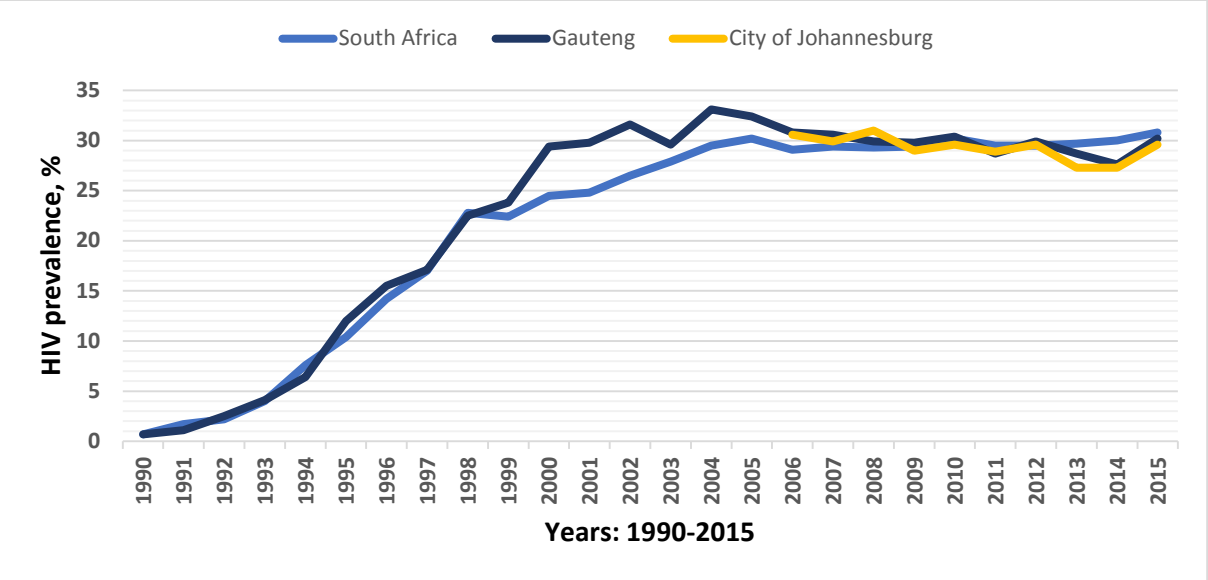


Figure 3.2: HIV prevalence among pregnant women attending antenatal clinics in South Africa and in the Gauteng Province, 1990-2015 [95,166]

These results are from the South African national antenatal HIV prevalence surveys that have been conducted since 1990. From 2006, antenatal HIV prevalence figures have been reported for individual districts within the provinces and the figures for the City of Johannesburg Health District are also presented in Figure 3.2. [95,166]

History of the Soweto PMTCT programme

The Soweto PMTCT programme was established in 2000 as the Demonstration of Antiretroviral Treatment (DART) programme initiated by the Perinatal HIV Research Unit (PHRU).[167] The programme was initially funded by the Elizabeth Glazer Paediatric AIDS Foundation (EGPAF), and the Gauteng Department of Health, and later fully funded by the United States President's Emergency Plan for AIDS Relief (PEPFAR) via the US Agency for International Development (USAID).[167] As part of the DART programme, pregnant women were offered voluntary counselling and testing (VCT) for HIV, and if found to be HIV-infected, maternal and infant single-dose nevirapine was given. A six-months supply of infant formula, from the Gauteng department of Health, was also available for HIV-infected women who elected not to breastfeed.[167]

As part of the collaboration between PHRU and the Gauteng Department of Health to establish the Soweto PMTCT programme, PHRU provided dedicated staff, professional nurses and lay counsellors with a focus on service provision. At the start of the programme, Chris Hani Baragwanath Academic Hospital (CHBAH) and 12 primary healthcare facilities were supported and approximately 30 000 pregnant women were seen in the programme annually. From 2009, the Soweto PMTCT programme has been supported by the Anova Health Institute (Anova), and from 2012 there was a shift from service provision to technical support, with a focus on training and mentoring of government employees to take over running of the programme.

Details on the evolution of the South African PMTCT and ART guidelines are given in Chapter 1, in the PMTCT literature review section, and changes in the Soweto PMTCT programme mirror these guideline changes. Prior to the introduction of NIMART within antenatal clinics in the Soweto programme, in 2010, antenatal clinics only provided PMTCT prophylaxis and pregnant women who were eligible for ART were referred to separate ART sites for treatment initiation and follow-up. Routine testing of HIV-exposed infants became widely available from 2007, and was done around six weeks of life, six weeks post cessation of breastfeeding, and again at 18 months if the initial tests were negative.

Up until May 2014, when Bheki Mlangeni District Hospital was opened in Soweto, CHBAH was the only referral hospital for regions D and G, and surrounding areas. The obstetrics unit at CHBAH is a high-volume unit with over 20 000 live births per annum reported in the past decade (Figure 3.3).

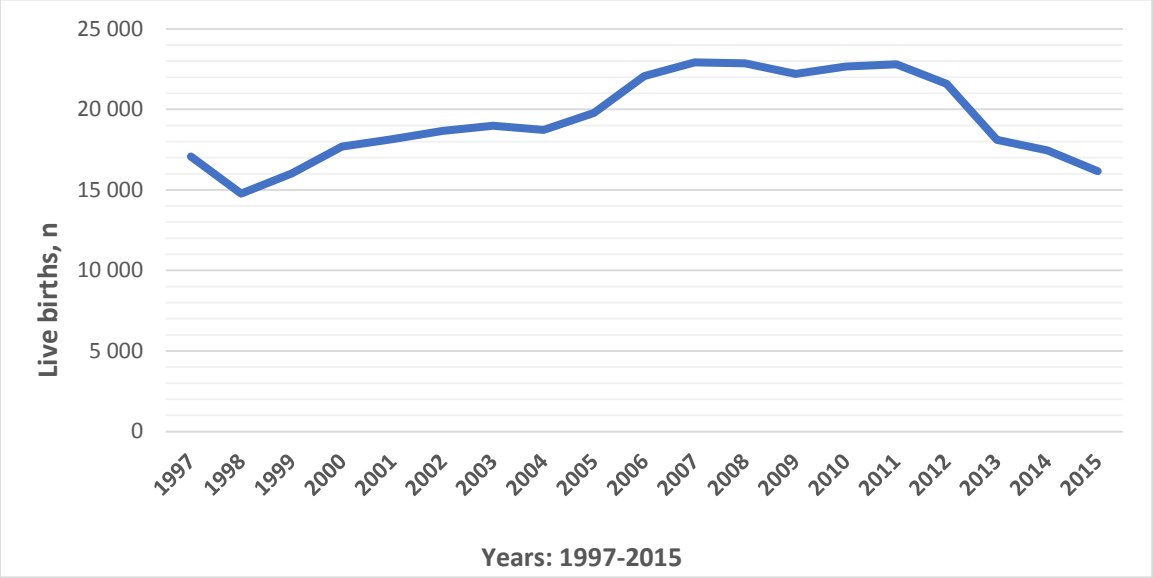


Figure 3.3: Live births at Chris Hani Baragwanath Academic Hospital: 1997-2015
Source: DHIS data

Two-thirds of the total number of live births in regions D and G occur at CHBAH, and the rest in the midwife obstetric units, in primary healthcare clinics in the two regions.[111]

3.2 Study design

Overall, the studies were quantitative, and details of the individual study methodologies are given in the manuscripts (Appendices 1 – 6). Below is a summary of the individual study methodologies and Table 3.1 gives an overview of the study populations and the methodologies.

3.2.1 Implementation of evolving PMTCT and ART interventions

In the first study (Paper 1), trends in HIV diagnosis and management in pregnancy, routine testing of HIV-exposed infants and rate of MTCT were analysed over a 14-year period of evolving PMTCT and ART guidelines. This was secondary data analysis of routinely collected PMTCT data in 13 facilities. Standard PMTCT indicators, adapted from the district health and information system (DHIS) indicators used for routine reporting in PMTCT programmes, were selected to describe the implementation of increasingly efficacious ARV interventions in line with changing guidelines.

3.2.2 Timing of antenatal care and ART initiation in HIV-infected pregnant women

This study (Paper 2) was a secondary analysis of routinely collected PMTCT data to assess the timing of antenatal care and ART initiation in HIV-infected pregnant women before and after introduction of NIMART within antenatal clinics.

3.2.3 Quality of care in PMTCT programmes

The third study (Paper 3) was a cross-sectional survey conducted in ten antenatal clinics in Greater Soweto. Pregnant HIV-infected women, and healthcare workers involved in PMTCT services, were interviewed, using structured questionnaires, to assess their knowledge of PMTCT guidelines and their experiences of the PMTCT programme.

3.2.4 Patient-related risk factors for mother-to-child transmission of HIV

This was a case control study (Paper 4) of HIV-infected women, with HIV-infected (cases) and HIV-uninfected (controls) infants diagnosed around six weeks of age as part of routine, early infant diagnosis. Structured interviews were conducted with a focus on history of HIV infection, and antenatal, intrapartum and immediate postpartum management of the mother-infant pairs. Patient-related risk factors for MTCT were identified.

3.2.5 Infant feeding intentions, practices, knowledge and perceptions

This study was a cross-sectional survey (Paper 5) conducted in ten public healthcare facilities in the Johannesburg Health District. Pregnant and postpartum HIV-infected and HIV-uninfected women were interviewed using a structured questionnaire. Infant feeding intentions and practices were determined among pregnant and postpartum women with infants up to 12 months old, respectively. Knowledge and perceptions of safe infant practices were also evaluated in both groups.

3.2.6 Maternal mortality in HIV-infected women

This was a retrospective record review (Paper 6) of maternal deaths in HIV-infected women, at CHBAH, over a 19-year period. Trends in HIV diagnosis and management in pregnancy and causes of maternal deaths were analysed over four time periods coinciding with the changes in PMTCT and ART guidelines (Figure 3.4).

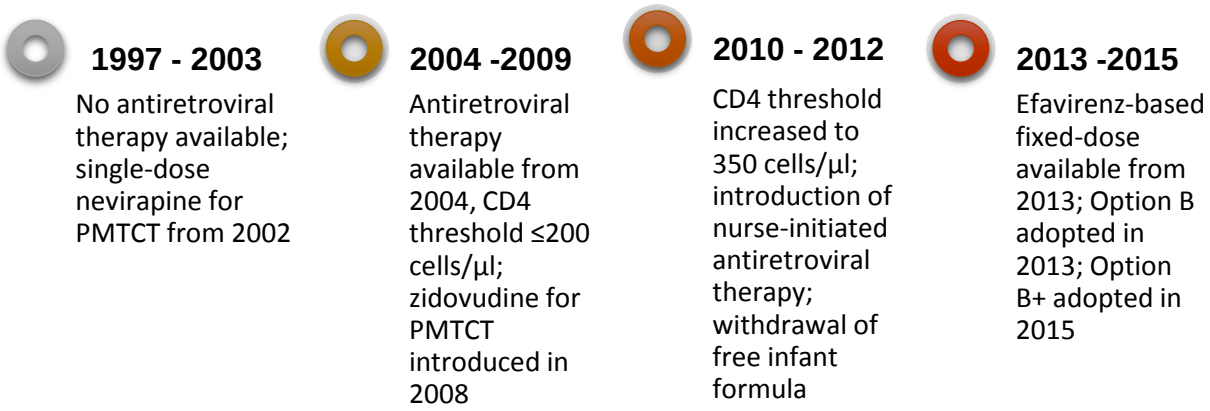


Figure 3.4: Analysis time periods and changes in South African PMTCT and ART guidelines

Table 3.1: An overview of the study populations and methodologies for the six studies that contributed to this PhD

	Study 1	Study 2	Study 3	Study 4	Study 5	Study 6
Focus of study	Implementation of evolving PMTCT interventions	Timing of antenatal care and ART initiation	Quality of care in PMTCT programmes	Patient-related risk factors for MTCT	Infant feeding intentions, practices, knowledge and perceptions	Maternal mortality in HIV-infected women
Data collection period	January 2002 to December 2015	October 2010 to March 2012	November to December 2009	November 2010 to May 2012	April 2014 to March 2015	January 1997 to December 2015
Methodology	Secondary data analysis	Secondary data analysis	Cross-sectional study	Case-control study	Cross-sectional survey	Record review
Data source and study population	Routinely collected PMTCT programme and DHIS data	Routinely collected PMTCT programme data	Structured interviews with HIV-infected pregnant women and healthcare workers	Structured interviews with HIV-infected postpartum women with HIV-infected and uninfected infants	Structured interviews with HIV-infected pregnant and postpartum women	Record review of maternal death cases
Sample size	___	1 436 ART-eligible, pregnant HIV-infected women	201 HIV-infected women 80 healthcare workers	154 HIV-infected women with HIV-uninfected infants, and 77 with HIV-infected infants	190 pregnant women, and 180 postpartum women	692 maternal death cases

CHAPTER 4: SUMMARY OF KEY FINDINGS

This chapter summarises the key findings from the six studies that contribute to this PhD. Table 4.1 outlines how each of the six manuscripts addresses the research objectives.

Table 4.1: A list of the thesis manuscripts and the research objectives they address

Objectives	Manuscripts
Objective 1	**1:** Evolution of a successful PMTCT programme in a high HIV prevalence setting, in Johannesburg, South Africa: 2002-2015. (To be submitted for publication) **2:** Timing of antenatal care and ART initiation in HIV-infected pregnant women before and after introduction of NIMART. ***S Afr J HIV Med*** **2014;15(2):55-56.** **3:** Challenges to delivering quality of care in prevention of mother-to-child transmission of HIV programme in Soweto. ***S Afr J HIV Med*** **2013;14(2):64-69.**
Objective 2	**4:** Patient factors to target for elimination of mother-to-child transmission of HIV. ***Global Health*** **2014;10:36.** **5:** Infant feeding intentions, practices, knowledge and perceptions among HIV-infected and HIV-uninfected women in Johannesburg, South Africa. ***Int Breastfeed J 2017;*****12:17.**
Objective 3	**6:** Trends in maternal deaths in HIV-infected women, on a background of changing HIV management guidelines in South Africa: 1997 to 2015. ***J Int AIDS Soc*** **2017;20:e25022.**

Detailed results and findings from each study are presented in the individual papers – Appendices 1 – 6. Paper 1 describes progress made in implementation of efficacious PMTCT interventions and ART coverage in HIV-infected pregnant women. The paper also documents the progressive decline in the MTCT rate and advances made towards eMTCT. The second paper describes the timing of antenatal care and ART initiation in HIV-infected women before and after the introduction of NIMART within antenatal clinics. Paper 3 discusses the challenges in delivering quality of care in PMTCT programmes. Paper 4 identifies patient-related risk factors to target for eMTCT, while Paper 5 presents data comparing infant feeding intentions, practices, knowledge and perceptions among HIV-infected and HIV-uninfected pregnant and postpartum women. The last paper, Paper 6, presents findings of a 19-year review of trends in HIV management and causes of maternal deaths in HIV-infected women, on a background of changing PMTCT and ART guidelines.

The detail on the key findings for each study will reflect the depth of data collected and analysis done for each study. There were three overarching themes that emerged from the studies, and these will be discussed in depth in the discussion section. The three themes are: delayed or lack of access to antenatal care among HIV-infected pregnant women and the impact on MTCT risk and maternal mortality; timing of HIV diagnosis and ART initiation in pregnant women; and knowledge of PMTCT interventions among healthcare workers and women accessing care.

KEY FINDINGS

4.1 Successful implementation of evolving PMTCT and ART guidelines and significant decrease in MTCT rate

4.1.1 Successful implementation of evolving PMTCT and ART guidelines

Since inception of the Soweto PMTCT programme in 2002, the HIV testing rate among pregnant women has remained high, with more than 95% of pregnant women presenting to the 13 facilities reviewed tested for HIV – Paper 1. Of the pregnant women identified as HIV-infected, the proportion presenting for antenatal care with an already known HIV status increased from 14.3% in 2009 to 45% in 2015, p=0.0000. Starting in 2010, the indicator on pregnant women accessing

antenatal care before 20 weeks was collected and the figure increased from 40.8% in 2010 to 51.3% in 2015, p=0.0000. CD4 count testing for ART eligibility became standard in 2006 and the proportion of ART-eligible pregnant women, based on a CD4 count of ≤200 cells/µl, was approximately 16% from 2006 to 2009. From 2010, with the increase in CD4 count threshold for ART initiation to ≤350 cells/µl, the proportion of pregnant women eligible for ART increased to around 40%. Prior to 2010, when ART services became decentralised and NIMART was introduced within antenatal clinics, ART initiation in pregnant women was low, increasing from 6.5% in 2006 to 37.3% in 2009. Consequent to the decentralisation of services and introduction of NIMART, the proportion of HIV-infected women initiated on ART increased significantly, with universal coverage of ART (≥80% coverage) achieved in 2011 (Figure 4.1).

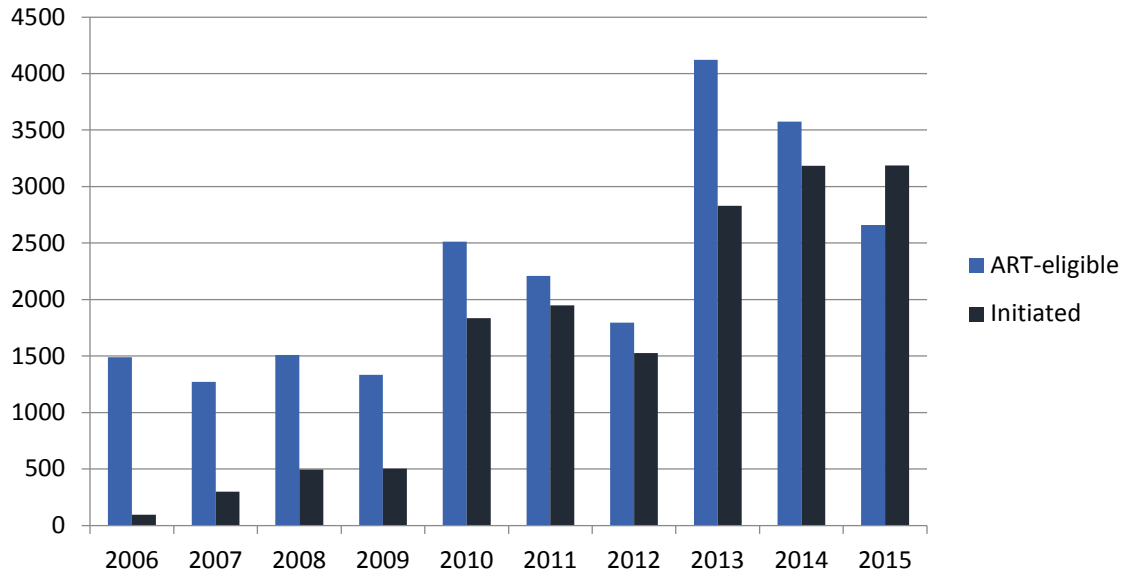


Figure 4.1: Number of ART-eligible pregnant women initiated on ART, 2006-2015

4.1.2 Significant decrease in the rate of mother-to-child transmission of HIV at early infant diagnosis

With scaling up and availability of efficacious prophylaxis and treatment regimes, the MTCT rate at early infant diagnosis around six weeks of age decreased

significantly to levels less than 2% by 2011 (Figures 4.2 and 4.3) – Paper 1. The MTCT rate decreased from 7.0% in 2007 to less than 1% in 2015, p=0.0000.

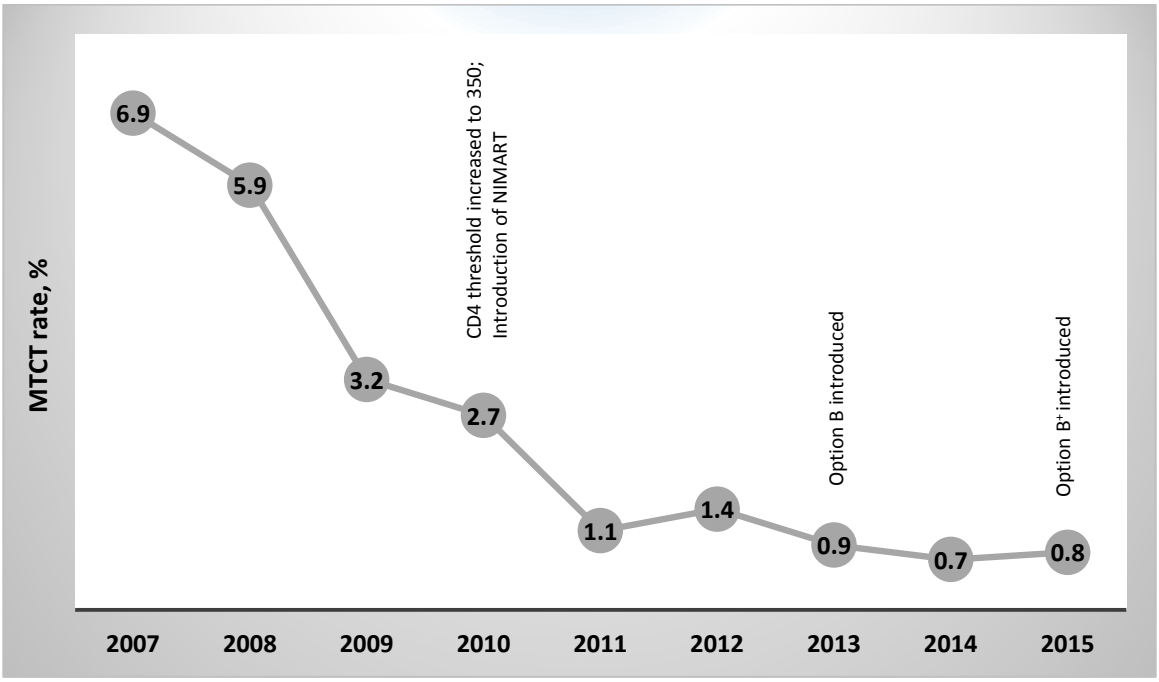


Figure 4.2: The rate of mother-to-child transmission of HIV at early infant diagnosis, 2007-2015.

4.2 Timing of antenatal care and ART initiation in pregnant women

In the secondary data analysis assessing timing of antenatal care and initiation of ART (Paper 2), HIV-infected pregnant women accessed antenatal care at a mean gestational age of 19.2±6.6 weeks, while the mean gestational age at ART initiation was 24.6±6.2 weeks. There were indications that ART initiation in pregnant women was prioritised, even prior to the introduction on NIMART within antenatal clinics. The median time to ART initiation prior to the introduction of NIMART was 3.4 weeks (IQR 2.0 - 5.9) while after the introduction of NIMART it was 3.0 weeks (IQR 1.4 - 5.4). Overall, the MTCT rate among 874 infants tested for HIV around six weeks of age was 0.2%.

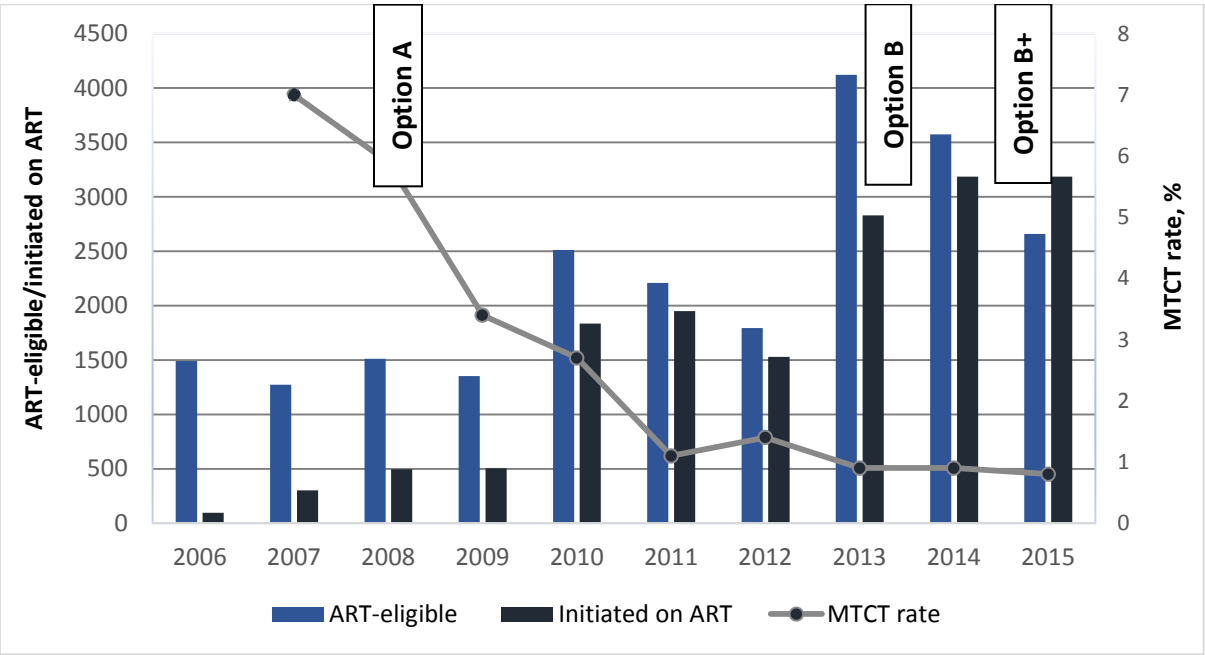


Figure 4.3: Proportion of ART-eligible pregnant women initiated on antiretroviral therapy and the rate of mother-to-child transmission of HIV at early infant diagnosis.

4.3 Challenges to delivering quality care in the Soweto prevention of mother-to-child transmission of HIV programme

In the study on challenges in delivering quality of care in the Soweto PMTCT programme (Paper 3), there were important gaps in knowledge of PMTCT interventions among both healthcare workers and pregnant HIV-infected women accessing the services. The gaps in knowledge among pregnant women were despite almost all of them (97.5%) receiving counselling, and the majority (67.7%) having had more than one counselling session at the time of the interview. Among healthcare workers, the level of knowledge was similar with a mean score of 5.4±1.6 for professional nurses and 5.2±1.9 for lay counsellors (p=0.586), in an 8-item questionnaire. The gaps in knowledge among healthcare workers were despite the fact that the majority (96.3%) felt confident about managing HIV-infected pregnant women. There were several negative opinions expressed by healthcare workers, about HIV-infected women having children, including some who thought that HIV-infected individuals should not have children and that social grants were an incentive to have more children.

4.4 Patient-related risk factors for mother-to-child transmission of HIV

In the case-control study (Paper 4) of HIV-infected women with HIV-infected infants (cases) and HIV-uninfected infants (controls), important patient-related risk factors for MTCT were identified. In a multivariate analysis, unknown HIV status prior to index pregnancy, first antenatal visit after 20 weeks of gestation, 11 years and less of formal education and unplanned pregnancies were associated with increased odds of MTCT – Table 4.2. Although the majority of cases and controls were diagnosed as HIV-infected during pregnancy, significantly more women with HIV-uninfected infants knew that they were HIV-infected prior to the index pregnancy – 43.5% (67/154), compared to 13% (10/77) of women with HIV-infected infants, p<0.001. Women with HIV-infected infants were more likely to access antenatal care at a later gestation with a median gestational age at first antenatal visit of 24.0 weeks (IQR 16 – 26), compared to a median gestational age of 16.0 weeks (IQR 12 – 20) for women with HIV-uninfected infants. They were also more likely not to access any antenatal care, despite some of them knowing that they were HIV-infected prior to the pregnancy. The most common reason given for not accessing antenatal care was fear of stigmatisation either by healthcare workers or their families.

Table 4.2: Multivariate analysis of risk factors for mother-to-child transmission of HIV at early infant diagnosis

Factors	Adjusted odds ratio AOR (95% CI)	P-value
Unplanned pregnancy	2.7 (1.2 – 6.3)	0.022
≤ 11 years of formal education	3.4 (1.6 – 7.5)	0.002
First antenatal visit after 20 weeks	4.3 (2.0 – 9.3)	<0.001
Unknown HIV status prior to index pregnancy	6.6 (2.4 – 18.4)	<0.001

AOR (95% CI) = adjusted odds ratio, 95% confidence intervals

A greater proportion of women with HIV-infected infants had unplanned pregnancies compared to women with uninfected infants – 83.1% (64/77) vs. 56.5%, ($p<0.001$). Early infant diagnosis was according to the guidelines, and once diagnosed as HIV-infected, there were no delays in ART initiation. The mean age at HIV diagnosis was 9.0±4.2 weeks, while the mean age at ART initiation was 10.8±4.4 weeks.

4.5 Infant feeding knowledge, perceptions and practices among HIV-infected and HIV-uninfected women

In Paper 5, which assessed infant feeding knowledge, perceptions and perceptions among HIV-infected and HIV-uninfected pregnant and postpartum women, there was evidence of changing infant feeding patterns among HIV-infected women. Compared to findings from the secondary analysis of routinely collected data (Paper 1), a greater proportion of HIV-infected women elected to breastfeed. HIV infection was however still an important determining factor in infant feeding intentions with significantly more HIV-uninfected pregnant women intending to breastfeed than HIV-infected women – 80.9% (93/115) compared to 64.9% (48/74) of HIV-infected pregnant women, $p=0.014$. Fear of infecting their infants with HIV was the main reason given by pregnant women who intended to formula feed or breastfeed for a shorter duration. In a multivariable logistic regression analysis of factors associated with an intention to exclusively breastfeed, the adjusted odds ratio for HIV infection was 0.278 (95% CI 0.116 – 0.665), $p=0.004$. Although not significant HIV infection was associated with greater odds of exclusive breastfeeding, adjusted odds ratio 2.604 (95% CI 0.571 – 11.872), $p=0.216$.

Similar to findings in Paper 2, there were knowledge gaps among both pregnant and postpartum women, but HIV-infected women had significantly better knowledge of safe infant feeding practices than HIV-uninfected women. There were strong perceptions in all groups of women in the study that although enough information was given in healthcare facilities to encourage women to exclusively breastfeed, it was difficult to exclusively breastfeed. Cultural factors and influence from elders were perceived to be detrimental to exclusive breastfeeding.

4.6 Trends in maternal mortality in HIV-infected women

Findings from Paper 6, the 19-year review of maternal deaths at CHBAH, highlight the challenges that still remain in decreasing maternal mortality, especially in HIV-infected women. While the majority (75.7%) of the 692 maternal deaths occurred postpartum, the events that led up to the deaths occurred in the antenatal and intrapartum periods. Almost a quarter of the women who died and had antenatal details had not accessed any antenatal care and throughout the review period, the majority of these unbooked women had an unknown HIV status. Of the women with a known HIV status, 83.8% were diagnosed as HIV-infected during pregnancy. Despite a low median antepartum CD4 count of 136 cells/μl (IQR 45 – 301), only 23.3% (78/335) of the HIV-infected women who died were on ART at the time of death. Even in the last three years of the review period, 2013-2015, where there was widespread availability of ART within antenatal clinics, 38.8% (19/49) of women who died were not on treatment. Among the women who died on non-pregnancy related infections, only 22.3% (46/206) were on ART at the time of death, despite a CD4 count ≤200 cells/μl in the majority of patients who had a CD4 count done.

Overall, non-pregnancy related infections, the majority respiratory infections, were the leading cause of death among HIV-infected women throughout the review period, accounting for 61.5% (206/335) of deaths. There was however a progressive decline in the proportion of women who died of non-pregnancy related infections, starting in the period 2010-2012 and coinciding with scale-up of ART availability and changes in PMTCT and HIV management guidelines. Of the women who died of direct causes of death, obstetric haemorrhage, pregnancy-related sepsis, and hypertensive disorders were the leading causes of death. In the women who died of obstetric haemorrhage and pregnancy-related sepsis, the majority were secondary to complications related to caesarean sections. The iMMR in HIV-infected women was three to eight-fold higher compared to the iMMR in HIV-uninfected women – Figure 4.4.

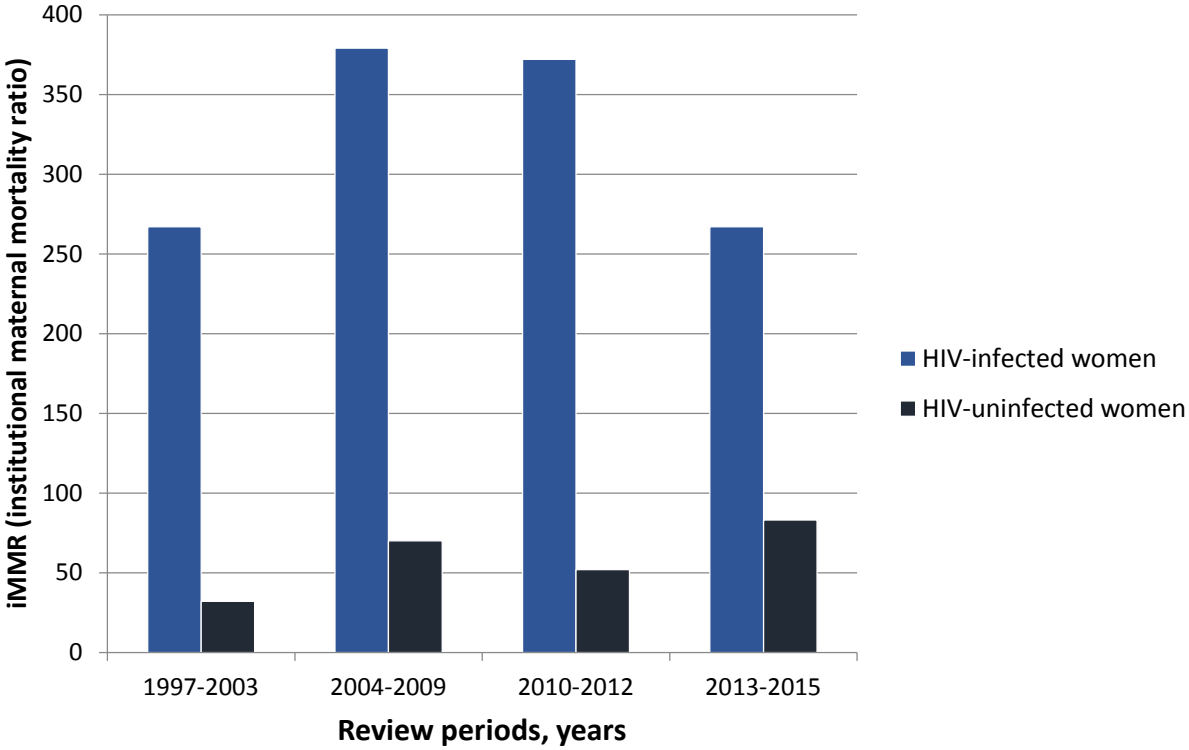


Figure 4.4: Trends in the institutional maternal mortality ratio in HIV-infected women at Chris Hani Baragwanath Academic Hospital, 1997 – 2015

CHAPTER 5: DISCUSSION AND CONCLUSION

This PhD thesis has shown the successful implementation of evolving PMTCT and ART guidelines and the impact this has had on MTCT rates and HIV-related maternal mortality, in a large PMTCT programme in Soweto, Johannesburg. With PMTCT data spanning a 14-year period, 2002-2015, antiretroviral interventions for PMTCT evolved from provision of only single-dose nevirapine to triple therapy for all HIV-infected pregnant and postpartum women (Paper 1). The period 2008-2015 saw a rapid evolution of interventions starting with the introduction of more efficacious PMTCT interventions, increase in the CD4 threshold for ART initiation in pregnant women and the integration of PMTCT and ART services within antenatal clinics. The integration of services and increased availability of efficacious antiretroviral regimens led to a decrease in the MTCT rate to levels below 2% at early infant diagnosis by 2011. There is evidence of a decrease in the MMR among HIV-infected women (Paper 6), coinciding with expansion of the South African ART programme, but the MMR remains unacceptably high. While there have been great achievements in the past decade, the denialism and lack of political will by the South African government in the 1990s and early 2000s led to countless lives being lost.

Despite the great achievements, this thesis, through evaluating various aspects of the continuum of care along the PMTCT cascade, highlights the challenges that still remain within PMTCT programmes. The majority of women still present for antenatal care late in pregnancy, beyond the first trimester, with a high reported rate of unplanned pregnancies (Papers 1-3). Also, the majority of women are diagnosed as HIV-infected during pregnancy and this has implications for the timing of initiation of antiretrovirals, whether for prophylaxis or treatment (Paper 1, 3-6). The delay in accessing antenatal care and diagnosis of HIV infection during pregnancy were identified as some of the significant risk factors associated with MTCT (Paper 4). The other risk factors were unplanned pregnancies and incomplete schooling. The importance of antenatal care was also highlighted in the 19-year review of maternal deaths (Paper 6). The majority of women who died were diagnosed as HIV-infected during pregnancy, and in those who died with an unknown HIV status, the majority did not access antenatal care. Timing of access to antenatal care and initiation of antiretrovirals highlight challenges with provision and uptake of services. The other challenge identified in the thesis relate to the quality of care

provided in PMTCT and ART programmes, as reflected in gaps in knowledge of PMTCT interventions among both healthcare workers and patients accessing care (paper 3 and 5). Findings from the research that make up this thesis make an important contribution to existing literature, highlighting achievements made and challenges that still remain. The discussion will reflect on the research findings in relation to existing literature. No data from a HIV programme the same magnitude as the Soweto PMTCT, spanning a period of almost two decades, has yet been published.

Three overarching themes emerged from the six studies that make up this thesis and Figure 5.1 illustrates how these (highlighted in pink) interact in the PMTCT continuum of care on the risk of MTCT and maternal mortality among HIV-infected women.

The overarching themes are:

- Delayed or lack of access to antenatal care
- Timing of HIV diagnosis and ART initiation among pregnant women
- Quality of care in PMTCT and ART programmes as reflected in the knowledge of PMTCT interventions

The next three sections will discuss each theme in turn.

5.1 Delayed or lack of access to antenatal care

Findings from the secondary analysis of routinely collected PMTCT data (Paper 1) indicate that from 2010 (when the indicator for timing of first antenatal visit was initially collected) to 2014, less than 50% of pregnant women accessed antenatal care before 20 weeks gestation, with the average at 42% for the five years. For 2015, the figure was just over 50%, at 51.3%. Our findings are similar to the DHIS data from South Africa which up until 2015 also show a low proportion of pregnant women accessing antenatal care early. For the period 2010-2011 only 38% of pregnant women presented for antenatal care before 20 weeks despite recommendations that women should present as early as the first missed menstrual period.[168–171] With data-driven quality improvement interventions, the proportion

of pregnant women accessing care before 20 weeks increased progressively to 50% in 2013 and to 54% in the financial year 2014/2015.[170–172] The increase has been more substantial in 2015/2016 and 2016/2017 with 61% and 65% of women presenting for antenatal care before 20 weeks, respectively.[172] The interventions implemented to increase the proportion of pregnant women presenting early include provision of daily antenatal services at health facilities; community mobilisation to increase awareness of the importance of early antenatal care and encouraging male partner involvement.[170] With positive results achieved, there is a need for sustained efforts to improve on these figures.

Accessing antenatal care late has an impact on the number of antenatal visits attended. From 2008 until the beginning of 2017, the recommendation in South Africa was for pregnant women to attend at least four antenatal visits and this was adapted from the WHO model for basic antenatal care.[168,173] The WHO basic or focused antenatal care model consists of goal-orientated visits at four critical times during pregnancy and is based on results from a randomized trial which showed that focused visits do not compromise maternal and perinatal outcomes.[173,174] However, global data show that in the period 2007-2014 only 64% of pregnant women attended the minimum four visits.[175] In South Africa the figures are better with data from the 2016 South African Demographic and Health Survey showing that in 2011-2015 76% of women had the minimum four visits.[24,168,176] In April 2017 South Africa increased the recommended number of antenatal visits to eight following revised WHO guidelines published in 2016.[175,176] The rationale behind the revision are data showing that the four-visit focused antenatal model does not offer pregnant women adequate contact with healthcare practitioners and is associated with an increased risk of stillbirths which peak in the third trimester.[175] Hence the revised antenatal schedule includes an additional visit late in the second trimester and three additional visits in the third trimester.

Cultural beliefs, financial considerations, and poor quality of services at antenatal clinics all contribute to women not accessing or delaying accessing antenatal care.[33] Even when women reach healthcare facilities they may not receive the appropriate care. In a cross-sectional survey to assess women's experiences of public antenatal care services and reasons for late antenatal care attendance in Johannesburg, South Africa, one of the reasons women who presented late for care

reported was that they knew that they would be turned away from clinics if they presented early.[177] Some of the women who reported being turned away from clinics ended up accessing no antenatal care.

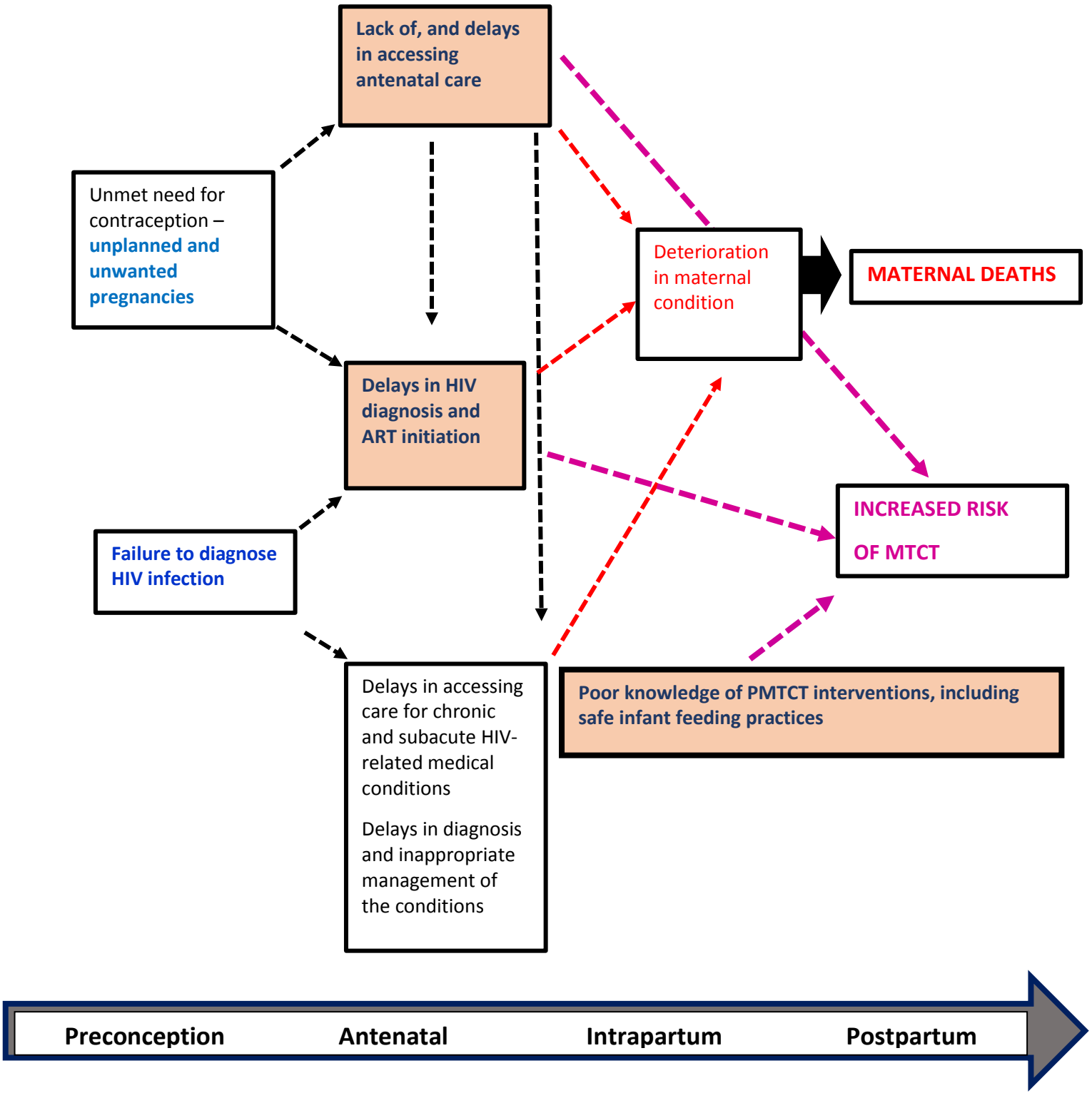


Figure 5.1: Conceptual framework for factors associated with the risk of MTCT and maternal mortality in HIV-infected women

Antenatal services that do not meet the needs and expectations of women may also be a barrier to uptake of care. While service providers view antenatal care as for the identification of risk factors and prevention of morbidity and mortality, for women and their families it is about a positive pregnancy experience.[178] In their systematic review of women's expectations of antenatal care services, Downe et al identified expectations that were universal, In addition to investigations and therapeutic interventions; women need relevant and timely information, and social and psychological support.[178] They also reported on the importance of healthcare providers' attitudes and behaviours. Hence in addressing barriers to lack of or delayed access to antenatal care, interventions need to address not just the availability of services but also the quality of care provided in these services, taking into account the social and cultural context.

Access and timing of antenatal care are critical for both elimination of MTCT and decreasing HIV-related maternal mortality. In the study on patient-related risk factors to target for elimination of MTCT (Paper 4), accessing antenatal care after 20 weeks gestation was associated with a 4.3-fold increased risk for MTCT. There were also women who accessed no antenatal care despite knowing that they were HIV-infected because of fears of being stigmatised by either healthcare workers or their families. While disclosure rates were high, similar to findings from Papers 3 and 5, stigma remains a reality for people living with HIV.

With regard to decreasing maternal mortality in HIV-infected women, in our setting and in many resource-limited settings, antenatal care remains the cornerstone for diagnosis and management of HIV infection. In HIV-infected women who die without accessing antenatal care there are often delays in seeking care and there may also be delays in diagnosis and inappropriate management of conditions.[179] Lack of antenatal care was identified in almost a fifth (19.1%) of HIV-infected women who died in the 19-year review of maternal deaths (Paper 6). Black et al, in their review of maternal deaths in the early period of ART roll-out (2003-2007), reported a higher figure with 40% of HIV-infected women who died accessing no antenatal care.[109] The lack of antenatal care in HIV-infected women who die is higher than that reported in South African national data for the pregnant population. In 2011-2015, 94% of women had at least one antenatal visit.[24] Access to antenatal care has a

bearing on timing of HIV diagnosis and initiation of antiretroviral therapy especially in settings where routine testing outside of pregnancy is not the norm.

5.2 Timing of HIV diagnosis and initiation of antiretroviral therapy among HIV-infected pregnant women

Findings from five of the six studies (Papers 1, and 3-6) indicate that the majority of pregnant women were diagnosed as HIV-infected during pregnancy, also reported in other studies conducted in sub-Saharan Africa.[64,180–182] This has implications on the timing of initiation of ART, and prophylaxis. While the routine PMTCT data (Paper 1) show that there has been an increase in the proportion of pregnant women presenting with a known HIV status – an increase from 14.3% in 2009, when the indicator was first collected, to 45.0% in 2015. HIV diagnosis outside of pregnancy will allow for early linkage to care and initiation of ART. Preconception ART is associated with the lowest risk of MTCT as it increases the likelihood of being virally suppressed at the time of delivery, the most important factor in determining the risk of MTCT.[183,184]

Notwithstanding the majority of pregnant women presenting in the second trimester and being diagnosed as HIV-infected during pregnancy, the proportion of ART-eligible pregnant women initiated on treatment has increased progressively as PMTCT and ART guidelines evolved. In the Soweto PMTCT programme, the percentage of pregnant women initiated on ART increased from less than 10% in 2006 to 88% in 2011 (Paper 1). The increase in the CD4 count threshold for ART eligibility among pregnant women and the introduction of NIMART within antenatal clinics had the greatest impact in increasing treatment initiation in the programme. South African national figures show that in 2010 only 30% of women received ART before or during pregnancy, increasing to 55% in 2012.[24] The rate of ART initiation among pregnant women in South Africa increased rapidly after 2012 with 76% started on ART in the financial year 2013/2014 and 94% in 2016/2017.[172,185] South Africa is one of a few countries in sub-Saharan African where more than 90% of pregnant women receive antiretrovirals during pregnancy.[2] The diagnosis of HIV infection in pregnancy, and consequently ART initiation only in pregnancy determines the duration of antenatal treatment. The duration of antenatal ART is directly related to the maternal viral load at the time of delivery, and consequently the risk of

MTCT.[183] The diagnosis and management of HIV infection in pregnancy also has an impact on maternal mortality. In the review of maternal deaths (Paper 6), the majority of women who died were diagnosed as HIV-infected during pregnancy. Published data show a significant survival benefit of pre-pregnancy ART.[120]

Timing of HIV diagnosis also has an impact on initiation of prophylaxis – co-trimoxazole and isoniazid – in HIV-infected individuals. The 2016 WHO ART guidelines acknowledge the benefits of co-trimoxazole prophylaxis even with expanded access to ART, and that these benefits extend beyond the prevention of AIDS-associated opportunistic infections to prevention of severe bacterial infections and malaria.[10] Isoniazid prophylaxis is also important in reducing morbidity and mortality in HIV-infected individuals, and in South Africa, a country with one of the world's worst TB epidemics driven by HIV, TB prevention has been a neglected part of TB control.[186]

Comprehensive data from the Saving Mothers reports have consistently shown non-pregnancy related infections as the leading cause of death and TB to be the most common cause of maternal deaths from non-pregnancy related infections.[94] Data from our review of maternal deaths (Paper 5) are consistent with these findings. While significant progress has been made in decreasing MTCT rates with availability of efficacious ARV regimens, the same level of success has not been seen in decreasing mortality in HIV-infected women. An important shortcoming of PMTCT programmes is that the focus has been on preventing HIV transmission to the infant, not on keeping mothers alive. Both patient-related and health system factors need to be addressed if we are to see a significant decrease in HIV-related maternal mortality. In our review the majority of maternal deaths occurred in postpartum period, but in most cases the conditions that led to the deaths occurred in the antenatal and intrapartum periods. This highlights several missed opportunities where HIV-infected women are in contact with health services during the antenatal and intrapartum periods.

5.3 Quality of care in PMTCT and ART programmes as reflected in the knowledge of PMTCT interventions

In Papers 3 and 5, important gaps in knowledge of PMTCT and ART interventions were identified among both healthcare workers and women accessing the services. These gaps exist despite staff being trained and women receiving counselling, and this reflects on aspects of quality of care provided in the programmes. While interventions have been simplified with the same antiretrovirals given for PMTCT and maternal health, knowledge of how the interventions work, including the importance of adherence to treatment, and practices that may impact on the risk of MTCT and maternal health remain important. This is especially important for safe infant feeding practices to prevent MTCT. As the MTCT rates at early infant diagnosis (reflecting intrauterine and intrapartum HIV transmission) have decreased significantly, breastfeeding transmission has become important.[2,59] UNAIDS estimates that in sub-Saharan Africa, the transmission rate after cessation of breastfeeding is almost double that at early infant diagnosis.[2] Data from a South African cohort also showed higher rates of MTCT beyond eight weeks, with 81% of cases of MTCT having occurred by six months postpartum.[59] These results highlight the ongoing risk of MTCT associated with breastfeeding, and hence the importance of safe infant feeding practices.

In the study assessing knowledge of safe infant practices (Paper 5), there were gaps in knowledge among both HIV-infected and -uninfected pregnant and postpartum women, but HIV-infected women had consistently better knowledge. Healthcare facilities were the main source of information for the majority of women overall, and this finding is consistent with reports from other studies.[187–190] The rapidly evolving guidelines on safe infant feeding practices in the context of HIV infection, in low-resource settings, have created confusion for both healthcare workers and women accessing care.[187,188] In counselling on safe infant feeding practises, the emphasis has been on HIV-infected women and an impression has been created that safe practices are only relevant for PMTCT.[190] There is a need for standardisation of messaging on safe infant feeding practices targeting both HIV-infected and -uninfected women. The information given to pregnant and postpartum women also needs to be accurate and consistent throughout the continuum of care.

Patient information should be simplified and reinforced at every opportunity. Understanding and adherence to treatment need not depend on level of education, although a low level of formal education was one of the risk factors for MTCT identified (Paper 4).

5.4 Limitations of the research

Limitations specific to each study have been discussed in Papers 1-6. An overall limitation was the use of routine, aggregate data, related to the quality and completeness of the data. In public healthcare facilities, paper-based registers are used to record patients' details and health information and these data are then captured and reported electronically. Discrepancies have been reported between the registers and the monthly facility reports and highlight problems with validation of data.[191] In the Soweto PMTCT programme, monitoring and evaluation officers and managers have always been available and are involved in the validation of data. Accuracy and completeness of data extracted from patients' records relies on notes made by clinicians, and also storage of the records. In the case of maternal death records, because maternal deaths are notifiable, there was meticulous storage of records.

The use of quantitative methods in the studies meant that while a large number of participants could be reached and precise estimates could be calculated, the depth and nuances of responses may have been missed. With any clinical research there are reporting biases, with social desirability one of the most important – participants may give responses that they think are expected of them. While all the studies that make up this PhD were conducted in one setting, the results may not be generalisable to other settings in South Africa and in sub-Saharan Africa. Soweto is unique in that it is combination of formal and informal settlements, and is a relatively mobile community with people moving from provinces in South Africa and from neighbouring countries. Due to often poor resources in rural areas, it is common practice that pregnant women move from rural to urban areas during pregnancy and move back home after delivery. The same reason is what drives pregnant women from neighbouring countries to South Africa, and Johannesburg, because of its location, is the most accessible city in South Africa. The Soweto PMTCT programme

is also not typical of public healthcare programmes in South Africa in that since its inception it has had strong partner support from non-governmental organisations, and had better resources in terms of staff and infrastructure.

5.5 Conclusion

The findings of this PhD provide valuable information on how the PMTCT and ART programmes evolved in Soweto, South Africa, as an example of high HIV-prevalence urban setting. With data spanning almost two decades, in one of the largest programmes in South Africa, these show how a successful collaboration can be achieved between the Department of Health and donor-funded organisations. For the future, the priority is to ensure that the gains made in decreasing the MTCT rate in the early postnatal period are sustained well into the postnatal period, beyond the cessation of breastfeeding. Strategies need to be in place to ensure long-term retention in care during pregnancy and postpartum. In women on ART, high rates of postpartum loss to follow-up is one of the greatest challenges identified.[66-68] Large-scale viral suppression during pregnancy, postpartum and long-term will require innovative interventions such as point-of-care viral load testing.

Factors and practices that increase the risk of MTCT also need to be addressed as availability of efficacious antiretrovirals alone is not enough. There is a need for research to investigate why there are still important gaps in the knowledge of PMTCT interventions. Also, research to determine why the rate of unplanned pregnancies and undiagnosed maternal HIV infection prior to conception remain high, and why there are still delays in accessing antenatal care. Interventions are also needed to address these challenges that still remain in PMTCT programmes. While progress has also been made in decreasing HIV-related maternal mortality, there are still many avoidable deaths in HIV-infected women. As we work towards the SDG targets on maternal mortality, there is an urgent need to address drivers of mortality in HIV-infected women.

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APPENDICES PAGE

ANNEXURES

Implementation of a successful PMTCT programme in a high HIV prevalence setting, in Johannesburg, South Africa: 2002-2015

(Manuscript to be submitted for publication)

Mnyani CN[1,2,3], Tait CL[4], Peters RPH4, Struthers H[4], Violari A[5], Gray G[5], Buchmann EJ[1], Chersich MF[6], McIntyre JA[4,7]

[1]*School of Clinical Medicine, Department of Obstetrics and Gynaecology, University of the Witwatersrand, Johannesburg, South Africa*

[2]*School of Public Health, University of the Witwatersrand, Johannesburg, South Africa*

[3]*SACEMA (DST/NRF Centre of Excellence in Epidemiological Modelling and Analysis), Stellenbosch University, Stellenbosch, South Africa*

[4]*Anova Health institute, Johannesburg, South Africa*

[5]*Perinatal HIV Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*

[6]*Wits Reproductive Health and HIV Institute, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*

[7]*School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa*

Abstract

Introduction: Great strides have been made in decreasing paediatric HIV infections, especially in sub-Saharan African countries which continue to bear the brunt of the HIV epidemic. In South Africa, one of the priority countries for elimination of mother-to-child transmission of HIV, new paediatric HIV infections decreased by 84% between 2009 and 2015. The great achievement is a result of a strong political will and the rapid evolution of the country's prevention of mother-to-child transmission of HIV (PMTCT) guidelines. In this paper we report on the implementation of a large PMTCT programme in Soweto, South Africa, a collaboration between the Department of Health and international donors, with PEPFAR funding playing a major role.

Methods: This was a retrospective review of routinely collected PMTCT data from 13 healthcare facilities, for the period 2002 to 2015. Of the 13 facilities, 12 are primary healthcare facilities and one a referral hospital. Antiretroviral therapy (ART) coverage among HIV-infected women and the MTCT rate at early infant diagnosis were evaluated.

Results: A total 360 751 pregnant women were seen in the facilities during the review period, and the HIV prevalence remained high throughout at around 30%. There was a significant increase in the proportion of pregnant women presenting with a known HIV status, from 14.3% in 2009 when the indicator was first collected, to 45% in 2015, p=0.0000. The proportion of pregnant women initiated on ART increased from less than 10% in 2006 to 88% in 2011. The MTCT rate decreased from 6.9% in 2007 to less than 1% by 2013, p=0.0000.

Conclusion: The achievements in decreasing paediatric HIV infections have been hailed as one of the greatest success stories in public health. The successful implementation of the Soweto programme reflects the strides made in the South African PMTCT programme even with the persistently high HIV prevalence among pregnant women.

Key words: PMTCT; South Africa; HIV-infected pregnant women; paediatric HIV infection

Background

Great strides have been made in the global fight to decrease new paediatric HIV infections. In 2011, the Joint United Nations Programme on HIV/AIDS (UNAIDS) launched the Global Plan to reduce new paediatric HIV infections by 90%, by 2015, with the baseline year being 2009.[1] The target was to decrease the mother-to-child transmission of HIV (MTCT) rate to 2% or less among non-breastfeeding women, and to 5% or less among breastfeeding women.[1] As part of the Global Plan, 22 priority countries, that together accounted for 90% of the global number of pregnant women living with HIV in 2009, were identified for intensified efforts for elimination of MTCT.[1] India and 21 countries in sub-Saharan Africa make up the 22 priority countries.[1]

According to the 2016 UNAIDS report, there was a 60% decrease in the overall MTCT rate in 21 priority countries, from 22.4% in 2009 to 8.9% in 2015.[2] Data were not available for India for the Global Plan period.[2,3] The decrease in the MTCT rate is largely due the increased availability and coverage of efficacious antiretrovirals for prevention of mother-to-child transmission of HIV (PMTCT).[2,4,5] South Africa was identified as one of the 22 priority countries, and through strong political will and rapid evolution of the country's PMTCT guidelines, new paediatric HIV infections decreased by 84% between 2009 and 2015, with an estimate 330 000 infections averted.[2] The UNAIDS estimate for the MTCT rate for South Africa in 2015 was 2%.

This was consistent with findings from a national survey conducted in 2012-2013, involving over 9 000 infant-caregiver pairs, with the MTCT rate at 4-8 weeks of 2.6%.[2,6]

Donor funding was critical in the establishment of the South African PMTCT and antiretroviral therapy (ART) programmes, with the country being the recipient of the largest grants from the United States President's Emergency Plan for AIDS Relief (PEPFAR).[7-11] PEPFAR funding of HIV programmes in South Africa started in 2004, with direct service provision through placement of staff and infrastructure in public healthcare facilities.[8,10] From 2012, there was a transition in PEPFAR funding from direct service provision to technical support, with the South African government increasingly taking ownership of the country's HIV programme.[8,11] By 2016, more than 75% of South Africa's HIV response was funded by the government.[12]

This paper reports on the achievements of a large PMTCT programme in Soweto, South Africa, and evaluates antiretroviral (ARV) coverage among HIV-infected pregnant women and the MTCT rate at early infant diagnosis. The programme was established through collaboration between the South African Department of Health, non-governmental organisations and international donors, with PEPFAR funding playing a major role.

Methods

History of the Soweto PMTCT programme

The Soweto PMTCT programme was established in 2000 as the Demonstration of Antiretroviral Treatment (DART) programme initiated by the Perinatal HIV Research Unit (PHRU).[13] The programme was initially funded by the Elizabeth Glaser Paediatric AIDS Foundation (EGPAF) with funding from USAID, the Fonds De Solidarité Thérapeutique International (FSTI) and the Gauteng Department of Health, and from 2004 funded by PEPFAR, via the US Agency for International Development (USAID).[13] As part of the DART programme, pregnant women were offered voluntary counselling and testing for HIV, and if HIV-infected received intrapartum single-dose nevirapine, with single-dose nevirapine also given to the infant immediately postpartum. A free six-month supply of infant formula was also available for HIV-infected women who elected not to breastfeed.

The programme has evolved in line with changes in the South African PMTCT and ART guidelines, and since 2009, the programme has been supported by the Anova Health Institute (Anova), a USAID/PEPFAR-funded non-profit organization. The donor-funded support was initially through direct service provision with placement of staff – doctors, professional nurses, data collectors and lay counsellors – in public health facilities working alongside government employees. There was also infrastructure, pharmacy and monitoring and evaluation support for the facilities providing HIV services. With the PEPFAR funding transition to technical support, the focus in support shifted to mentoring and quality improvement of the programmes through monitoring and evaluation.

Evolution of the South African PMTCT guidelines

Prior to 2002, no ARV prophylaxis or treatment was available in the South African public health sector, and ARVs were only available as part of research projects. From 2002 until 2007, only mother-infant single-dose nevirapine was available for PMTCT (Table 1). Additional zidovudine (AZT) monotherapy for PMTCT prophylaxis was introduced in 2008, initially started at 28 weeks gestation, and from 2010 initiated at 14 weeks gestation.[14-16] ART became available in South Africa in 2004 and the eligibility criterion was a CD4 count of <200 cells/μl, or World Health Organization (WHO) stage 4 disease.[17] CD4 count testing to assess ART eligibility became routinely available from 2005. The CD4 count threshold for ART initiation in pregnant women was increased in 2010 to ≤350 cells/μl.[16] In the same year, nurse-initiated and managed ART (NIMART), where professional nurses, including midwives, could initiate and manage patients on ART was introduced. Introduction of NIMART was a task-shifting intervention to increase the number of patients started on ART.[18] Postpartum, the women were transitioned to adult HIV care for follow-up. From 2002 until 2011, a six-month supply of free infant formula was available for all HIV-infected women who elected not to breastfeed.

In 2013, Option B, where all HIV-infected pregnant and postpartum women were initiated on an efavirenz-based fixed dose combination, was introduced.[19] Treatment was stopped postpartum if not breastfeeding, or after cessation of breastfeeding, if the woman was not eligible for lifelong ART for her own health.[19] The most recent PMTCT guideline change was in 2015 when all HIV-infected pregnant and postpartum women became eligible for lifelong treatment regardless of CD4 count level.[20]

Pregnant women who initially tested HIV negative were routinely retested during pregnancy and intrapartum, and women who presented intrapartum or postpartum with an unknown HIV status were also tested. Routine testing of HIV-exposed infants, using HIV DNA PCR, became standard of care from 2007, and was offered at around six weeks of age. Also part of routine care, an HIV antibody test was done at 18 months in infants who initially tested negative at early infant diagnosis. Since 2015, routine testing of HIV-exposed infants is now done at birth, 10 weeks of infant age, six weeks post cessation of breastfeeding, and at 18 months.

It is on this background of evolving guidelines and changing focus of donor funding that we evaluated the Soweto PMTCT programme.

Study setting and study design

We conducted a retrospective study of routinely collected PMTCT data from 13 public healthcare facilities which have been part of the Soweto PMTCT programme since its inception in 2002. Of the 13 facilities, one is a referral hospital, and 12 are primary healthcare facilities, of which six have delivery units.

Table 1: Evolution of the South African PMTCT and ART guidelines, 2002-2015

	2002	2004	2008	2010	2012	2013	2015
PMTCT guidelines	Intrapartum single-dose nevirapine		Option A – zidovudine monotherapy for PMTCT, for pregnant women not eligible for lifelong treatment	Integration of ART initiation within antenatal clinics	Withdrawal of free infant formula for HIV-infected women who elect not to breastfeed	Option B – triple therapy for all HIV-infected pregnant women, with postpartum withdrawal of therapy in those not eligible for lifelong treatment	Option B+ – lifelong ART for all HIV-infected pregnant, regardless of level of immune suppression
ART guidelines	------	Triple therapy Eligibility criteria: CD4 <200 cells/µl, or WHO stage 4 disease ------		ART eligibility criteria for pregnant women: CD4 ≤350 cells/µl, or WHO stage 3 or 4 disease	------	------	ART for all HIV-infected pregnant, regardless of level of immune suppression

Soweto is an area of mixed urban and informal settlements with an estimated population of approximately 1.7 million people.[21] Up to September 2010, the antenatal clinics in the 12 primary healthcare facilities only provided antiretroviral prophylaxis for PMTCT, and pregnant women who were eligible for lifelong ART were referred to a separate ART initiation site. In that time period, the only antenatal clinic that initiated ART was at Chris Hani Baragwanath Academic Hospital, the referral hospital for high-risk pregnancies. At other sites the ART initiation site that pregnant women were referred to could be in a different section of the same healthcare facility, or in a different facility. Over a period of 18 months, beginning in October 2010, NIMART was introduced in the antenatal clinics, with HIV-infected pregnant women receiving their antenatal and HIV care in the same facility.

Data management and analysis

As part of routine reporting to the District Health and Information System (DHIS), PMTCT data were collected on HIV-infected women and HIV-exposed infants, and the indicators collected changed over time with evolving PMTCT guidelines. We extracted aggregate data from paper-based and electronic registers on core PMTCT indicators for the period 2002 to 2015. The indicators that we collected data for include: pregnant women presenting for their first antenatal visit and gestational age at first visit; pregnant women tested for HIV during pregnancy and those presenting already known HIV-infected; HIV-infected women who were issued with single-dose nevirapine prophylaxis antenatally; HIV-infected women who had a CD4 count done during pregnancy and those who had a CD4 count <200 cells/µl and ≤350 cells/µl; the number of ART-eligible pregnant women who were initiated on ART; and the number of HIV-exposed infants who were tested for HIV and those found to be HIV-infected.

HIV prevalence among pregnant women was calculated using the number of pregnant women presenting already known to be HIV-infected and those newly diagnosed as HIV-infected during pregnancy as the numerator and the total number of pregnant women as the denominator. The proportion of ART-eligible pregnant women was calculated using the number of women with a CD4 count <200 cells/µl or ≤350 cells/µl, depending on the CD4 count threshold at the time, divided by the total number of HIV-infected pregnant women. The number of HIV-exposed infants who were found to be HIV-infected at around 6 weeks of age was used to calculate the MTCT rate. Data were analysed using Stata® version 14.0 (Stata Corporation, College Station, USA). Ethics approval for the study was obtained from the University of the Witwatersrand's Human Research Ethics Committee and permission to conduct the review was granted by the Gauteng Province Department of Health.

Results

From January 2002 to December 2008, around 30 000 pregnant women presenting for their first antenatal visit were seen in the programme annually – Table 2. As services became decentralised, and more facilities started providing antenatal services, PMTCT and ART care, the number of pregnant women seen in the 13 facilities decreased between 2009 and 2015. The majority of pregnant women presented for antenatal care after 20 weeks gestation, but there was an increase in the proportion presenting before 20 weeks from 40.8% in 2010 when the indicator was first collected, to 51.3% in 2015, p=0.0000. There was also a progressive increase in pregnant women presenting already known to be HIV-infected, from 4.7% in 2009 to 12.4% in 2015, p=0.0000. HIV testing rates during pregnancy were high throughout the study period, increasing from 95.8% in 2002 to 100% by 2010. The HIV prevalence was high from the beginning of the review period in 2002 with 28.9% of pregnant women HIV-infected, and it reached a peak in 2009 at 33.1% - Table 2. From 2002 to 2007, when only single-dose nevirapine was available for PMTCT prophylaxis and issued at the first antenatal visit, the proportion of women who received prophylaxis peaked at 96.1% within one year of implementation of the programme. Over time, the proportion of women who were issued with nevirapine prophylaxis at the first antenatal visit decreased as there was a shift to issuing of the prophylaxis intrapartum.

With the CD4 count threshold for ART eligibility at <200 cells/µl from 2005 to 2009, approximately 16% of HIV-infected pregnant women were eligible for ART. When the CD4 count threshold was increased to ≤350 cells/µl in 2010, the proportion of ART-eligible pregnant women increased to around 40%. There was a progressive increase in the proportion of eligible women initiated on ART, from less than 10% in 2006 to over 80% by 2011 – Table 3 and Figure 1. From 2013, all HIV-infected pregnant women were eligible to be started on ART regardless of the CD4 count level. The MTCT rate at around six weeks of age decreased from 7.0% in 2007 to less than 1% by 2013, p=0.0000 – Figure 1.

Discussion

In this 14-year review of the Soweto PMTCT programme, there was a progressive decline in the MTCT rate, at early infant diagnosis, to less than 1% by 2013. The decrease coincides with an increase in the proportion of HIV-infected pregnant women initiated on ART, as the PMTCT guidelines evolved. Coverage of HIV testing of pregnant women was high throughout the study period. The HIV prevalence remained high, with just under one-third of pregnant women HIV-infected. Donor funding and local NGO support was critical in the establishment of the Soweto PMTCT programme, and the collaboration with the South African Department of Health ensured sustainability of the programme.

While nevirapine and zidovudine monotherapy prophylaxis were important in decreasing the risk of MTCT in low-resource settings with limited access to ART, the greatest risk of transmission is in women with low CD4 counts who, when eligibility criteria existed for starting ART, were eligible for lifelong treatment.[22] The decrease in the perinatal transmission rate in the Soweto programme became evident in the period 2008-2013, a period of rapid evolution of the South African PMTCT guidelines. The period saw the introduction of dual prophylaxis for PMTCT, an increase in the CD4 threshold for ART eligibility in pregnant women, and also the introduction of NIMART within antenatal clinics.[15,16,19] The decline in the MTCT rate to levels below 2% coincides with the rapid increase in number of ART-eligible pregnant women initiated on treatment in the programme. Integration of antenatal and HIV services, which was introduced in the programme in 2010, has been shown to increase the proportion of ART-eligible pregnant women started on ART.[23,24]

Despite gains made towards elimination of MTCT in South Africa, several challenges remain.[25] Limited progress has been made in prevention of new HIV infections among women of reproductive age, an important aspect of PMTCT.[2]

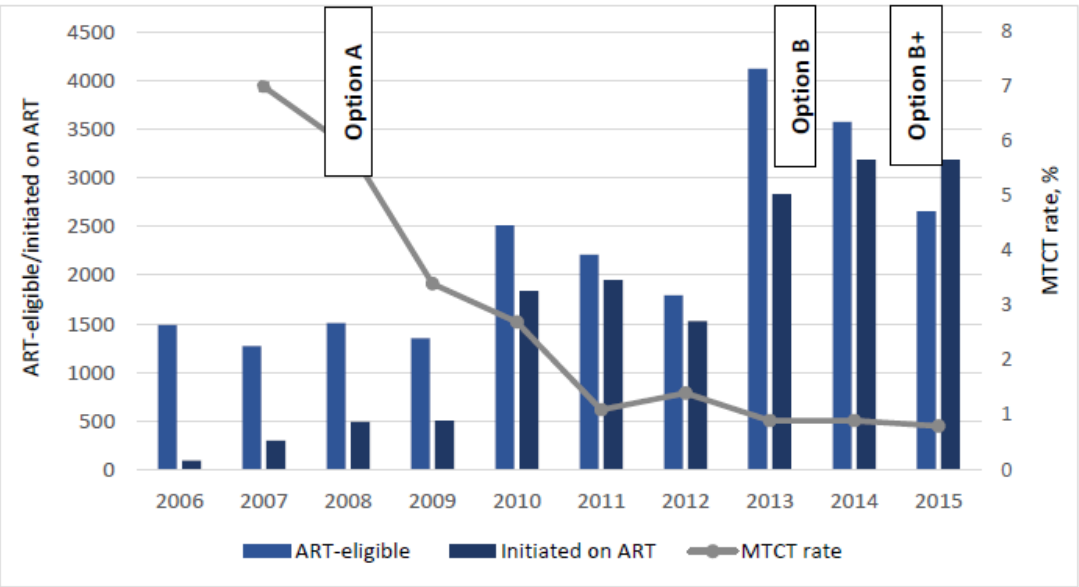

Figure 1: ART-eligible pregnant women initiated on ART and MTCT rate, 2006-2015

South Africa is reported to have had the highest number of new HIV infections among women of reproductive age globally in the period 2009-2015, and this is reflected in the high HIV prevalence among pregnant women, a consistent finding throughout the review period in our study.[2,26]Pregnant women in South Africa still present at an advanced gestational age for their first antenatal visit, with just over 50% reported to have presented before 20 weeks in 2014, albeit an increase from 36.7% in 2010.[5] We found similar figures in our study. The delayed presentation for antenatal care results in late ART initiation in those diagnosed as HIV-infected during pregnancy. In our study, the majority of women were first diagnosed as HIV-infected during their pregnancies, a finding reported in several studies conducted in South Africa and other sub-Saharan African countries.[27-30] While we did not have figures on breastfeeding transmission, postpartum MTCT remains a challenge with the 2016 UNAIDS report estimating that more than 50% of new HIV infections among children occur during the breastfeeding period.[2]

One of the limitations of using aggregate data is that the denominators used to calculate rates for some of the indicators are proxy indicators. Prior to 2013, for the indicators on HIV-infected pregnant women assessed for ART eligibility and initiated on treatment, the numerator and denominator do not reflect the same group of women seen in one month, but the numbers even out over several months. There are also additional limitations with using routine, aggregate data and these are related to the completeness and accuracy of the data.[31,32] In their assessment of routinely collected PMTCT data from 57 public health facilities in South Africa, Nicol et al raised concerns about the quality and consistency of reported data.[32] The main discrepancies identified were between data in paper-based registers and the monthly facility reports.[32] The discrepancies highlighted problems with data capturing related to lack of manpower, and competence in recording and validation of data.[32] In the Soweto PMTCT programme there have always been dedicated data collectors and data managers involved in monitoring and evaluation of the programme. While recording of data in the facility registers remains the primary responsibility of staff working at the healthcare facilities, data managers are involved in validation of data.

Despite the limitations of using routine data, the Soweto PMTCT programme is a success story of collaboration between donor-funded organisations and the South African Department of Health. The strength of this study is that it reports on a large PMTCT programme, over a long review period. To our knowledge, no PMTCT data of this magnitude have been published from a low-resource, high HIV prevalence setting. Data from the programme illustrate that it is possible to significantly decrease the MTCT rate even in a high HIV prevalence setting. It is important to ensure that the gains made towards elimination of MTCT are sustained beyond the immediate postpartum period.

Table 2: Antenatal HIV testing and HIV prevalence among pregnant women at 13 healthcare facilities in Soweto, 2002-2015

*Indicators	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
First antenatal visits, n	30 064	28 840	30 066	30 291	30 739	30 090	30 174	28 652	23 663	21 709	20 490	20 324	17 951	17 698
First visits <20 weeks, n (%)	—	—	—	—	—	—	—	—	9 643 (40.8)	8 476 (39.0)	8 196 (40.0)	8 458 (41.6)	8 365 (46.6)	9 072 (51.3)
Known HIV-infected, n (%)	—	—	—	—	—	—	—	1 356 (14.3)	886 (12.4)	1 120 (18.1)	1 232 (21.4)	2 255 (35.4)	2 195 (38.0)	2 192 (45.0)
HIV unknown tested, n (%)	28 802 (95.8)	27 305 (94.7)	29 054 (96.6)	29 327 (96.8)	30 123 (98.0)	29 707 (98.7)	29 965 (99.3)	28 535 (99.6)	23 665 (100.0)	20 569 (99.9)	19 249 (99.4)	18 468 (102.2)	15 993 (101.5)	15 341 (98.9)
Newly diagnosed HIV-infected, n	8 316	7 392	8 917	8 721	8 872	8 850	8 774	8 130	6 243	5 062	4 536	4 121	3 575	2 663
#Total HIV-infected, n	8 316	7 392	8 917	8 721	8 872	8 850	8 774	9 486	7 129	6 182	5 768	6 376	5 770	4 855
HIV prevalence, %	28.9	27.1	30.7	29.7	29.5	29.8	29.3	33.1	30.1	28.5	27.6	31.4	32.1	27.4
Received single-dose nevirapine at antenatal visit, n (%)	5 966 (71.7)	7 103 (96.1)	8 295 (93.0)	7 782 (89.2)	7 704 (86.8)	7 910 (89.4)	7 966 (90.8)	6 031 (74.2)	—	—	—	—	—	—

*Routinely collected indicators changed as the PMTCT guidelines evolved; #Total HIV-infected = known and newly diagnosed HIV-infected

— indicates that data for the indicator were not collected during that period

Table 3: HIV-infected pregnant women assessed for ART eligibility and initiated on treatment at 13 healthcare facilities in Soweto, 2005 – 2015

Indicator	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Newly-diagnosed HIV-infected, n	8 721	8 872	8 850	8 774	8 130	6 243	5 062	4 536	4 121	3 575	2 663
CD4 counts done, n (%)	4 453 (51.1)	8 767 (98.8)	8 912 (100.7)	8 775 (100.0)	8 163 (100.4)	6 741 (108.0)	5 525 (109.0)	4 811 (106.1)	4 299 (104.3)	3 694 (103.3)	—
CD4 <200, n (%)	719 (16.2)	1 489 (17.0)	1 272 (14.3)	1 511 (17.2)	1 353 (16.6)	973 (14.4)	906 (16.4)	740 (15.4)	—	—	—
CD4 ≤350, n (%)	—	—	—	—	—	2 513 (37.3)	2 209 (40.0)	1 795 (37.3)	—	—	—
*Initiated on ART, n (%)	—	96 (6.5)	300 (23.6)	495 (32.8)	505 (37.3)	1 836 (73.1)	1 949 (88.2)	1 528 (85.1)	2 830 (68.7)	3 185 (89.1)	3 187 (119.7)

*Percentage initiated on ART is out of the percentage eligible for ART

— indicates that data for the indicator were not collected during that period

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ORIGINAL ARTICLE

Challenges to delivering quality care in a prevention of mother-to-child transmission of HIV programme in Soweto

C N Mnyani,[1] BA, MB ChB, FCOG (SA); **J A McIntyre**,[1,2] MB ChB, FRCOG

[1] *Anova Health Institute, Johannesburg, South Africa*
[2] *Centre for Infectious Diseases Epidemiology and Research, School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa*

Corresponding author: *C N Mnyani (mnyani@anovahealth.co.za)*

Background. There has been little focus on the quality of care provided in the prevention of mother-to-child transmission (PMTCT) of HIV services in South Africa (SA).

Objective. To assess the quality of care in PMTCT services in Soweto, SA, focusing on the knowledge and experiences of healthcare workers and HIV-infected pregnant women accessing the services.

Methods. A cross-sectional survey was conducted in November - December 2009. A total of 201 HIV-infected pregnant women and 80 healthcare workers from 10 antenatal clinics were interviewed using standardised questionnaires.

Results. Among the HIV-infected pregnant women, the median gestational age was 20 weeks at the first antenatal visit and 32 weeks at the time of the interview. The majority of the women interviewed (71.5%) discovered that they were HIV-infected in the index pregnancy, and 87.9% disclosed their HIV status. Overall, 97.5% received counselling and 33.5% were members of a support group. Knowledge of antenatal and intra-partum PMTCT interventions was accurate in 62.7% and 43.3% of the women, respectively. Support group membership and current use of antiretroviral prophylaxis did not impact on the quality of knowledge. Of the healthcare workers, 43.8% were professional nurses and 37.5% were lay counsellors. The majority (80.0%) felt satisfied with their knowledge of the PMTCT guidelines and 96.3% felt competent in managing HIV-infected pregnant women. Yet, there were important deficiencies in the knowledge of the guidelines.

Conclusion. In our study, the knowledge of PMTCT interventions was low in both clients and healthcare workers. This points to the need to improve quality of care in PMTCT services, especially with increasingly complex PMTCT interventions recommended by international policies.

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In the past few years, South Africa (SA) has made significant progress in the provision of prevention of mother-to-child transmission (PMTCT) of HIV services, both in the delivery of more efficacious PMTCT interventions and also an increase in the proportion of women receiving the interventions.[1] According to a UNAIDS report, ~95% of HIV-infected pregnant women in SA received some antiretroviral therapy (ART) intervention for PMTCT in 2010.[2] While progress has been made, there are still several challenges in scaling up PMTCT services in the SA public healthcare sector. These relate to coverage at different steps of the PMTCT cascade, and also to the quality of care rendered in the services. According to a qualitative study documenting women's experiences of accessing ART and PMTCT programmes in several facilities in SA, health system weaknesses impacted negatively on access.[3]

Healthcare system and patient factors are important in the scale-up and success of HIV programmes (including PMTCT)[4-7] and the availability of interventions alone is not sufficient to guarantee appropriate implementation and uptake.[4,5,8,9] Healthcare facilities need to be well-resourced with competent and motivated staff to provide the services, and there needs to be service uptake and treatment adherence by patients.[4-7] The providers' and patients' knowledge and attitudes are also important.[7,8] There is evidence to suggest that the patient-provider relationship may have an effect on decision-making during the antenatal period, and on the uptake of PMTCT interventions.[10] Yet, quality of care has not been a focus in most PMTCT services in SA; most are focused on increasing coverage in the PMTCT cascade. Several reviews have found poor performance and coverage in PMTCT programmes, despite the simplicity of some interventions; hence, the focus has been on increasing coverage.[5,11,12]

We conducted a cross-sectional survey to investigate key aspects of the quality of care in PMTCT services in antenatal clinics in Soweto, SA, focusing on the PMTCT programme knowledge and experiences of (*i*) healthcare workers and (*ii*) HIV-infected pregnant women accessing the services. This was performed against the backdrop of recently updated

PMTCT guidelines in 2008, when zidovudine (AZT) monotherapy became available for prophylaxis.[13]

Methods

The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand. All participants signed written informed consent to participate.

Until March 2008, all antenatal clinics in Soweto had only intrapartum single-dose nevirapine (NVP) for PMTCT for pregnant women who were not eligible for life-long ART. AZT was rolled out in phases across the antenatal clinics in March - October 2008. Prior to implementation of the guidelines, staff at the antenatal clinics, including lay counsellors, were trained on the new guidelines. The PMTCT service at each clinic was staffed by a professional nurse – a 'PMTCT co-ordinator' in charge of PMTCT services, including supervision of lay counsellors.

The study was conducted in November - December 2009; all facilities had at least 12 months of routine services under the 2008 PMTCT guidelines. Participating clinics were a mixture of low- and high-volume clinics, with 50 - 300 pregnant women presenting to each clinic per month. The HIV prevalence was 29% in 2009, and 15 - 20% of pregnant women were eligible for ART under the guidelines in place at the time (criterion: $CD4^+$ count ≤200 cells/μl).

HIV-infected pregnant women

Using consecutive sampling, ART-eligible and -ineligible HIV-infected pregnant women presenting to the selected antenatal clinics for repeat visits were interviewed using a structured questionnaire. Their experiences of being HIV-infected and their knowledge of available PMTCT interventions were determined. Eight key-knowledge questions were selected; each was assigned a score of 1 for a correct answer and 0 for an incorrect answer (maximum score of 8).

Healthcare workers

Healthcare workers from the same clinics were interviewed using a different questionnaire assessing their opinions and experiences of working in a PMTCT programme and their knowledge of the PMTCT guidelines. Consecutive sampling was used to select participants. Similar to the knowledge score devised for patients, a scoring system based on eight key questions was formulated. All interviewers received training on the questionnaire, and all were fluent in the local vernacular languages.

Data analysis

Data were analysed using Stata version 12.0. Descriptive statistics used employed means and standard deviations (SDs) or medians and interquartile ranges (IQRs) (for continuous variables) and proportions (for categorical variables). We compared knowledge scores on subgroups using Student's *t*-tests and Fisher's exact tests. All statistical tests were two-sided (alpha=0.05).

Results

HIV-infected pregnant women

A total of 201 HIV-infected pregnant women were interviewed (Table 1). The mean age was 27.7 years (SD ±4.8); median gestational age was 20 weeks (IQR 16 - 24) at the first antenatal visit and 32 weeks (IQR 24 - 32) at the time of the interview. The majority of women (71.5%) discovered that they were HIV-infected in the index pregnancy. Of the women diagnosed in a previous pregnancy, 84.1% (37/44) had previously taken single-dose NVP for PMTCT. A baseline $CD4^+$ cell count was available for 92.0% of the participants: median 395 cells/μl (IQR 294 - 500); mean 420 cells/μl (SD ±190).

Overall, 87.5% (175/200) of the women had disclosed their HIV status; the majority (90.9%; 159/175) had done so to their partners. This finding did not differ according to timing of HIV diagnosis. Of the women who discovered that they were HIV-infected in the index pregnancy, 68.0% had disclosed their status. There were various reasons for non-disclosure to the partner, including fear that the partner would leave, be violent, or accuse the woman of being unfaithful and infecting him with HIV. Less than half (45.3%) of the women knew their partner's HIV status. There was a significant difference in the knowledge of the partner's HIV status between women who had, and those who had not disclosed their HIV status: 89 (50.9%) v. 0 (0%) knew the partner's HIV status, respectively ($p<0.001$). Of the partners with known HIV status, 81.3% were HIV-infected.

Of the women, 62.7% and 43.3% had accurate knowledge on antenatal and intrapartum prophylaxis, respectively. Overall, 97.5% (196/201) had received some counselling, 67.7% had received more than one counselling session, 88.6% (178/201) felt that the time spent on counselling was adequate, and 33.5% were part of a support group. There was no significant difference in knowledge between pregnant women who were members of a support group (mean score 5.29; SD ±0.98)), and those who were not (mean score 5.18; SD ±1.41) ($p=0.542$) (Table 2). There was a significant difference in knowledge between women who were already receiving AZT prophylaxis (mean score 5.44; SD ±1.18) and those who were not (mean score 4.94; SD ±1.34) (Table 3) ($p=0.005$).

Table 1. Characteristics of pregnant women (*N*=201)

Characteristics	
Age (years), mean (±SD)	27.7 (±4.8)
Parity, median (IQR)	2 (1 - 2)
Gravidity, median (IQR)	2 (1 - 3)
Gestational age at booking (weeks), median (IQR)	20 (16 - 24)
Gestational age at interview (weeks), median (IQR)	32 (24 - 32)
$CD4^+$ cell count (cells/μl), median (IQR)	395 (294 - 500)
When HIV status discovered (*N*=200)	
Current pregnancy	143 (71.5)
Previous pregnancy	44 (22.0)
Outside of pregnancy	13 (6.5)
Disclosed HIV status (*N*=199), *n* (%)	175 (87.9)
To whom disclosed, *n* (%)	
Partner	159 (90.9)
Parent	61 (34.9)
Sibling	42 (24.0)
Friend	30 (17.1)
Other	5 (2.9)

SD = standard deviation; IQR = interquartile range.

Table 2. Characteristics and knowledge of pregnant women who were members of a support group (*N*=67) v. those who were not (*N*=133)

Members of a support group	Yes *n* (%)	No *n* (%)	*p*-value
Characteristics			
Age (years)			
<25	18 (26.9)	35 (26.3)	
25 - 35	47 (70.1)	91 (68.4)	
>35	2 (3.0)	7 (5.3)	0.764
Parity			
≤2	58 (86.6)	109 (81.9)	
3 - 5	9 (13.4)	24 (18.1)	0.407
When HIV status discovered:			
Current pregnancy	44 (65.7)	98 (74.2)	
Previous pregnancy	21 (31.3)	23 (17.4)	
Outside of pregnancy	2 (3.0)	11 (8.3)	0.043
Disclosed HIV status	56 (83.6)	118 (88.7)	0.356
Correct knowledge			
AZT prophylaxis			
Indication	66 (98.5)	124 (93.2)	0.143
Timing of initiation	64 (95.5)	119 (90.2)	0.188
Duration of use	26 (38.8)	99 (74.4)	<0.001
Prophylaxis during labour	18 (26.9)	69 (51.9)	0.001
Need for infant prophylaxis	63 (94.0)	111 (83.5)	0.036
Type of infant prophylaxis	7 (10.5)	18 (13.5)	0.553
Duration of infant prophylaxis	52 (77.6)	62 (39.1)	<0.001
Duration of exclusive breastfeeding	59 (88.1)	87 (65.4)	0.001
Overall score, mean (±SD)	5.3 (±0.98)	5.2 (±1.41)	0.542

AZT = zidovudine; SD = standard deviation.

Table 3. Difference in knowledge in pregnant women who were already on zidovudine (AZT) prophylaxis (*N*=114) and those who were not (*N*=86)

AZT prophylaxis	Yes *n* (%)	No *n* (%)	*p*-value
Correct knowledge			
Indication for AZT	111 (97.4)	79 (91.9)	0.137
Timing of AZT initiation	101 (88.6)	82 (95.4)	0.125
Duration of use of AZT	79 (69.3)	47 (54.7)	0.034
Intrapartum prophylaxis	63 (55.3)	24 (27.9)	<0.001
Score, mean (±SD)	5.44 (±1.18)	4.94 (±1.34)	0.005

Healthcare workers

Of the healthcare workers interviewed, 43.8% were professional nurses and 37.5% were lay counsellors; the majority (81.3%) had been in their current position for longer than a year (Table 4). Less than a half (47.5%) were satisfied with their working conditions. The most dissatisfaction was in terms of remuneration; only 28.8% were satisfied with their salary. In terms of workload, 80.0% of the workers felt that the new PMTCT programme increased their workload, and 92.5% felt that there was a need for more staff for the programme.

Most healthcare workers were satisfied with their knowledge of the PMTCT guidelines (80.0%) and with their general knowledge of HIV/AIDS (91.3%). In managing HIV-infected pregnant women, 96.3% were satisfied with their competence. Training received on the new guidelines was perceived to be adequate by 63.6%. The mean score for the workers' knowledge of the PMTCT guidelines was 5.15 (SD ±1.85): 5.41 (SD ±1.56) for professional nurses v. 5.19 (SD ±1.89) for lay counsellors (p=0.586). There was no significant difference between the mean score of those who were satisfied with their knowledge of the guidelines (5.29; SD ±1.88) and those who were not (4.56; SD ±1.63) (p=0.157) (Table 5). There was also no difference between the mean score of healthcare workers who thought that the training they received was adequate (5.10; SD ±1.9) and those who did not (5.14; SD ±1.7) (p=0.926).

Table 4. Characteristics of healthcare workers (*N*=80)

Characteristics	*n* (%)
Gender (*N*=79)	
Female	74 (93.7)
Staff categories	
Professional nurse	35 (43.8)
Auxiliary nurse	9 (11.3)
Lay counsellor	30 (37.5)
Other	6 (7.5)
Time in current position	
<6 months	7 (8.8)
6 months - 1 year	8 (10.0)
>1 - 5 years	33 (41.3)
>5 - 10 years	22 (27.5)
>10 years	10 (12.5)

A high percentage of healthcare workers (86.3%) thought that HIV-infected pregnant women did not disclose their HIV status. There were a number of adverse opinions about HIV-infected women having children: 21.3% of healthcare workers thought that HIV-infected individuals should not have children; 53.8% thought HIV-infected individuals were having too many children; and 46.3% thought that social grants were an incentive for HIV-infected women to have children.

Discussion

In this cross-sectional survey, several challenges were identified in the Soweto PMTCT programmes. The majority of pregnant women discovered that they were HIV-infected during pregnancy, and although disclosure to partners was high, less than half knew their partner's HIV status. There were important deficiencies in the

Table 5. Characteristics and knowledge of healthcare workers who were satisfied with their knowledge of PMTCT (*N*=64) v. those who were not (*N*=16)

Satisfied with knowledge of PMTCT	Yes, *n* (%)	No *n* (%)	*p*-value
Characteristics			
Staff categories			
Midwife	14 (21.9)	6 (37.5)	
PMTCT coordinator	10 (15.6)	0 (0)	
PCR nurse	4 (6.1)	2 (12.5)	
Lay counsellor	28 (43.8)	2 (12.5)	
Other	8 (12.5)	6 (37.5)	
Time in current position			
<6 months	4 (6.3)	3 (18.8)	
6 months - 1 year	7 (10.9)	1 (6.3)	
2 - 5 years	30 (46.9)	3 (18.8)	
6 - 10 years	19 (29.7)	3 (18.8)	
>10 years	4 (6.3)	6 (37.5)	
Correct knowledge			
Single-dose NVP			
Efficacy	55 (85.9)	11 (68.8)	0.211
Repeat in same pregnancy	52 (81.3)	10 (62.5)	0.410
Use in subsequent pregnancies	51 (79.7)	12 (75.0)	0.933
ART use in pregnancy	44 (68.8)	8 (50.0)	0.191
Sero-conversion during pregnancy	42 (65.5)	10 (62.5)	0.754
Exclusive breastfeeding and risk of MTCT	26 (40.6)	9 (56.3)	0.190
Extended breastfeeding and risk of MTCT	50 (78.1)	12 (75.0)	0.704
Contraception for HIV-infected women	19 (29.7)	1 (6.3)	0.105
Overall score, mean (±SD)	5.3 (±1.88)	4.6 (±1.63)	0.157

PMTCT = prevention of mother-to-child transmission of HIV; PCR nurse = nurse responsible for HIV PCR tests in infants; NVP = nevirapine; ART = antiretroviral therapy; MTCT = mother-to-child transmission of HIV.

women's knowledge of the available PMTCT interventions, despite receiving counselling and their perception that the counselling that they received was adequate. Neither the number of counselling sessions received, nor participation in a support group, had an impact on the quality of knowledge.

Staff in the PMTCT programme felt well prepared and well informed prior to the rollout of the updated PMTCT programme. The majority thought that the training received was adequate and almost all felt confident about managing HIV-infected women; yet, there were several important gaps in the knowledge of the PMTCT guidelines. Job satisfaction was low, mostly in terms remuneration. Moreover, several staff members expressed negative opinions about HIV-infected women having children.

The findings of this cross-sectional survey have important implications for PMTCT programmes in SA. Routine HIV testing for women, and men, of reproductive age needs to be encouraged, and linkages to care provided for those who test HIV-positive. This is especially important in women who are ART-eligible, as they carry a high risk of mother-to-child transmission, and ART initiated preconception decreases this risk significantly.[14] It will be important to assess the impact of the SA national HIV counselling and testing (HCT) drive on testing outside of pregnancy.[15]

Unpublished data from the Soweto PMTCT programmes indicate that the number of pregnant women presenting for antenatal care with a known HIV-positive status and already receiving ART has increased in the past 2 years (C Mnyani, unpublished data). The rate of disclosure among HIV-infected pregnant women in this survey was higher than that reported for most of sub-Saharan Africa, but similar to the findings of another study conducted in SA.[16-18] Disclosure has been shown to be important in women's uptake and adherence to PMTCT interventions.[16]

Our data on the women's knowledge of PMTCT interventions suggest that the quality of counselling given can be improved. Incorrect information, and hence incorrect practices, will be harmful in the context of PMTCT and may significantly increase the risk of mother-to-child transmission. While health knowledge is only one component of quality of care, there is evidence to suggest that poor quality of counselling, which translates to poor patient knowledge, is an important contributing factor to non-adherence to PMTCT interventions.[5,19] Poor quality of counselling has been reported even in well-functioning PMTCT sites where counsellors, some nurses, had received structured training.[20] The SA public healthcare sector depends on the services of lay counsellors who receive a stipend, and also receive variable training. Counselling services are often interrupted, and there is evidence to suggest that this has a negative effect on PMTCT services.[21]

As we scale up PMTCT programmes and introduce more complex interventions, staff preparedness, including knowledge, needs to be improved.[22,23] There needs to be a review and standardisation of training providers, and also of training content. Support using trained peers who are experts in HIV care and management has been shown to be an important intervention in building capacity.[6] Negative staff attitudes towards HIV-infected women also need to be addressed. There is evidence that HIV-infected women who fear and/or experience stigmatisation may avoid participating in PMTCT programmes.[24]

Study limitations

While our findings do have important implications, there are several limitations to this survey. Like all questionnaire-based research, the results may have been influenced by reporting biases. In this case, participants may have felt social desirability to report satisfaction with their PMTCT-related knowledge, but this potential bias was unlikely to have influenced their ability to report factual knowledge correctly. In addition, although the study was conduced under a different set of PMTCT policy guidelines, the findings are particularly noteworthy given the subsequent implementation of more complex PMTCT guidelines in SA and many other parts of Africa. The study was conducted in one urban community of high HIV prevalence and with established PMTCT services, and the results should be generalised to other settings with caution. Healthcare workers were generally reluctant to be interviewed, and this warrants further investigation. Also, we used a consecutive sampling strategy; although routine in this form of health services research, this may be more prone to bias than random sampling strategies. There are plans to perform a similar survey to assess experiences with, and knowledge of the latest SA PMTCT guidelines. Despite the limitations, there are strengths to the survey that warrant merit, including the large number of pregnant women and different categories of staff who were interviewed.

Conclusion

There are still several challenges in PMTCT services. Most importantly, knowledge of PMTCT interventions is surprisingly low in both clients and healthcare providers, and there is a need for enhanced interventions to improve the quality of care in PMTCT services. This is particularly important as PMTCT interventions become more complex during the ante- and postnatal periods.

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Timing of antenatal care and ART initiation in HIV-infected pregnant women before and after introduction of NIMART

C N Mnyani,[1,2] MB ChB, FCOG; **E Marinda**,[3,4] PhD; **H Struthers**,[2,5] MSc, MBA; **M Gulley**;[2] **R Machepa**;[2] **J McIntyre**,[2,6] MB ChB, FRCOG

[1] *Department of Obstetrics and Gynaecology and School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
[2] *Anova Health Institute, Johannesburg, South Africa*
[3] *Health and Development Africa, Mott MacDonald South Africa*
[4] *Epidemiology and Biostatistics Unit, School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
[5] *Department of Infectious Diseases, Faculty of Health Sciences, University of Cape Town, South Africa*
[6] *School of Public Health and Family Medicine, University of Cape Town, South Africa*

Corresponding author: *C N Mnyani (coceka.mnyani@wits.ac.za)*

In this review of routinely collected data from five community health centres in the Johannesburg Health District, we assess timing of antenatal care and antiretroviral therapy (ART) initiation in HIV-infected pregnant women before and after the introduction of nurse-initiated management of ART in antenatal clinics. There are important lessons to be learnt as we reflect on the South African prevention of mother-to-child transmission of HIV programme.

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It is widely acknowledged that the highest risk of mother-to-child transmission (MTCT) of HIV is in HIV-infected women with low CD4+ counts, who are eligible for antiretroviral therapy (ART).[1] Timely initiation of ART in this group is critical to decreasing paediatric HIV infection and HIV-related maternal morbidity and mortality.[2,3] ART initiation in pregnancy is also associated with better maternal immunological and virological outcomes compared with starting ART after pregnancy.[4]

Prior to the current prevention of MTCT (PMTCT) guidelines, criteria for ART initiation in pregnant women were based on a CD4+ count of ≤350 cells/μl, or World Health Organization (WHO) stage 3 or 4 disease regardless of CD4+ count.[5] Reflecting on the history of the PMTCT programme in South Africa, two of the main early challenges to initiating ART in pregnancy were that HIV treatment sites were physically separate from antenatal clinics and ART initiation was largely physician led.[6] This led to delays in referral and initiating treatment, and as a result, a significant proportion of ART-eligible pregnant women would go through pregnancy without starting treatment.[7] Nurse-initiated and managed ART (NIMART) in antenatal clinics was introduced to address these challenges, supported by evidence that integration of ART with antenatal care decreases time to initiation and increases the proportion of pregnant women initiated.[8-10] Pregnant women need to access antenatal care early for timeous treatment initiation.

This retrospective review of routinely collected data assesses timing of antenatal care and ART initiation in HIV-infected, eligible pregnant women presenting to five community health centres in the Johannesburg Health District.

Method

Time to initiation in pregnant women who presented prior to the introduction of NIMART was compared with those who presented after. Between October 2010 and March 2012, a total of 1 436 ART-eligible pregnant women were identified.

The study was approved by the University of Cape Town's Human Research Ethics Committee, and by the Gauteng Province office for policy, planning and research.

Results

Characteristics of the women are presented in Table 1. The mean gestational age when accessing antenatal care was 19.2 weeks (standard deviation (SD) of 6.6), and the mean gestational age at ART initiation was 24.6 weeks (SD 6.2). There was no significant reduction in time to initiation after the introduction of NIMART. Overall, the median time to initiation prior to the introduction of NIMART was 3.4 weeks (interquartile range (IQR) 2.0 - 5.9) whereas after the introduction of NIMART, it was 3.0 weeks (IQR 1.4 - 5.4). Assessing data from individual clinics, there was evidence of an increase in time to starting ART in some facilities. However, overall there was an increase in the proportion of eligible pregnant women who started ART after the introduction of NIMART, in all the facilities. Data on pregnancy outcomes were

Table 1. Baseline characteristics and timing of ART initiation

	Facilities				
	A	B	C	D	E
Baseline CD4⁺ count (cells/µl)					
Mean (±SD)	211 (±85)	223 (±86)	215 (±87)	240 (±112)	228 (±81)
Median (IQR)	214 (151 - 284)	234 (147 - 299)	225 (152 - 286)	245 (174 - 299)	235 (169 - 296)
Range	15 - 344	27 - 350	23 - 350	25 - 650	45 - 351
Gestational age at 1st antenatal visit (weeks)					
Mean (±SD)	20.7 (±6.4)	17.4 (±6.2)	19.9 (±5.9)	18.1 (±6.9)	19.5 (±6.9)
Median (IQR)	20 (16 - 24)	18 (12 - 20)	20 (16 - 24)	16 (12 - 24)	20 (15 - 24)
Range	8 - 36	4 - 30	8 - 32	4 - 36	5 - 36
Gestational age at ART initiation (weeks)					
Mean (±SD)	25.4 (±6.4)	22.0 (±5.8)	24.3 (±5.5)	24.6 (±6.6)	25.1 (±6.3)
Median (IQR)	25 (21 - 30)	21 (18 - 27)	25 (20 - 28)	24 (20 - 30)	25 (21 - 30)
Range	12 - 37	8 - 34	14 - 36	11 - 39	10 - 38
Time to initiation prior to NIMART (weeks)					
Mean (±SD)	1.6 (±0.5)	4.0 (±2.7)	5.5 (±2.5)	2.6 (±0.8)	3.3 (±1.8)
Median (IQR)	1.9 (1.3 - 2.3)	3.1 (2.0 - 5.1)	5.6 (1.7 - 7.0)	2.4 (1.9 - 3.2)	2.8 (1.9 - 5.1)
Range	1.0 - 2.3	0.9 - 10.6	1.1 - 12.6	1.6 - 4.0	1.3 - 5.9
Time to initiation after NIMART (weeks)					
Mean (±SD)	2.0 (±1.9)	4.4 (±3.3)	3.8 (±3.5)	5.7 (±3.8)	6.6 (±3.9)
Median (IQR)	1.3 (1.0 - 2.3)	3.7 (2.4 - 5.1)	2.1 (1.4 - 4.9)	4.1 (3.0 - 8.1)	6.0 (4.0 - 8.8)
Range	0 - 9.7	0 - 18.9	0.7 - 15.7	0.7 - 18.4	0.6 - 18.7

ART = antiretroviral therapy; SD = standard deviation; IQR = interquartile range; NIMART = nurse-initiated management of antiretroviral therapy.

available for 61.8% of the women, namely 881 live births, 1 neonatal death, 4 stillbirths and 2 miscarriages. Of the 881 infants tested at ~6 weeks of age, only two (0.2%) were HIV-infected.

Discussion

The data provided an interesting reflection on the PMTCT programme. While pregnant women in the review accessed antenatal care relatively late, in the second trimester, there were no lengthy delays in initiating ART in patients who reached the HIV management sites, even prior to the introduction of NIMART in antenatal clinics. Despite several challenges in the antiretroviral (ARV) roll-out in the past few years, the data showed that there were pockets of excellence. In the facilities where the intervention increased time to initiation, there are several possible reasons for this: there could have been a shortage of skilled and properly trained staff to manage ART-eligible pregnant women in the antenatal clinics; and during the early stages of the introduction of NIMART, antenatal clinics were only able to initiate treatment on select days.

Conclusion

While the updated PMTCT guidelines recommend starting all HIV-infected pregnant women on ART at the first antenatal visit, to reduce delays in initiating therapy, focus needs to shift from quantity to quality. As the number of patients on treatment increases, clinicians need to ensure that they provide high-quality services with appropriate clinical and laboratory monitoring, and long-term retention of patients in care.

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GLOBALIZATION AND HEALTH

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Patient factors to target for elimination of mother-to-child transmission of HIV

Coceka N Mnyani[1,2*], Adonia Simango[2], Joshua Murphy[2], Matthew Chersich[3,4,5] and James A McIntyre[2,6]

Abstract

Background: There is great impetus to achieve elimination of mother-to-child transmission of HIV (eMTCT) by 2015, and part of this is to identify factors to target to achieve the goal. This study thus identified key patient factors for MTCT in a high HIV prevalence setting in Johannesburg, South Africa. Between November 2010 and May 2012, we conducted a case–control study among HIV-infected women with HIV-infected (cases) and uninfected (controls) infants diagnosed around six weeks of age as part of routine, early infant diagnosis. Mothers and infants were identified through registers in six healthcare facilities that provide antenatal, postpartum and HIV care. Structured interviews were conducted with a focus on history of HIV infection, antenatal, intrapartum and immediate postpartum management of the mother-infant pair. Patient-related risk factors for MTCT were identified.

Results: A total of 77 women with HIV-infected infants and 154 with –uninfected infants were interviewed. Among HIV-infected cases, 13.0% of the women knew their HIV status prior to conception, and 83.1% reported their pregnancies as unplanned. Antenatal antiretroviral coverage was high in the control group – only 1/154 (0.7%) reported receiving no prophylaxis or treatment compared with 17/74 (22.9%) of cases. In multivariate analysis, key patient-related risks for HIV transmission were: unknown HIV status prior to conception (adjusted odds ratio [AOR] = 6.6; 95% CI = 2.4 – 18.4; $p < 0.001$); accessing antenatal care after 20 weeks gestation (AOR = 4.3; 95% CI = 2.0 – 9.3; $p < 0.001$); less than 12 years of formal education (AOR = 3.4; 95% CI = 1.6 – 7.5; $p = 0.002$); and unplanned pregnancy (AOR = 2.7; 95% CI = 1.2 to 6.3; $p = 0.022$). Mean age at first HIV test was 6.6 weeks (SD = 3.5) for infants who were diagnosed as HIV-infected, and the mean age at antiretroviral treatment initiation was 10.8 weeks (SD = 4.4). HIV-uninfected infants were diagnosed at a mean age of 6.0 weeks (SD = 0.2).

Conclusions: Undiagnosed maternal HIV infection prior to conception, unplanned pregnancies, delays in accessing antenatal care, and low levels of education were the most significant patient risk factors associated with MTCT. While the emphasis has been on increasing availability and coverage of efficacious antiretroviral regimens, and strengthening health systems within eMTCT initiatives, there is a need to also address patient-related factors if we are to achieve eMTCT goals.

Keywords: Elimination of mother-to-child transmission, HIV and pregnancy, Patient factors

Background

In 2009, UNAIDS, the Joint United Nations Programme on HIV/AIDS, made a global call for the elimination of mother-to-child transmission of HIV (eMTCT) by 2015, and there is great impetus to achieve the target as the deadline approaches [1-3]. Coupled with this was a call for a 50% reduction in HIV-related maternal mortality [1]. Elimination is defined as a 90% reduction in the number of new paediatric HIV infections, or a MTCT rate below 5% [1]. Great strides have been made in the field of prevention of mother-to-child transmission (PMTCT), both globally and in South Africa [3]. Rates of HIV transmission to children have decreased substantially – among the 21 Global Plan priority countries in sub-Saharan Africa, including South Africa, MTCT rates have decreased by around a half or more since 2009 [3]. This decrease is largely attributable to the availability of efficacious antiretroviral regimens at high coverage [3].

* Correspondence: Coceka.Mnyani@wits.ac.za
[1]Department of Obstetrics and Gynaecology, and School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
[2]Anova Health Institute, 12 Sherborne Road, Parktown, 2193 Johannesburg, South Africa
Full list of author information is available at the end of the article

However, success of PMTCT initiatives depends on more than the availability of antiretrovirals. The World Health Organization's (WHO's) comprehensive strategic approach for PMTCT also includes primary prevention of HIV infection; prevention of unintended pregnancies in HIV-infected women; and a family-centred approach to HIV care [4]. There is also a need to integrate PMTCT into routine maternal, neonatal, child and women's health services [5]. Several studies have demonstrated the benefits of integration of services, in both the delivery and utilisation of services [5].

Patient and health system factors are critical in determining success of PMTCT programmes and attainment of eMTCT goals [6-9]. While there are effective biomedical interventions for HIV and pregnancy prevention, patients need timely access to care and then to utilise the interventions appropriately. Women who are already pregnant need to access healthcare early and if identified as HIV-infected, be initiated on antiretrovirals timeously and also adhere to therapy during the ante- and postpartum periods. While it is well-recognised that the highest risk of MTCT is among women with undiagnosed and/or untreated HIV infection, and also in known HIV-infected women who either do not start or delay treatment, there are still health system factors that fail to address these [10-13]. Also, antenatal and HIV services remain largely segregated, and there is still failure to prioritise pregnant women for initiation of antiretroviral therapy (ART) [12,13]. Pregnant women may not access antenatal care early; may decline ART; or fail to adhere to antiretroviral regimens. This study thus focused on, and identified key patient-centred risks for MTCT in a high HIV prevalence setting in Johannesburg, South Africa.

Methods

Study design

Between November 2010 and May 2011, consecutive mothers with HIV-infected infants who were referred to a paediatric HIV clinic for ART initiation were enrolled (cases). Mothers of uninfected infants (controls), identified through clinic registers, were recruited at five primary care facilities between December 2011 and May 2012. Mothers of both HIV-infected and –uninfected infants were all HIV-infected. The decision to obtain controls was taken after analysis of data on mothers of infected infants showed interesting patterns on patients' health-seeking behaviour and care accessed during pregnancy. The controls and cases were similar with respect to site of antenatal care, place and date of delivery, and where infant HIV testing was done. Both group of infants were also born in the same period, but controls were recruited slightly later than cases.

Twice as many controls as cases were enrolled and a convenience sample was selected. The initial plan was to enrol more controls, but due to difficulties with recruitment of mothers with uninfected infants and concerns about recall bias from the lengthy period between the cases and controls, the ratio was decreased to 2:1. Of the controls that were contacted, a quarter of them could be reached and were available to be interviewed. There were several reasons why mothers of uninfected infants were unavailable for interview, and these included the women having returned to work and unable to take time off; migration; and contact number unavailable or changed. The 2:1 ratio was deemed adequate for detecting differences between the two groups.

Participants were interviewed using a structured questionnaire and data on the following parameters were collected from the interviews: history of HIV infection – whether preconception HIV testing was done, and whether ART was initiated in those identified as HIV-infected; baseline CD4 cell count; knowledge of partner's HIV status; whether the pregnancy was planned; previous exposure to PMTCT interventions; antenatal and intrapartum prophylaxis; infant prophylaxis and feeding option; and timing of early infant diagnosis. Additional data were collected on management of infant HIV infection in cases of HIV-infected infants. Infants diagnosed as either HIV-infected or –uninfected, through early infant diagnosis, were identified through facility registers. Interviewers were fluent in the local vernacular languages used in the interviews. Internal audit processes were conducted on the study data, including validation of information collected from interviews against facility records.

Study setting

Within routine care, all facilities in Soweto, Johannesburg where the women accessed care provided PMTCT services during the antenatal and postnatal periods. HIV testing was routinely offered to all pregnant women, and if HIV-infected, either antiretroviral prophylaxis or lifelong treatment was initiated, depending on a woman's CD4 cell count. All antenatal clinics provided antiretroviral prophylaxis, while ART initiation for those eligible occurred only at selected sites over the study period. Postnatal testing was offered if a woman's HIV status was unknown, and also in those who tested HIV negative during pregnancy and did not have a repeat test antenatally. A free six months' supply of infant formula was given to HIV-infected women who elected to formula feed. All health facilities offered routine early infant diagnosis around six weeks of age, but management of infected infants occurred only at one paediatric HIV clinic at the time of the study.

Over the study period, uptake of HIV testing within the antenatal clinics was 99%, and the HIV prevalence in pregnant women was around 25% (unpublished programme data). MTCT risk around six week was 2.7% in

2010 and 1.1% in 2011. The study period coincided with PMTCT guideline changes (Table 1); most notable was the initiation of zidovudine prophylaxis from an earlier gestational age and an increase in CD4 cell count threshold for ART initiation, from 200 to 350 cells/mm^3. There was also a transition from zidovudine to nevirapine syrup for infant prophylaxis.

Data analysis

Data were analysed with Stata® version 12.0 (Stata Corporation, College Station, USA). Continuous data were summarized using means and medians as appropriate. Standard statistical methods were utilised to assess differences between children with and without HIV infection. Descriptive analyses included variable description and cross tabulation, and inferential analyses included tests of association by chi-square test. Multivariate logistic regression analysis was done to identify factors associated with risk of MTCT and results presented as adjusted odds ratios (AOR) with 95% confidence intervals (CI). Potential confounding factors associated with the outcome and exposure ($p < 0.10$) were included in the initial multivariate logistic regression models using backward-fitting. Variables with $p < 0.05$ were used in the final model, and those that did not markedly alter the model fit were removed.

Ethics approval

The study was approved by the University of the Witwatersrand's Human Research Ethics Committee, and also by the Gauteng Provincial Department of Health. Written informed consent was obtained from study participants.

Results

Demographics and antenatal parameters

In total, 77 women with HIV-infected infants (cases), and 154 mothers with HIV-uninfected infants (controls) were interviewed. Mean age for the cases was 28.1 years (standard deviation (SD) = 6.4), and for the controls 30.9 years (SD = 5.5), $p = 0.001$; (Table 2). The proportion of participants with under 12 years of formal education was 68.8% for the cases and 44.8% for the controls, $p < 0.001$. Median parity and gravidity were two for both groups. Among women with HIV-infected infants, 83.1% (64/77) had unplanned pregnancies, compared with 56.5% (87/154) of women with uninfected infants, $p < 0.001$. Median gestational age at first antenatal visit was 16.0 weeks (interquartile range (IQR) =12 – 20) for controls, and 24.0 weeks (IQR = 16 – 26) for cases, $p < 0.001$. The proportion of women who did not access any antenatal care was 1.9% (3/154) for controls and 14.3% (11/77) for cases. Of the women who did not access antenatal care and had an HIV-infected infant, six knew that they were HIV-infected. Most reasons for not accessing antenatal care revolved around fear of stigmatisation by either health workers or family.

History of HIV infection

Of women with uninfected infants, 43.5% (67/154) knew that they were HIV-infected prior to the index pregnancy compared to 13.0% (10/77) of women with infected infants, $p < 0.001$. Slightly more than half of the women with HIV-uninfected infants knew their partner's HIV status (56.5%; 87/154), and of the known, three-quarters were HIV-infected (73.6%), while in the group with infected infants, 37/77 (48.1%) knew their partner's HIV status, and 94.6% were HIV-infected. Median baseline CD4 cell count was 315 cells/mm^3 (IQR: 203 – 420) for the cases (n = 58), and 355 cells/mm^3 (IQR: 210 – 480) for the controls (n = 111). Of women with HIV-infected infants, 22.9% (17/74) received no antenatal antiretroviral prophylaxis or treatment, while in the group with uninfected infants only one reported no antenatal antiretrovirals. In the cases, 11.7% (9/77) of the women received antenatal ART, while 42.9% (66/154) received ART in the control group.

Intrapartum and postpartum management

A proportion of women in both groups reported receiving no intrapartum antiretrovirals – 11 (7.1%) in the

Table 1 Summary of key changes in South African PMTCT guidelines

Date	PMTCT guidelines
2002 to February 2008	Only intrapartum and infant sdNVP available for prophylaxis
2004	ART became available; CD4 threshold for ART initiation 200 cells/mm^3
February 2008	Maternal AZT (from 28 weeks gestation) and infant AZT, for prophylaxis. One to four weeks of infant AZT, depending on duration of maternal prophylaxis or treatment
April 2010	Gestational age for AZT initiation reduced to 14 weeks, CD4 threshold for ART initiation increased to 350 cells/mm^3, Infant NVP syrup prophylaxis introduced for breastfeeding period – six weeks if preconception initiation of maternal ART; extended to cover breastfeeding period if no maternal ART
April 2012	Withdrawal of free infant formula, EFV-based ART regimen approved for pregnant women
April 2013	EFV-based FDCs for prophylaxis and treatment introduced

sdNVP single-dose nevirapine; AZT zidovudine; EFV efavirenz; FDCs fixed-dose combinations.

Table 2 Demographics and antenatal parameters of cases and controls

Characteristics	Cases (n = 77)	Controls (n = 154)	*P*-value
Age, mean (SD)	28.1 (6.4)	30.9 (5.5)	0.001
Parity, median (IQR)	2 (1 – 5)	2 (1 – 7)	0.514
Gravidity, median (IQR)	2 (1 – 6)	2 (1 – 7)	0.054
Formal education, n (%)			
≤11 years	53 (68.8)	69 (44.8)	<0.001
Knew HIV status prior to index pregnancy, n (%)	10 (13.0)	67 (43.5)	<0.001
Knew partner's HIV status, n (%)	37 (48.1)	87 (56.5)	0.230
Unplanned pregnancy, n (%)	64 (83.1)	87 (56.5)	<0.001
Gestational age at 1st antenatal visit, weeks, n (%)			
≤20 weeks	32 (45.5)	115 (78.2)	<0.001
*Baseline CD4 count (cells/mm^2), n (%)			
≤350	34 (58.6)	54 (48.7)	0.220
Antenatal antiretrovirals received, n (%)			
AZT	48 (62.3)	83 (53.9)	<0.001
ART	9 (11.7)	66 (42.9)	
None	17 (22.9)	1 (0.7)	
Unknown	3 (3.9)	4 (2.6)	
Intrapartum antiretrovirals received, n (%)			
sdNVP	7 (9.1)	35 (22.7)	<0.001
sdNVP and AZT	43 (55.8)	15 (9.7)	
AZT only	13 (16.9)	36 (23.4)	
ART	8 (10.4)	57 (37.0)	
None	6 (7.8)	11 (7.1)	

*CD4 cell count known for 75.3% of cases (n = 58) 72.1% of controls (n = 111).

group with HIV-uninfected infants, and 6 (7.8%) in the group with infected infants. Fewer women with infected infants (68/77; 88.3%) than with uninfected infants elected to formula feed (147/154, 95.4%; $p = 0.044$). In the control group, 147/148 (99.3%) infants received prophylaxis, while 72/76 (94.7%) of the cases did. The mean infant age at first HIV test was 6.0 weeks (SD = 0.2) for the uninfected infants, and 6.6 weeks (SD = 3.5) for the infected infants, $p = 0.200$. At time of interview, 73/77 (94.8%) of the infected infants had already been initiated on ART, and the mean age at ART initiation was 10.8 weeks (SD = 4.4; Table 3).

Risk factors for MTCT

In multivariate analysis, unknown HIV status prior to conception, unplanned pregnancy, accessing antenatal care after 20 weeks gestation, and less than 12 years of formal education were all identified as important risk factors for MTCT (Table 4). The odds were 6.6 times more with an unknown HIV status, while there was a 4.3 fold increase in women presenting for antenatal care beyond 20 weeks gestation. HIV transmission was 3.4 times more likely among women with less than 12 years of formal education than those with more education (AOR 95% CI = 1.6 – 7.5), and with unplanned pregnancies it was 2.7 fold higher (AOR 95% CI = 1.2 – 6.3).

Discussion

This study identified several patient groups at high risk of MTCT. These were patients with unknown HIV status prior to conception; those with unplanned pregnancies; accessing antenatal care after 20 weeks gestation; and having less than 12 years of formal education. Slightly more mothers of HIV-infected infants elected to breastfeed – 11.7% compared to 4.6% of mothers with – uninfected infants, but this difference was not significant. While causality may not be definitively ascertained from this study, the findings highlight several important risk factors that must be targeted for eMTCT; availability of antiretrovirals alone is not enough.

Of women with HIV-infected infants, only 13.0% knew that they were HIV-infected prior to conception. The lowest risk of MTCT is with preconception ART and the duration of ART is directly related to MTCT risk [14,15]. HIV-infected women who initiate ART prior to pregnancy are more likely to be virally suppressed at the time of delivery – the most important determinant of MTCT. Even if ART is not initiated prior to pregnancy, there is an increased likelihood of women with known HIV status accessing PMTCT care [16]. For those women who initiate ART during pregnancy, earlier initiation of treatment is associated with a decreased risk of MTCT, and each additional week of treatment confers a cumulative reduction in risk [15,17,18].

If we are to eliminate MTCT, there needs to be routine HIV testing for all women and men of reproductive age, and ART initiation for those found to be HIV-infected and eligible for treatment. South Africa implemented large population-based HIV-testing campaigns in recent years, but it is uncertain if these have impacted on PMTCT and linkage to care. However, recent unpublished programmatic data from the Soweto PMTCT programme, where this study was conducted, shows an increasing proportion of pregnant women presenting with an already known HIV status, and an increasing number already on treatment. As HIV testing and treatment programmes expand and become functional, more women will know their HIV status preconception. They will however still need to present for antenatal care timeously for early initiation and continuation of appropriate PMTCT interventions. Healthcare services need to

Table 3 Infant delivery and HIV diagnosis details

Variable	Cases (n = 77)	Controls (n = 154)	*P*-value
Mode of delivery, n (%)			
NVD	48 (62.3)	106 (68.8)	0.690
C-section	29 (37.7)	46 (29.9)	
Assisted delivery	0 (0.0)	2 (1.3)	
*Birth weight (g), median (IQR)	2850 (2450 – 3100)	2950 (2600 – 3200)	0.122
Infant antiretroviral prophylaxis, n (%)			
Prophylaxis received*	72 (94.7)	147 (99.3)	0.030
Infant feeding method, n (%)			
Breastfeeding	9 (11.7)	7 (4.6)	0.044
Formula feeding	68 (88.3)	147 (95.4)	
Age at 1st HIV test, mean weeks; (SD)	6.6 (3.5)	6.0 (0.2)	0.200
Infant age at HIV-positive diagnosis, mean weeks (SD)	9.0 (4.2)	—	—
Infant age at ART initiation, mean weeks (SD)	10.8 (4.4)	—	—

NVD normal vaginal delivery; C-section caesarean section.
*Prophylaxis received: AZT syrup or NVP syrup; n = 76 for cases and n = 148 for controls.
*Birth weight, n = 158 for controls – 4 sets of twins.

be able to manage the increased demand for both HIV testing and initiation of ART in those found to be eligible.

One area that is under-researched, but increasingly shown to be important in the success of PMTCT interventions, is male partner involvement [19-21]. Encouraging male partners to be involved in antenatal care, including routine HIV testing for themselves, has been shown to increase the likelihood of HIV-infected pregnant women accessing and adhering to treatment [19,20]. More importantly, it has been linked with a decreased risk of MTCT, and increased HIV-free survival in HIV-uninfected infants [21]. In our study, less than half of the women with infected infants knew their partners' HIV status, and of the known, the majority were HIV-infected; the proportions were marginally better for women with HIV-uninfected infants, but still suboptimal. There are several barriers to male partner involvement in PMTCT programmes, and more broadly in sexual and reproductive health services. Some of the most pertinent barriers identified include the cultural perception, and often societal norm, that men do not participate in reproductive health services and that the facilities where these are offered are not male-friendly [22]. Various strategies have been utilised to encourage more male partner participation, and amongst them, healthcare provider-driven initiatives to invite men to be part of reproductive and PMTCT programmes, and community-based strategies which include male peer support groups and community campaigns [22,23].

Table 4 Multivariate analysis of risk factors for MTCT

Factors	Adjusted odds ratio AOR (95% CI)	*P*-value
Unplanned pregnancy	2.7 (1.2 – 6.3)	0.022
≤ 11 years of formal education	3.4 (1.6 – 7.5)	0.002
First antenatal visit after 20 weeks	4.3 (2.0 – 9.3)	<0.001
Unknown HIV status prior to index pregnancy	6.6 (2.4 – 18.4)	<0.001

Rates of unplanned pregnancies were high, especially amongst women who had infected infants – 83.1% of the pregnancies were unplanned. Family planning, and consequently prevention of unintended pregnancies, has long been the most underutilised PMTCT intervention, with only modest progress to date [24]. In addition to decreased risk of MTCT, planned pregnancies are also associated with better obstetric outcomes, with decreased maternal morbidity and mortality [24]. There remains a high unmet need for contraception among HIV-infected women, and even in those who have access to reproductive health services, rates of unplanned pregnancies remain high [25,26]. Integration of reproductive health and PMTCT is one of the suggested strategies for improving the reproductive health outcomes of HIV-infected women [27]. There is however a need for stronger programmatic efforts and implementation research for integration to work [27].

Timing of antenatal care influences diagnosis and appropriate management of maternal HIV infection. In our study, accessing antenatal care beyond 20 weeks gestation was associated with an increased MTCT risk. This is consistent with findings from other studies where late presentation for antenatal care delayed initiation of appropriate PMTCT interventions, increasing the risk of perinatal transmission [16,17]. Lack of integration of

antenatal and HIV services also contributes to the delay in HIV-infected women initiating treatment [28]. There are several reasons why pregnant women either do not access antenatal care, or delay doing so, and these include lack of access to care; poor knowledge about timing and need to present for care; and unavailability of services [29]. It is also important that once HIV-infected women access antenatal care, they remain in care. While adherence to ART has been shown to be higher prenatally than postpartum, there is still significant loss to follow-up in the PMTCT continuum of care, and patient and health system factors have been identified as contributing factors [16]. There is a need for targeted interventions, both prenatally and postpartum, to ensure that HIV-infected women remain in care.

While there is increased public knowledge of HIV infection, stigma remains a reality for many, especially women. In our study, there were women who knew that they were HIV-infected, but still did not access antenatal care due to fear of being stigmatised by either health workers or family. There's a need to address stigma at all levels, as it has been shown to impact health-seeking behaviour and adherence to treatment [30]. Patient information on PMTCT interventions should be simplified and reinforced at every opportunity; understanding and adherence to treatment need not depend on level of education. A low level of formal education was one of the risk factors for MTCT identified. Inadequate knowledge of PMTCT interventions among health workers was also highlighted in a cross-sectional survey assessing quality of care within the same Soweto programme as this study [31].

Despite the challenges identified, the study provides several reassuring findings. Routine early infant diagnosis, and ART initiation in those found to be HIV-infected were timeous. At the time of the study, 94.8% of the HIV-infected infants had already been initiated on ART, and the mean age at ART initiation was 10.8 weeks.

While this study makes an important contribution to our knowledge of the requirements for an effective PMTCT programme, and highlights the importance of patient factors as we work towards elimination of MTCT, there are limitations. Causality cannot be inferred between the negative patient factors identified and risk of MTCT. There was also a lag period between the interviews of cases and that of controls, and this could have contributed to recall bias amongst the controls as they were interviewed at a much later period post-delivery. The sample of controls might also not have been representative as there was a high percentage that could not be reached, and some of the infants might have died during the lag period as it is a recognised fact that despite being uninfected, the morbidity and mortality rate in HIV-exposed infants remains significant. We also relied on self-reported information, but this was found to be reliable when compared to hospital records.

Conclusions

Despite the limitations, the study provides important insights as we work towards eMTCT. As much as availability and implementation of efficacious PMTCT interventions are key in preventing HIV infection in children, individual patient factors are also important and need to be targeted. Undiagnosed maternal HIV infection prior to conception, unplanned pregnancies, delays in accessing antenatal care, and low levels of education were the most significant patient risk factors associated with MTCT in our study. The focus in resource-constrained settings has largely been on establishing functioning systems to facilitate implementation of efficacious PMTCT interventions, and great strides have been made in this regard, including in South Africa [24,32]. While continued strengthening of health systems is crucial, our study highlights the considerable importance of individual patient factors for further reducing paediatric HIV infections. There is a need for further research on why rates of unplanned pregnancies, and consequently considerable delays in accessing antenatal care, remain high. Also, why the rates of preconception HIV testing remain low in resource-constrained settings, despite the availability of interventions to address these factors.

Abbreviations

AIDS: Acquired Immune Deficiency Syndrome; AOR: Adjusted odd ratio; ART: Antiretroviral therapy; AZT: Zidovudine; CI: Confidence intervals; C-section: Caesarean section; EFV: Efavirenz; eMTCT: Elimination of mother-to-child transmission of HIV; FDCs: Fixed dose combinations; HIV: Human Immunodeficiency Syndrome; IQR: Interquartile range; MTCT: Mother-to-child transmission of HIV; NVD: Normal vaginal delivery; NVP: Nevirapine; PMTCT: Prevention of mother-to-child transmission of HIV; SD: Standard deviation; sdNVP: single-dose nevirapine; UNAIDS: Joint United Nations Programme on HIV/AIDS; WHO: World Health Organization.

Competing interests

We declare that we have no conflicts of interest.

Authors' contributions

CNM conceptualised the study and wrote the manuscript. AS performed the statistical analysis. MC helped to draft the manuscript. JM assisted with the statistical analysis. JAM participated in the study design and helped to draft the manuscript. All authors read and approved the final manuscript.

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Author details

[1]Department of Obstetrics and Gynaecology, and School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa. [2]Anova Health Institute, 12 Sherborne Road, Parktown, 2193 Johannesburg, South Africa. [3]Centre for Health Policy, School of Public

Health, University of Witwatersrand, Johannesburg, South Africa. [4]Wits Reproductive Health and HIV Research Institute, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa. [5]International Centre for Reproductive Health, Department of Obstetrics and Gynaecology, Ghent University, Ghent, Belgium. [6]School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa.

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Infant feeding knowledge, perceptions and practices among women with and without HIV in Johannesburg, South Africa: a survey in healthcare facilities

Coceka N. Mnyani[1,2,3*], Carol L. Tait[4], Jean Armstrong[5], Duane Blaauw[2], Matthew F. Chersich[6,7], Eckhart J Buchmann[1], Remco P. H. Peters[4] and James A McIntyre[4,8]

Abstract

Background: South Africa has a history of low breastfeeding rates among women with and without Human Immunodeficiency Virus (HIV). In this study, we assessed infant feeding knowledge, perceptions and practices among pregnant and postpartum women with and without HIV, in the context of changes in infant feeding and Prevention of Mother-to-Child Transmission of HIV (PMTCT) guidelines.

Methods: This was a cross-sectional survey conducted from April 2014 to March 2015 in 10 healthcare facilities in Johannesburg, South Africa. A total of 190 pregnant and 180 postpartum women (74 and 67, respectively, were HIV positive) were interviewed using a semi-structured questionnaire. Multiple regression analyses assessed factors associated with an intention to exclusively breastfeed, and exclusive breastfeeding of infants less than six months of age.

Results: Women with HIV had better overall knowledge on safe infant feeding practices, both in general and in the context of HIV infection. There were however gaps in knowledge among women with and without HIV. Information from healthcare facilities was the main source of information for all groups of women in the study. A greater percentage of women without HIV 80.9% (93/115), reported an intention to exclusively breastfeed, compared to 64.9% (48/74) of women with HIV, $p = 0.014$. Not having HIV was positively associated with a reported intention to breastfeed, Adjusted Odds Ratio (AOR) 3.60, 95% CI 1.50, 8.62. Other factors associated with a reported intention to exclusively breastfeed were prior breastfeeding experience and higher knowledge scores on safe infant feeding practices in the context of HIV infection. Among postpartum women, higher scores on general knowledge of safe infant feeding practices were positively associated with reported exclusive breastfeeding, AOR 2.18, 95% CI 1.52, 3.12. Most women perceived that it was difficult to exclusively breastfeed and that cultural factors were a barrier to exclusive breastfeeding.

Conclusions: While a greater proportion of women are electing to breastfeed, HIV infection and cultural factors remain an important influence on safe infant feeding practices. Healthcare workers are the main source of information, and highlight the need for accurate and consistent messaging for both women with and without HIV.

Keywords: Breastfeeding, Infant feeding, HIV, PMTCT, South Africa

* Correspondence: coceka.mnyani@wits.ac.za
[1]Department of Obstetrics and Gynaecology, School of Clinical Medicine, University of the Witwatersrand, 7 York Road, Parktown, 2193 Johannesburg, South Africa
[2]School of Public Health, University of the Witwatersrand, Johannesburg, South Africa
Full list of author information is available at the end of the article

Background

Safe infant feeding practices remain an integral part of prevention of mother-to-child transmission of HIV (PMTCT). The 2010 World Health Organization (WHO) guidelines on infant feeding in the context of HIV infection recommend that infant feeding practices should support the greatest likelihood of infant HIV-free survival, while also protecting against non-HIV morbidity and mortality [1]. Countries were encouraged to support one infant feeding option; either breastfeeding with antiretroviral (ARV) interventions, or avoidance of all breastfeeding by women with HIV [1]. Up until 2011, South Africa supported both options, with the provision of a free six months' supply of infant formula for women with HIV who elected to formula feed. Amidst much criticism about supporting two options and the likelihood of confusion and inappropriate feeding practices, South Africa then selected one strategy; that of promoting exclusive breastfeeding for women with HIV, and thus withdrew the provision of free infant formula [2–4]. The current recommendation is for women with HIV to breastfeed for up to 12 months, with provision of infant and maternal ARVs [5].

South Africa has a history of low breastfeeding rates among both women with and without HIV [6]. While breastfeeding initiation rates at birth are high, very few women exclusively breastfeed for six months, with cultural factors one of the main drivers of mixed feeding [6]. Even in the early years of the national PMTCT programme, a study done from 2002 to 2003 showed poor infant feeding practices among both women with and without HIV, with less than 10% exclusively breastfeeding at 12 weeks [7]. High rates of formula feeding were also reported among women with HIV, when free infant formula was available [8–10]. In a study done in Cape Town, over 90% of postpartum women with HIV reported ever using infant formula, including a large proportion of women who had also breastfed [8]. Also, in a large, national facility-based evaluation conducted in 2010, almost two-thirds of HIV exposed infants aged four to eight weeks were reported to have received infant formula and no breast milk [9].

Between 2010 and 2015, there have been several changes in infant feeding and PMTCT guidelines in South Africa, with the withdrawal of free infant formula, provision of extended infant and maternal ARV prophylaxis for breastfeeding women, and the most recent change in 2015 being the adoption of Option B+, lifelong antiretroviral therapy (ART) for all pregnant and postpartum women with HIV, regardless of the level of immune suppression or infant feeding mode [4, 5, 11]. Most of the available literature on infant feeding practices in South Africa predates implementation of these policy changes, and tends to focus on women with HIV. Hence, we conducted a cross-sectional survey in Johannesburg, South Africa, to evaluate infant feeding knowledge, perceptions, and practices among both women with and without HIV.

Methods

Study setting and participants

A survey was undertaken from April 2014 to March 2015 in Soweto, Johannesburg. Ten medium and high volume public healthcare facilities, with 50–100 first antenatal care visit patients per month, and providing both antepartum and postpartum care, were selected for the study. Five facilities were selected from each of the two sub-districts in Soweto, a densely populated low and middle income area. At the time of study, the HIV prevalence among pregnant women attending antenatal clinics in Soweto was approximately 29% (unpublished programme data). All pregnant women receive group counselling on infant feeding, with individual counselling also provided for women with HIV. Group and individual counselling on safe infant feeding practices is provided by trained lay-counsellors and professional nurses, and at the time of the study reflected the 2013 and 2015 South African PMTCT guidelines, which are adapted from the WHO guidelines on infant feeding in the context of HIV infection [1, 5, 11]. In both the 2013 and 2015 South African guidelines, the recommendation is for women with HIV to exclusively breastfeed for six months, with introduction of complementary food from six months and continued breastfeeding for up to 12 months [5, 11]. In the 2013 guidelines, there was provision for either extended infant or maternal antiretroviral prophylaxis for the duration of breastfeeding in women who did not need lifelong ART for their own health [11]. The current recommendation, based on the 2015 guidelines, is for all pregnant and breastfeeding women with HIV to be initiated on lifelong ART, regardless of level of immune suppression [5]. Women without HIV are counselled to exclusively breastfeed for six months, with introduction of complementary food from six months and continued breastfeeding for up to two years or more [5].

A systematic sampling procedure was used to recruit women with and without HIV during pregnancy and up to 12 months postpartum. Every fifth pregnant or postpartum client to enter the facility was invited to participate in the study, and if she declined the next client was recruited. Pregnant women were recruited if they were attending a follow-up antenatal visit, and postpartum if they were attending a clinic visit beyond the sixweeks visit. The study was approved by the University of the Witwatersrand Human Research Ethics Committee (No. M130801), and access to the facilities was granted by the Johannesburg District Health Department.

Data collection

Women who agreed to be part of the study, and were 18 years and older, were interviewed using a semi-structured questionnaire. All study participants provided written informed consent. Approximately 20 antepartum and 20 postpartum women were interviewed in each facility. The questionnaire was in English and the interviews were conducted by lay-educators who had a good understanding of the infant feeding guidelines as they provided PMTCT education sessions at the sites. The interviewers completed the questionnaire and were trained on how to explain the technical terms, and where necessary, translated from the English interview into the two predominant vernacular languages in Soweto, Sesotho and Zulu. A field manager and the study investigators provided supervision throughout the study period.

The questionnaire had subsections in the following order: demographics, self-reported HIV status and ART use if HIV-infected, infant feeding intentions among pregnant women and practices among postpartum women, and factors influencing the intentions and practices, sources of infant feeding information, general knowledge on infant feeding, perceptions on exclusive breastfeeding, knowledge of infant feeding in the context of HIV infection, and factors supportive of exclusive breastfeeding. The questions in the questionnaire were a mixture of open-ended and closed questions. The closed questions had predefined options of Yes/No, True/False, and multiple response items. The Food and Agriculture Organization of the United Nations (FAO) guidelines for assessing nutrition-related knowledge, attitudes and practices manual lists open-ended and closed questions as types of questions that can be used in infant feeding surveys [12].

In formulating the knowledge questions, we identified key items that are integral to core knowledge on safe infant feeding practices in general and in the context of HIV infection. The questions were based on the WHO definitions and guidelines on infant feeding, South African PMTCT guidelines and published literature [1, 5, 11, 13, 14]. Several studies on infant feeding, conducted in sub-Saharan Africa, have used questions based on WHO definitions and guidelines on infant feeding to assess knowledge in pregnant and postpartum women with and without HIV [7, 15–19]. In our survey, a total of 16 key-knowledge questions were selected for both pregnant and postpartum women (Table 1). Questions on general knowledge of safe infant feeding practices were asked first, followed by questions on infant feeding in the context of HIV infection, and the questions were ordered such that earlier questions in the questionnaire did not influence responses to later questions. Each question was assigned a score of 1 for a correct answer, and 0 for an incorrect answer, with a maximum score of 16. To assess perceptions on exclusive breastfeeding, we formulated four statements with response options of True, False and Don't know. The four statements were on perceived ease of exclusive breastfeeding and factors that impact on this practice. Our statements to assess perceptions on exclusive breastfeeding are similar to those used by Kafulafula et al. and Mogre et al. in assessing attitudes towards exclusive breastfeeding [19, 20].

Table 1 Questions on safe infant feeding practices

General knowledge questions on safe infant feeding practices
1. If one chooses to exclusively breastfeed, how long should it be for?
2. If one chooses to exclusively formula feed, how long should it be for?
3. If exclusive breastfeeding is the option chosen, what else can be given to the baby?
4. If exclusive formula feeding is the option chosen, what else can be given to the baby?
5. When an infant cries it always means that it's hungry.
6. Breast milk is better than formula milk.
7. Formula milk is almost as good as breast milk.
8. Infants who are breastfed are less likely to get infections.
9. All mothers should breastfeed for up to two years.
Questions on safe infant feeding practices in the context of HIV
1. Does the HIV-infected mother who is breastfeeding need to take any medication?
2. If she needs to take medication, what does she need to take?
3. If she takes medication, how long does she need to take it for?
4. Does the baby need to take medication during breastfeeding?
5. If the baby needs to take medication, what does it need to take?
6. If the baby takes medication, how long does it need to take it for?
7. With the HIV-infected mother, when is the infant tested again after stopping breastfeeding?

Data analysis

Study data were collected and managed using REDCap electronic data capture tools hosted at the University of the Witwatersrand, and analysed using Dell Statistica (data analysis software system), version 12, software.dell.com, Dell Inc. (2015) [21]. Means, with standard deviations (SD), and medians with interquartile ranges (IQR) were calculated for continuous data, and frequencies were determined for categorical data. Student's t-tests and Mann-Whitney tests were used for comparison of means and medians, respectively. Chi-squared and Fisher's exact tests were used for categorical data and statistical significance was accepted as the two-tailed $p < 0.05$. Multiple logistic regression analyses were done to determine associations between independent variables and the binary outcome of intention to exclusively breastfeed among pregnant women and exclusive breastfeeding among postpartum women with infants less than six months of age. Variables that had an association with the binary outcomes with a p - value of 0.20 or less in the bivariate analyses were included in the final multivariate model. Variables of particular interest in this study, such as HIV status and feeding knowledge scores, were also included in the final models, irrespective of their significance in the bivariate analyses. The Wald test statistic was used to assess the significance of association between the independent variables, and the intention and practice of exclusive breastfeeding.

Results

A total of 190 pregnant and 180 postpartum women met the inclusion criteria and were included in the final analysis. The demographic and socio-economic characteristics of study participants are presented in Table 2. Among pregnant women, 38.9% (74/190) were HIV positive, and 65/74 (87.8%) had disclosed their HIV status, 54/65 (83.1%) to their partner. The mean age of pregnant women with HIV was 29.3 ± 6.6 years, and 15.1% (11/73) were primigravida. Pregnant women without HIV were younger with a mean age of 27.0 ± 6.2 years ($p = 0.019$), and a greater proportion, 26.4% (29/110), were primigravida ($p = 0.070$). At the time of interview, the mean number of antenatal clinic visits attended was similar for both groups of pregnant women, 3.1 ± 1.0 for women with HIV and 3.0 ± 1.1 for women without HIV, $p = 0.375$. Among postpartum women, 67/180 (37.2%) were HIV positive, and 61 (91.0%) disclosed their HIV status, 82.0% (50/61) to their partner. Postpartum women without HIV were a mean 2.1 years younger than postpartum women with HIV, $p = 0.042$.

Infant feeding knowledge, intentions and perception among pregnant women

Pregnant women with HIV had better overall knowledge on safe infant feeding practices, scoring a mean two points higher than pregnant women without HIV, $p < 0.001$ (Table 3). This difference related both to better knowledge about infant feeding in the context of HIV and to general infant feeding practices. Women without HIV scored poorly on questions relating to definition and duration of exclusive breastfeeding and formula feeding, and also on questions related to antiretroviral prophylaxis for the HIV exposed infant.

A greater percentage of women without HIV, 80.9% (93/115), reported that they intended to exclusively breastfeed, compared to 64.9% (48/74) of pregnant women with HIV, $p = 0.014$ (Table 4). In the multiple logistic regression analysis (Table 5), prior breastfeeding experience and higher knowledge scores on safe infant feeding practices related to HIV were positively associated with a reported intention to exclusively breastfeed. HIV infection, older maternal age, and advanced gestation at the time of interview were all negatively associated with an intention to exclusively breastfeed. Not having HIV was positively associated with an intention to breastfeed, adjusted odds ratio (AOR) 3.60, 95% CI 1.50, 8.62, $p = 0.004$. Although not statistically significant, higher levels of education and having discussed infant feeding intentions were negatively associated with intended exclusive breastfeeding. There was no significant association between marital status, employment, living with parents and a reported intention to exclusively breastfeed.

The majority of women reported that their infant feeding choice was based on information received from attending antenatal clinics, 83.6% ($n = 73$) and 73.3% ($n = 116$) for women with and without HIV, respectively. However, 27 of the 74 women with HIV (36.5%), including 12 (44.4%) diagnosed during the index pregnancy, were influenced by their HIV status in deciding on an infant feeding option. Of these 27 women, 19 (70.4%) elected to formula feed,

Table 2 Characteristics of pregnant ($n = 190$) and postpartum women ($n = 180$)

	Pregnant women			Postpartum women		
	HIV infected	HIV uninfected	*p*-value	HIV infected	HIV uninfected	*p*-value
Socio-demographic variables						
Age in years, mean (SD)	29.3 (6.6)	27.0 (6.2)	0.019	29.7 (6.0)	27.6 (6.8)	0.042
Employed, *n* (%)	29/74 (39.2)	35/115 (30.4)	0.214	19/67 (28.4)	34/113 (30.1)	0.806
Level of education, *n* (%)						
≤ 11 years of school	37/74 (50.0)	33/116 (28.4)	0.006	34/67 (50.7)	37/113 (32.7)	0.009
Completed school	29/74 (39.2)	57/116 (49.1)		30/67 (44.8)	56/113 (49.5)	
Tertiary education	8/74 (10.8)	26/116 (22.4)		3/67 (4.5)	20/113 (17.7)	
House with electricity and water, *n* (%)	64/74 (86.5)	108/116 (93.1)	0.129	54/67 (81.8)	99/113 (87.6)	0.289
Living with parents, *n* (%)	17/72 (23.6)	44/112 (39.3)	0.028	24/67 (35.8)	45/112 (40.2)	0.562
Obstetric history						
Gestational age in weeks, mean (SD)	27.2 (8.9)	27.4 (7.8)	0.857	–	–	–
Infant age in months, mean (SD)	–	–	–	5.9 (3.0)	5.5 (3.0)	0.408
Number of previous pregnancies, median (IQR)	2 (1–2)	1 (0–2)	0.028	2 (1–3)	2 (1–2)	0.018
Ever breastfed, *n* (%)	42/74 (56.8)	61/116 (52.6)	0.573	49/67 (73.1)	58/110 (52.7)	0.007
Pre-pregnancy HIV diagnosis, *n* (%)	28/74 (37.8)	–	–	22/67 (32.8)	–	–
On ART, *n* (%)	69/74 (93.2)	–	–	58/66 (87.9)	–	–

Table 3 Infant feeding knowledge among pregnant ($n = 190$) and postpartum ($n = 180$) women

	Pregnant women			Postpartum women		
	HIV infected ($n = 74$)	HIV uninfected ($n = 116$)	p-value	HIV infected ($n = 67$)	HIV uninfected ($n = 113$)	p-value
[a]Mean score (SD)						
General infant feeding knowledge	7.0 (1.6)	6.1 (2.2)	0.001	6.4 (2.1)	6.5 (2.1)	0.639
HIV-related infant feeding knowledge	5.5 (1.2)	4.4 (1.7)	<0.001	5.7 (1.0)	4.0 (1.6)	<0.001
Overall knowledge	12.5 (2.3)	10.4 (3.3)	<0.001	12.1 (2.5)	10.6 (2.9)	0.001

[a]General knowledge scores are out of a maximum of 9, HIV-related knowledge out of 7 and overall knowledge out of 16

five (18.5%) reported that they would breastfeed for six months or less because of fear of infecting their infants, and three (11.1%) were undecided about what infant feeding option to choose.

The perception among both groups of pregnant women was that enough information was given in healthcare facilities to encourage mothers to exclusively breastfeed, 87.8% (65/74) among women with HIV and 86.8% (99/114) among women without HIV. However, the majority of pregnant women thought it was difficult to exclusively breastfeed and that most mothers do not practice exclusive breastfeeding (Table 7). Cultural factors and influence from elders in the family were perceived to be barriers to exclusive breastfeeding in both groups. About a third of both groups of pregnant women, 32.9% (24/73) of women with HIV and 35.3% (41/116) of women without HIV, thought that if a mother elects to formula feed, people will think that she has HIV.

Infant feeding knowledge, practices and perceptions among postpartum women

Differences were observed in overall knowledge between postpartum women with and without HIV (Table 3). Women with HIV had a mean 1.7 higher score on knowledge of safe infant feeding practices in the context of HIV infection, while the knowledge scores on general infant feeding were similar for both groups.

Among postpartum women, 53.7% (36/67) of women with HIV and 56.6% (64/113) of women without HIV had infants less than six months of age. The mean age of the infants less than six months was 3.6 ± 1.3 months and 3.2 ± 1.3 months for women with and without HIV, respectively, $p = 0.160$. There was no difference in the proportion that reported exclusive breastfeeding – 23/36 (63.9%) among women with HIV and 45/64 (70.3%) among women without HIV, $p = 0.509$ (Table 4). A total of 6/36 (16.7%) women with HIV reported that they were exclusively formula feeding, and 7/36 (19.4%) that they were mixed feeding. The results of the multiple regression analysis of factors associated with exclusive breastfeeding in postpartum women with infants less than six months of age are presented in Table 6. Higher scores on general knowledge of safe infant feeding practices were positively associated with exclusive breastfeeding, AOR 2.18, 95% CI 1.52, 3.12, $p < 0.001$. Although not statistically significant, having HIV was positively associated with exclusive breastfeeding. Women who were employed, single and had older infants had significantly lower odds of exclusive breastfeeding. There was no association between exclusive breastfeeding and level of education or living with parents among postpartum women.

For the majority of postpartum women, 72.2% (130/180), reported that the main source of information on infant feeding was that from healthcare facilities. Perceptions expressed on factors relating to exclusive breastfeeding

Table 4 Infant feeding intentions among pregnant women, and feeding practices in postpartum women

Infant feeding intentions (Antepartum)	HIV infected n (%)	HIV uninfected n (%)	p - value
Intention to exclusively breastfeed	48/74 (64.9)	93/115 (80.9)	0.014
Discussed infant feeding intention	67/74 (90.5)	105/116 (90.5)	0.995
With partner	55/67 (82.1)	83/105 (79.0)	0.676
With family	20/67 (29.9)	39/105 (37.1)	0.338
Infant feeding practices (Postpartum)	HIV-infected n (%)	HIV-uninfected n (%)	p-value
Exclusive breastfeeding, infants < 6 months	23/36 (63.9)	45/64 (70.3)	0.509
Any breastfeeding, infants ≥ 6 months	14/31 (45.2)	28/49 (57.1)	0.296
Discussed infant feeding decision	55/67 (82.1)	101/112 (90.2)	0.118
With partner	39/55 (70.9)	80/101 (79.2)	0.085
With family	25/55 (45.5)	41/101 (40.6)	0.890

Table 5 Multivariable logistic regression analysis of factors associated with intention to exclusively breastfeed among pregnant women

Factors	Adjusted odds ratios	95% confidence intervals	*p*-value
Maternal age (per year)	0.93	0.87, 0.99	0.033
Gestational age (per week)	0.94	0.90, 0.99	0.015
HIV-uninfected	3.60	1.50, 8.62	0.004
≥ 12 years of school	0.47	0.20, 1.07	0.070
Breastfeeding in previous pregnancy	3.86	1.61, 9.23	0.002
Discussed feeding intentions with someone	0.14	0.02, 1.16	0.068
General knowledge score (per unit increase)	1.04	0.84, 1.28	0.719
HIV-related knowledge score (per unit increase)	1.23	0.93, 1.63	0.004

Chi-square = 33.65; $R^2 = 0.159$; Log likelihood ratio = − 88.90

were similar to those of pregnant women (Table 7). Of postpartum women with HIV, 40.1% (26/65) thought that women who elect to formula feed would be thought of as having HIV, compared to 27.9% (31/111) of women without HIV, $p = 0.099$.

Discussion

Findings from our study suggest that infant feeding patterns among women with HIV have changed, following changes in infant feeding guidelines. A greater proportion of postpartum women with HIV, than reported previously in the South African literature, reported exclusive breastfeeding, and the majority of pregnant women with HIV reported an intention to breastfeed [6]. HIV infection was, however, still a significant factor associated with breastfeeding intentions. Pregnant women who expressed an intention to exclusively breastfeed, compared with other feeding methods, had 3.6 times increased adjusted odds of not having HIV. For all groups of women in the study, healthcare facilities were reported to be the main source of information on infant feeding, and influenced feeding intentions and practices. There were however important knowledge gaps on safe infant feeding practices among both pregnant and postpartum women. Women with HIV had higher knowledge scores than women without HIV, particularly for infant feeding in the context of HIV infection. The perception expressed by most women in the study was that it was not easy to exclusively breastfeed for six months, and that cultural factors and influence from elders in families prevented most mothers from exclusively breastfeeding. There was also a perception in about a third of the participants; those women who elect to formula feed will be perceived as having HIV. This perception on the association of formula feeding with having HIV has been reported previously, and was common when infant formula was available for free in South Africa, for women with HIV who elected to formula feed [22, 23]. Despite this perception, a number of pregnant women with HIV in our study reported an intension to formula feed because of fears of infecting their infants.

Table 6 Multivariable logistic regression analysis of factors associated with exclusive breastfeeding among postpartum women

Factors	Adjusted odds ratios	95% confidence intervals	*p*-value
Maternal age (per year)	1.09	0.98, 1.21	0.098
Infant age (per month)	0.59	0.38, 0.94	0.025
HIV-infected	1.94	0.44, 8.62	0.382
Not married or cohabiting	0.19	0.05, 0.77	0.020
Employed	0.08	0.02, 0.35	0.001
General knowledge score (per unit increase)	2.18	1.52, 3.12	< 0.001
HIV-related knowledge score (per unit increase)	0.74	0.50, 1.10	0.135

Chi-square = 50.40; $R^2 = 0.402$; Log likelihood ratio = − 37.48

We found high rates of reported exclusive breastfeeding among women with and without HIV. In a study done in Malawi, Kafulafula et al. [20] found higher parity, previous positive experience with breastfeeding and positive beliefs about exclusive breastfeeding all associated with a greater intention to exclusively breastfeed among women with HIV. In our study, similar to findings from the Malawian study, prior breastfeeding experience was associated with an intention to exclusively breastfeed. Although not significant, higher knowledge scores on safe infant feeding practices were also linked to a greater probability of an intention for breastfeed. Having HIV infection was associated with decreased adjusted odds of an intention to breastfeed, with a proportion of women with HIV reporting an intention to formula feed because of fears of infecting their infants. Similar to other studies, higher levels of maternal education and discussing infant feeding intentions with others were associated with decreased adjusted odds of an intention to exclusively breastfeed [8, 20]. Zulliger et al. [8] found that women with HIV, with lower levels of education, were more likely to express an intention to breastfeed. Women with higher levels of education are likely to be employed and hence be able to afford infant formula [20]. Disclosure of HIV status has been associated with decreased intended duration of breastfeeding among women with HIV, perhaps because women fear disapproval of extended breastfeeding with the risks of HIV transmission, but this was not significant in our study [20].

Consistent with our study findings, greater knowledge of exclusive breastfeeding has been associated with

Table 7 Perceptions on exclusive breastfeeding

	Antepartum		Postpartum	
	HIV infected *n* (%)	HIV uninfected *n* (%)	HIV infected *n* (%)	HIV uninfected *n* (%)
It is easy to exclusively breastfeed for six months	26/74 (35.1)	36/116 (31.0)	29/67 (43.3)	45/113 (39.8)
Most mothers exclusively breastfeed for six months	21/72 (29.2)	31/116 (26.7)	23/67 (34.3)	49/113 (43.4)
Cultural factors prevent most mothers from exclusively breastfeeding	55/73 (75.3)	70/116 (60.3)	42/67 (62.7)	73/113 (64.6)
Influence from elders prevent most mothers from exclusively breastfeeding	61/73 (83.6)	89/116 (76.7)	50/67 (74.6)	81/113 (71.7)

increased likelihood of exclusive breastfeeding, while maternal employment and infant age have been associated with a decreased practice of exclusive breastfeeding [19, 22]. Studies have shown that women who are employed are more likely not to breastfeed or wean early, and that this is related to the need to return to work after giving birth, the demands of being employed and also the practicalities of breastfeeding while at work [8, 24, 25]. Younger infants are likely to be exclusively breastfed, and this could be related to the perception that breast milk only is inadequate for the older infant [19]. Contrary to the finding on intention to breastfeed, HIV infection was positively associated with exclusive breastfeeding among postpartum women, but the association was weak. A South African cohort study also found that women with HIV were more likely to exclusively breastfeed than women without HIV [7]. This could be a reflection of the misconception that only women with HIV need to practice exclusive breastfeeding, to prevent HIV transmission, and is optional for women without HIV [26]. In most sub-Saharan countries, including South Africa, mixed feeding is the norm and adherence to exclusive breastfeeding raises suspicions of HIV infection, and to avoid the stigma, women with and without HIV may elect to 'mix feed' [26–28]. This is somewhat a contradiction given that, as discussed earlier, there is a perception that formula feeding is also associated with having HIV [22, 23]. Availability of male partner support is one of the factors found to mitigate the stigma and encourage exclusive breastfeeding in women with and without HIV [24]. Consistent with this finding, we found not being married and not cohabiting associated with decreased adjusted odds of exclusive breastfeeding. Several other factors contribute to suboptimal infant feeding practices, and include previous experience with infant feeding; perceived inadequacy of exclusive breastfeeding; family and cultural influences; and a need to return to work [8, 24, 27, 29]. Poor knowledge in mothers, as well as inconsistent and inadequate infant feeding counselling by healthcare workers also contribute to unsafe infant feeding practices [8, 24, 27, 29].

It is well-established that mixed feeding is associated with a high risk of MTCT in the absence of either infant or maternal ARV prophylaxis [1]. While maternal ART is protective of breast feeding transmission, adherence to treatment throughout the breastfeeding period is essential for prevention of HIV transmission [30]. In a study done in Zambia, where women received continuous ART starting in pregnancy and throughout breastfeeding, the majority of cases of MTCT occurred in infants older than six months, and adherence to maternal ART was suboptimal in all the cases [30].

Healthcare workers remain the main and important source of information on infant feeding, as we found in our study [27, 31, 32]. The messages need to be consistent as rapidly changing guidelines on infant feeding in the context of HIV infection have led to confusion among both healthcare providers and women accessing care [27, 31, 33]. Data from an established Option B+ PMTCT programme in Malawi however highlighted that most infant feeding counselling still occurs during pregnancy and delivery, with minimal counselling during the postpartum period [32]. Our finding of better knowledge among women with HIV is consistent with findings from other studies as there has been a greater emphasis on counselling and educating women with HIV on safe infant feeding practices and exclusive breastfeeding [26]. A perception has been created that women without HIV do not have to adhere to safe feeding practices, and that exclusive breastfeeding is a recommendation only for women with HIV, for prevention of HIV transmission [26]. This is of concern, as poor infant feeding practices are associated with increased infant morbidity and mortality, independent of HIV infection [24, 34]. Hence safe infant feeding messaging needs to target both women with and without HIV, and continue throughout pregnancy and the postpartum period.

Reported disclosure rates, especially to partners, were high among pregnant and postpartum women with HIV in our study. Disclosure of HIV status to partners, and to family members in those who live in extended families, is associated with adherence to PMTCT interventions, including safe infant feeding practices [27, 33]. Cultural factors and influence from elders have been

identified as important factors that impact negatively on breastfeeding practices, consistent with perceptions expressed by the majority of participants in our study [35]. Cultural barriers to exclusive breastfeeding need to be addressed and the interventions must be specific to the local context [35].

There are several limitations to our study. It would have been more desirable to do a longitudinal study to compare intentions and actual postpartum practices in the same group of women, to determine how intentions translate to practice. The study design used was the most efficient use of available resources, and there are several challenges with mobility and loss to follow-up among postpartum women [28]. There could also have been a social desirability bias in reporting of infant feeding intentions and practices, and because the study was quantitative, we did not explore in detail the motivation behind the intentions and practices. Also, undertaking the interviews in the healthcare facilities might have been perceived as a test of the women's uptake of information given in the facilities rather than their true intentions and practices. Social desirability could have also influenced perceptions expressed by the study participants. The other limitation is that the questionnaire was not translated into the local vernacular languages, but steps were undertaken to minimise any measurement bias by training the interviewers and standardising the translation of technical terms. While the questionnaire used in our survey was not formally evaluated for validity and reliability, similar questions to assess knowledge and perceptions have been used in several infant feeding studies done sub-Saharan Africa, as discussed in the methods section. The HIV prevalence among participants in our study was higher than that reported in the PMTCT programme data and in national surveys, and hence there may have been an overrepresentation of women with HIV. It is likely that women with HIV visit healthcare facilities more frequently for follow-up and to access treatment.

Conclusions

There is evidence of positive changes in infant feeding patterns, especially among women with HIV, in line with the changing infant feeding guidelines. While the study cannot be generalised to the wider South African population, our findings highlight important issues that still need to be addressed to promote safe infant feeding knowledge and practices among both women with and without HIV. The most important one is to ensure accurate and consistent messaging on safe infant feeding practices for all women during the antepartum and postpartum periods. There is also a need to address cultural factors that are barriers to optimal feeding practices.

Abbreviations

ART: Antiretroviral therapy; ARV: Antiretrovirals; PMTCT: Prevention of mother-to-child transmission of HIV; WHO: World Health Organization

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Availability of data and materials

The datasets generated and analysed during the study are available from the corresponding author on request.

Authors' contributions

CNM initiated the study, contributed to the study design, and was the main investigator responsible for the data analysis, interpretation of results and drafting of the manuscript. CT was the main investigator responsible for the data collection and contributed to the drafting of the manuscript. JA contributed to the initiation of the study, data collection and drafting of the manuscript. DB contributed to the data analysis and drafting of the manuscript. MFC and EJB contributed to the data analysis and drafting of the manuscript. RP contributed to the data collection and drafting of the manuscript. JAM contributed to the study design and drafting of the manuscript. All authors reviewed, contributed to and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The study was approved by the University of the Witwatersrand Human Research Ethics Committee (No. M130801), and access to the facilities was granted by the Johannesburg District Health Department. All participants signed written informed consent.

Publisher's Note

Author details

[1]Department of Obstetrics and Gynaecology, School of Clinical Medicine, University of the Witwatersrand, 7 York Road, Parktown, 2193 Johannesburg, South Africa. [2]School of Public Health, University of the Witwatersrand, Johannesburg, South Africa. [3]SACEMA (DST/NRF Centre of Excellence in Epidemiological Modelling and Analysis), Stellenbosch University, Stellenbosch, South Africa. [4]Anova Health Institute, Johannesburg, South Africa. [5]HIVSA, Johannesburg, South Africa. [6]Wits Reproductive Health and HIV Institute, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa. [7]International Centre for Reproductive Health, Department of Obstetrics and Gynaecology, University of Ghent, Ghent, Belgium. [8]School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa.

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RESEARCH ARTICLE

Trends in maternal deaths in HIV-infected women, on a background of changing HIV management guidelines in South Africa: 1997 to 2015

Coceka N Mnyani[1,2,3], Eckhart J Buchmann[1], Matthew F Chersich[4,5], Karlyn A Frank[1] and James A McIntyre[6,7]

Corresponding author: Coceka N Mnyani, Faculty of Health Sciences, University of the Witwatersrand, 7 York Road, Parktown, 2193, Johannesburg, South Africa. Tel: +27 (11) 488 3179. (coceka.mnyani@wits.ac.za)

Abstract

Introduction: As work begins towards the Sustainable Development Goal target of reducing the global maternal mortality ratio (MMR) to less than 70 deaths per 100,000 live births by 2030, much needs to be done in ending preventable maternal deaths. After 1990, South Africa experienced a reversal of gains in decreasing maternal mortality, with an increase in HIV-related maternal deaths. In this study, we assessed trends in maternal mortality in HIV-infected women, on a background of an evolving HIV care programme.

Methods: This was a cross-sectional, retrospective record review of maternal deaths in the obstetrics unit at Chris Hani Baragwanath Academic Hospital, in Johannesburg, South Africa, a referral hospital in a high HIV prevalence setting where the prevalence among pregnant women has plateaued around 29.0% for the past decade. Trends in HIV diagnosis and management in pregnancy, and causes of maternal deaths in HIV-infected women were analysed over different time periods (1997 to 2003, 2004 to 2009, 2010 to 2012, and 2013 to 2015) reflecting major guideline changes.

Results: From January 1997 to December 2015, there were 692 maternal deaths in the obstetrics unit. Of the 490 (70.8%) maternal deaths with a documented HIV status, 335 (68.4%) were HIV-infected. A Chi-squared test for trends showed that the institutional MMR (iMMR) in women known to be HIV-infected peaked in the period 2004 to 2009 at 380 (95% CI 319 to 446) per 100,000 live births, with a decline to 267 (95% CI 198 to 353) in 2013 to 2015, $p = 0.049$. This decrease coincided with changes in the South African HIV management guidelines, mainly increased availability of antiretroviral therapy (ART). Non-pregnancy related infections were the leading cause of death throughout the review period, accounting for 61.5% (206/335) of deaths. Only 23.3% (78/335) of the women who died were on ART at the time of death, this in the context of advanced immune suppression and an overall median CD4 count of 136 cells/μl (interquartile ranges (IQR) 45 to 301).

Conclusion: In this 19-year review of maternal deaths in Johannesburg, South Africa, there was evidence of a decrease in the iMMR among HIV-infected women, but it remains unacceptably high. Efforts to address drivers of mortality and barriers to accessing ART need to be accelerated if we are to see substantial decreases in maternal mortality.

Keywords: maternal mortality; HIV-infected pregnant women; antiretroviral therapy; HIV treatment guidelines; South Africa; high HIV prevalence

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1 | INTRODUCTION

Decreasing maternal deaths remains a global priority. While progress has been made, many countries failed to achieve the Millennium Development Goal 5 (MDG 5) target of reducing the maternal mortality ratio (MMR) by 75%, between 1990 and 2015 [1,2]. As work begins towards the Sustainable Development Goal target of reducing the global MMR to less than 70 deaths per 100,000 live births by 2030, much needs to be done in ending preventable maternal deaths [1,3]. While a large proportion of maternal deaths are still due to direct obstetric causes, such as haemorrhage, hypertension, sepsis, and complications of unsafe abortion, the past 20 years saw an increase in HIV-related maternal deaths, with an estimated 90% of these occurring in sub-Saharan Africa [1,4].

South Africa, one of the sub-Saharan countries with a high HIV prevalence among women of reproductive age, experienced an increase in the MMR in the late 1990s and in the first decade of the 2000s, largely due to the HIV epidemic [1,5,6]. There has been some reduction in HIV-related maternal deaths in the country since the scale-up of antiretroviral therapy (ART) [6,7]. However, HIV infection still contributes significantly to maternal deaths in South Africa, with almost a third of deaths in 2015 estimated to be AIDS-related [8].

HIV-infected women experience excess pregnancy-related mortality compared with HIV-uninfected women [9,10]. A

systematic review found an eight-fold increased risk of mortality in HIV-infected pregnant and postpartum women compared to uninfected women [9]. In the review, only two studies from sub-Saharan Africa included women on ART and most were initiated at very low CD4 counts [9]. Hence, data are limited on the effect of ART on HIV-attributable maternal mortality, in high HIV prevalence settings, as they predate the expansion of HIV programmes, evolution of HIV management guidelines and widespread availability of ART [9,10]. There remains a need to identify the leading causes of maternal mortality in HIV-infected women, and also the characteristics of women who die, if we are to decrease HIV-related maternal deaths [11].

In this 19-year review, we assessed trends in maternal mortality and leading causes of death in HIV-infected women, in a referral hospital in Johannesburg, South Africa, on a background of an evolving HIV care programme.

2 | METHODS

2.1 | Study setting

The study was conducted at Chris Hani Baragwanath Academic Hospital (CHBAH), a referral hospital in Soweto, Johannesburg, an area of mixed urban and informal settlements. The obstetrics unit at CHBAH is a high-volume unit, with 19,804 live births recorded for 2015. Low-risk births are conducted in midwife-run clinics in Soweto. Antenatal care is provided at around 60 community health centres, with referral of high-risk pregnancies to the CHBAH antenatal clinic. Between 3% and 5% of women who give birth at CHBAH access antenatal care at the hospital (District Health Information System data). The area served by the hospital is a high HIV prevalence setting, and the HIV prevalence among pregnant women peaked at 30.7% in 2004, and has plateaued around 29.0% for the past decade (Unpublished PMTCT programme data). The figures are similar to those in published South African antenatal surveys [12].

South Africa has seen a rapid evolution of prevention of mother-to-child transmission of HIV (PMTCT) and ART guidelines. ARVs for PMTCT became available only in 2002, and between then and 2008, when short-course antepartum zidovudine was introduced, only single-dose nevirapine was available [13,14]. ART was introduced in South Africa in 2004 [15], and universal coverage for ART in pregnant women, i.e. ≥80% coverage, was achieved in the Soweto PMTCT programme in 2012 (Unpublished PMTCT programme data). Up to 2013, when ART became available for all HIV-infected pregnant women, CD4 count threshold or World Health Organization (WHO) clinical stage determined ART eligibility [16,17]. Option B+, lifelong triple therapy for all pregnant women, regardless of CD4 count or WHO stage, was adopted in South Africa in January 2015 [18]. HIV-infected pregnant women seen at the Soweto facilities and at CHBAH were managed and continue to be managed according to the South African PMTCT and ART guidelines.

2.2 | Study design

This was a cross-sectional retrospective record review of maternal deaths in the obstetrics unit at CHBAH from January 1997 to December 2015. Since 1997, maternal deaths have been notifiable in South Africa, and the antenatal and hospital admission records for all maternal deaths have been kept safely in the offices of the obstetrics unit, at CHBAH. Data were extracted from these records and transcribed onto a structured data extraction tool. Data on the following parameters were collected: demographics, history of HIV diagnosis and management, details of antenatal care, admission details, laboratory and radiological investigations, delivery details, and clinical information about the circumstances of the deaths. The hospital registers and the National Health Laboratory Services (NHLS) were accessed for any information and laboratory test results that were missing in the patient records. Two obstetricians were involved in the data collection, verification and validation. One obstetrician viewed the original case notes and entered the data onto the extraction tool. The South African National Committee for Confidential Enquiries into Maternal Deaths (NCCEMD) classification was used to categorise causes of maternal deaths, and the two obstetricians were responsible for assigning the cause of death for each case [8]. The NCCEMD provides ten disease categories for the cause of death and these are: hypertension, obstetric haemorrhage, ectopic pregnancy, miscarriage, pregnancy-related sepsis, anaesthetic complications, embolism, acute collapse (cause unknown), non-pregnancy related infections, and medical and surgical disorders. There is also a category for unknown, where the cause of death could not be determined. For each category, there are conditions listed to guide in determining the cause of death. The second obstetrician, who is a former member of the NCCEMD, reviewed all the data on the extraction tool and entered the data into Epi-Info software©. Queries and disagreements about the causes of death were resolved by review of the case notes and consensus between the two obstetricians.

Results on the overall causes of maternal deaths and the MMR up to 2012 have been published elsewhere [7]. This study analysed trends in maternal mortality and leading causes of deaths in HIV-infected women, over different time periods reflecting evolving HIV management and PMTCT guidelines. The four time periods are: (1) 1997 to 2003: no ART was available for lifelong treatment, and only single-dose nevirapine was available for PMTCT [13]. All pregnant women were offered routine HIV testing and this period saw a rapid increase in the HIV prevalence among pregnant women attending antenatal care facilities in South Africa [12]. (2) 2004 to 2009: HIV management guidelines in South Africa changed to introduce lifelong ART in 2004, with eligibility based on CD4 count ≤200 cells/μl or WHO stage 3 or 4 disease [15]. Zidovudine monotherapy for PMTCT, to augment single-dose nevirapine, was introduced in 2008 for women not eligible for ART [14]. (3) 2010 to 2012: Routine third trimester retesting of pregnant women who initially test HIV negative was introduced [16]. The CD4 count threshold for ART initiation in pregnant women increased to 350 cells/μl in 2010 [16]. This change in guideline, together with the introduction of nurse-managed ART in 2012, increased the proportion of eligible pregnant women initiated on ART (Unpublished PMTCT programme data). (4) 2013 to 2015: all HIV-infected pregnant and breastfeeding women were initiated on an efavirenz-based fixed dose ART combination from 2013 and this was stopped postpartum if the woman did not fulfil criteria

for lifelong treatment [17]. From 2015, all HIV-infected pregnant and breastfeeding women became eligible for lifelong ART [18]. The retesting guidelines for women who initially test HIV negative were also updated in 2015 with introduction of routine retesting every three months during pregnancy and breastfeeding, with additional retesting intrapartum and six weeks postpartum [18]. The study was approved by the Johannesburg's University of the Witwatersrand Human Research Ethics Committee, and by the hospital's medical advisory committee.

2.3 | Data analysis

Data were categorised into the four time periods described above, and analyses were done with Stata® version 13.0 (Stata Corporation, College Station, USA). Continuous data (gestational age, CD4 count, days in hospital) were summarised using medians with interquartile ranges (IQRs). All other variables were categorical and analysed using proportions and percentages, with 95% confidence intervals (CI) where appropriate. The overall institutional MMR (iMMR) was calculated using the number of live births at CHBAH, during the four time periods. To calculate the HIV status-specific iMMR, the number of live births in HIV-infected and HIV-uninfected women was estimated using the HIV prevalence among pregnant women attending antenatal clinics in Soweto [12, unpublished PMTCT data]. The HIV prevalence was calculated for each of the four time periods. For the groups of women with unknown HIV status at the time of death, the iMMR could not be determined as no data were available on the proportion of women with unknown HIV status at the time of delivery. Therefore, a sensitivity analysis was done by imputing time-period and cause-of-death specific HIV seropositivity proportions to women with unknown HIV status. Inferential analyses included tests of association by Chi-squared or Fisher's exact tests for categorical data, and Chi-squared test for trend where appropriate. The Wilcoxon rank-sum test was used for comparison of continuous data. Statistical significance was accepted as the two-tailed $p < 0.05$.

3 | RESULTS

From January 1997 to December 2015, a total of 692 women died at CHBAH during pregnancy or within 42 days of delivery, of whom 490 (70.8%) had documented HIV status – 335 HIV-infected and 155 HIV-uninfected. The demographics of all the maternal deaths during the study period are presented in Table 1. Just over a half of all deaths, 55.0% (376/684), occurred in the age group 25 to 35 years, with a higher proportion of deaths among HIV-infected women in this age group at 60.9% (204/335). In the 614 maternal deaths with antepartum information, 76.4% (n = 469) accessed antenatal care, with the majority accessing care at a gestational age of 20 weeks or later. There was an increase in the proportion of HIV-infected maternal deaths who had no antenatal care in the later time periods, with almost one-third from 2013 to 2015 not accessing antenatal care ($p = 0.008$). Also, a high proportion of women with unknown HIV status had not accessed antenatal care throughout the review period.

While 83.8% of women (281/335) were diagnosed as HIV-infected during pregnancy, trends in HIV diagnosis changed over time. The HIV testing rate increased from 48.5% (101/208) in 1997 to 2003, to 84.3% (86/102) in 2013 to 2015 ($p < 0.001$). Pre-pregnancy diagnosis of HIV infection increased from 2.8% (2/71) in 1997 to 2003, to 34.7% (17/49) in 2013 to 2015 ($p < 0.001$; Table 2). Assessment for ART eligibility with an antepartum CD4 count also increased from 8.4% (6/71) in 1997 to 2003, with a peak in testing of 70.4% (50/71) in 2010 to 2012. There was a decline in CD4 testing in 2013 to 2015, coinciding with guideline changes where all HIV-infected pregnant women became eligible for ART. Overall, 133 women (39.7%) had an antepartum CD4 count, with a median of 136 cells/μl (IQR 45 to 301 cells/μl). There was a non-significant trend towards an increase in the median antepartum CD4 count from 102 cells/μl (IQR 56 to 289) in 1997 to 2003 to 220 cells/μl (IQR 61 to 361) in 2013 to 2015 ($p = 0.071$), and also a trend towards a decrease in the proportion of women with advanced immune suppression (Table 2). While ART initiation peaked in the period 2010 to 2012, there was a decline in the proportion of women initiated on ART in 2013 to 2015, when all HIV-infected women were eligible for ART. In the 19 women who were not started on ART in the period 2013 to 2015, the median antepartum CD4 count was 173 cells/μl (IQR 16 to 340), and 12 of the 19 women did not access antenatal care.

Overall, 75.3% of women (521/692) were still pregnant at the time of admission, while 75.7% of deaths (524/692) occurred postpartum. The proportions were similar for HIV-infected women, with 75.2% (252/335) admitted either antenatally or intrapartum and 79.1% (265/335) dying postpartum – Table 3. Women with unknown HIV status were more likely to die within the first 24 hours of admission, with a median time from admission to death of one day (IQR 0 to 3), less than in women with known HIV status, who died after a median of three days (IQR 1 to 7), $p < 0.001$. Among HIV-infected women, the median time from admission to death was three days (IQR 1 to 7), while that in HIV-uninfected women was two days (IQR 1 to 6), $p = 0.011$. The median gestational age at delivery or death was lower among HIV-infected women (31 weeks; IQR 27 to 35 weeks) compared with HIV-uninfected women (35 weeks; IQR 31 to 38 weeks), $p < 0.001$. In the later time periods, women with unknown HIV status died at a relatively early gestational age, median of 28 weeks (IQR 18 to 35) in 2010 to 2012, and 17 weeks (IQR 10 to 26) in 2013 to 2015 (Table 3).

The causes of death in all women who died during the study period are presented in Table 4. Non-pregnancy related infections were the leading cause of death in HIV-infected women throughout the review period, accounting for 61.5% (206/335) of deaths. The proportion of deaths due to these infections, among HIV-infected women, peaked in 1997 to 2003 at 69.0% (49/71), with a decrease to 44.9% (22/49) in 2013 to 2015, $p < 0.001$ (Table 2). Among the non-pregnancy related infections, the leading causes of death were respiratory infections, accounting for 56.3% (116/206) of the deaths. Tuberculosis, pulmonary and extrapulmonary, accounted for 32.5% (67/206) of the non-pregnancy related infections. Of the HIV-infected women who died of non-pregnancy related infections and had antepartum CD4 count testing, 79.3% (65/82) had a CD4 count ≤200 cells/μl, compared with 31.4%

Table 1. Demographic data in maternal deaths of HIV-infected and HIV-uninfected women, and women with unknown HIV status (n; %), n = 692

	1997 to 2003			2004 to 2009			2010 to 2012			2013 to 2015		
	HIV-infected (n = 71)	HIV-uninfected (n = 30)	HIV unknown (n = 107)	HIV-infected (n = 144)	HIV-uninfected (n = 63)	HIV unknown (n = 61)	HIV-infected (n = 71)	HIV-uninfected (n = 25)	HIV unknown (n = 18)	HIV-infected (n = 49)	HIV-uninfected (n = 37)	HIV unknown (n = 16)
Age (n = 684)												
<18	2 (2.8)	1 (3.3)	4 (4.0)	2 (1.4)	2 (3.2)	1 (1.7)	2 (2.8)	2 (8.0)	1 (5.6)	0 (0.0)	0 (0.0)	1 (6.2)
18 to 24	25 (35.2)	1 (3.3)	23 (23.0)	21 (14.6)	20 (31.8)	13 (21.7)	11 (15.5)	5 (20.0)	2 (11.1)	7 (14.3)	13 (35.1)	3 (18.8)
25 to 35	36 (50.7)	18 (60.0)	49 (49.0)	94 (65.3)	28 (44.4)	30 (50.0)	43 (60.6)	12 (48.0)	11 (61.1)	31 (63.3)	18 (48.6)	6 (37.5)
>35	8 (11.3)	10 (33.3)	24 (24.0)	27 (18.7)	13 (20.6)	16 (26.6)	15 (21.1)	6 (24.0)	4 (22.2)	11 (24.4)	6 (16.2)	6 (37.5)
Parity (n = 648)												
0	23 (23.3)	5 (17.9)	24 (25.3)	33 (23.6)	28 (45.2)	9 (16.7)	12 (17.4)	7 (28.0)	4 (33.3)	6 (13.0)	14 (38.9)	3 (25.0)
1 to 4	45 (65.2)	18 (64.3)	64 (67.3)	103 (73.7)	31 (50.0)	42 (77.8)	56 (81.2)	17 (68.0)	8 (66.7)	39 (84.8)	20 (55.6)	9 (75.0)
≥5	1 (1.5)	5 (17.8)	7 (7.4)	4 (2.8)	3 (4.8)	3 (5.5)	1 (1.4)	1 (4.0)	0 (0.0)	1 (2.2)	2 (5.5)	0 (0.0)
Accessed antenatal care (n = 614)												
Yes	61 (85.9)	19 (63.3)	58 (54.2)	106 (73.6)	57 (90.5)	24 (39.3)	50 (70.4)	23 (92.0)	3 (16.7)	33 (67.3)	35 (94.6)	0 (0.0)
No	6 (8.5)	2 (6.7)	33 (30.8)	26 (18.1)	5 (7.9)	23 (37.7)	13 (18.3)	0 (0.0)	12 (66.6)	14 (28.6)	1 (2.7)	10 (62.5)
Unknown	4 (5.6)	9 (30.0)	16 (15.0)	12 (8.3)	1 (1.6)	14 (23.0)	8 (11.3)	2 (8.0)	3 (16.7)	2 (4.1)	1 (2.7)	6 (37.5)
Gestational age at accessing antenatal care (n = 428)												
<20 weeks	27 (47.4)	5 (29.4)	14 (26.4)	34 (35.1)	19 (38.0)	5 (21.7)	12 (26.7)	10 (43.5)	2 (66.7)	15 (53.6)	19 (59.4)	0 (0.0)
≥20 weeks	30 (52.6)	12 (70.6)	39 (73.6)	63 (64.9)	31 (62.0)	18 (78.3)	33 (73.3)	13 (56.5)	1 (33.3)	13 (46.4)	13 (40.6)	0 (0.0)

Table 2. Diagnosis and management of HIV infection, n = 335

	1997 to 2003 (n = 71)	2004 to 2009 (n = 144)	2010 to 2012 (n = 71)	2013 to 2015 (n = 49)	*p*-value
Timing of HIV diagnosis, n (%)					
Pre-pregnancy	2 (2.8)	4 (2.8)	4 (5.6)	17 (34.7)	<0.001
Antepartum	61 (86.0)	129 (89.6)	66 (93.0)	25 (51.0)	
Intrapartum/postpartum	7 (9.8)	9 (6.2)	0 (0.0)	4 (8.2)	
Unknown	1 (1.4)	2 (1.4)	1 (1.4)	3 (6.1)	
Antenatal CD4 count done, n (%)					
Yes	6 (8.4)	52 (36.1)	50 (70.4)	25 (51.0)	<0.001
No	65 (91.6)	92 (63.9)	21 (29.6)	24 (49.0)	
Nadir CD4 count, cells/μl, n (%)[a]					
Total done	24 (33.8)	102 (70.8)	64 (90.1)	32 (65.3)	<0.001
<100	17 (70.8)	62 (60.8)	28 (43.8))	14 (43.7)	0.061
100 to 200	3 (12.5)	19 (18.6)	13 (20.3)	6 (18.7)	
201 to 350	1 (4.2)	12 (11.8)	18 (28.1)	6 (18.7)	
>350	3 (12.5)	9 (8.8)	5 (7.8)	6 (18.7)	
ART eligible, n (%)[b]	0 (0.0)	37/52 (71.1)	41/50 (82.0)	49/49 (100.0)	<0.001
Initiated on ART, n (%)	0 (0.0)	19 (51.4)	29 (70.7)	30 (61.2)	0.600
Timing of ART, n (%)					
Preconception	0 (0.0)	6 (4.2)	7 (9.8)	14 (28.6)	<0.001
Antepartum	0 (0.0)	13 (9.0)	22 (31.0)	16 (32.7)	
Not started/ unknown	71 (100.0)	125 (86.8)	42 (59.2)	19 (38.7)	

[a]Nadir CD4 count done either antenatally or during admission when the death occurred.
[b]ART, antiretroviral therapy eligibility: in 1997 to 2003, no women; in 2004 to 2009, women with CD count ≤200 cells/μl; in 2010 to 2012, women with CD4 count ≤350 cells/μl; in 2013 to 2015, all HIV-infected women irrespective of CD4 count.

(16/51) among women who died from other causes ($p < 0.001$). A total of 46/206 (22.3%) HIV-infected women who died of non-pregnancy related infections were on ART at the time of death. Among the HIV-infected women who died of pregnancy-related sepsis, the median antepartum CD4 count was 236 cells/μl (IQR 110 to 325), and 10/25 (40.0%) were on ART. Puerperal sepsis following caesarean section accounted for 64.0% (16/25) of cases of pregnancy-related sepsis among HIV-infected women. Complications related to hypertensive disorders were the leading cause of death among HIV-uninfected women and women with unknown HIV status. Autopsies were performed in 2.6% (18/692) of the maternal deaths.

The majority of the autopsies were done in cases of acute collapse, and in cases of medical and surgical disorders complicating pregnancy, where the cause of death was not clear, or of clinical interest.

The iMMR in HIV-infected women peaked in the period 2004 to 2009 at 380 per 100,000 live births, with a decline to 267 in 2013 to 2015, $p = 0.049$ (Table 5). It was three- to eightfold higher in the different time periods compared to the iMMR in HIV-uninfected women. The overall iMMR decreased from 209 per 100,000 live births in 2004 to 2009, to 162 in 2013 to 2015 ($p = 0.02$). The iMMR showed an upward trend in HIV-uninfected women ($p < 0.001$). A sensitivity analysis was done to determine the effect of unknown HIV status on these findings. Observed proportions of HIV infections were imputed for the unknown groups in each cause-of-death category, in each time period. For example, in 1997 to 2003, the HIV-infected proportion for women with non-pregnancy related infections was 49/57 (0.86, Table 4). This proportion was applied to the 11 women whose HIV status was unknown, giving nine HIV-infected and two HIV-uninfected women. The process was repeated for all seven cause-of-death categories as shown, for each of the four time periods. For women thus assumed HIV-infected, the iMMR decreased from 476 to 464 to 413 to 322 per 100,000 live births in the four time periods starting 1997 to 2003 ($p = 0.01$). For women assumed HIV-uninfected, the corresponding trend was 86 to 101 to 73 to 97 per 100,000 live births ($p = 0.91$), suggesting a stable iMMR.

4 | DISCUSSION

In this 19-year review of the evolution of HIV diagnosis and management in pregnancy, and trends in maternal deaths, the iMMR in HIV-infected women peaked in 2004 to 2009, followed by a progressive decline in the last six years of the review period, with a more substantial decrease in 2013 to 2015. This decrease in the iMMR coincides with several changes in the South African PMTCT and HIV management guidelines [13–18]. The overall iMMR showed a similar trend to that in HIV-infected women, while that in HIV-uninfected women showed no downward trend. This highlights the importance of deaths in HIV-infected women in influencing trends in maternal mortality, and is also reflected in the South African National Confidential Enquiries into maternal deaths, which also report on the iMMR [6]. Data from the National Confidential Enquiries for the period 2011 to 2013 show a decline

Table 3. Timing of admission and timing of death (n;%), n = 692

	1997 to 2003			2004 to 2009			2010 to 2012			2013 to 2015		
	HIV-infected (n = 71)	HIV-uninfected (n = 30)	HIV unknown (n = 107)	HIV-infected (n = 144)	HIV-uninfected (n = 63)	HIV unknown (n = 61)	HIV-infected (n = 71)	HIV-uninfected (n = 25)	HIV unknown (n = 18)	HIV-infected (n = 49)	HIV-uninfected (n = 37)	HIV unknown (n = 16)
Timing of admission												
Antenatal	44 (62.0)	16 (53.3)	71 (66.3)	75 (52.1)	33 (52.4)	24 (39.3)	46 (64.8)	14 (56.0)	10 (55.5)	27 (55.1)	23 (62.2)	12 (75.0)
Intrapartum	14 (19.7)	5 (16.7)	16 (15.0)	32 (22.2)	15 (23.8)	18 (29.5)	6 (8.5)	5 (20.0)	3 (16.7)	8 (16.3)	4 (10.8)	0 (0.0)
Postpartum	13 (18.3)	9 (30.0)	20 (18.7)	37 (25.7)	15 (23.8)	19 (31.1)	19 (26.7)	6 (24.0)	5 (27.8)	14 (28.6)	10 (27.0)	4 (25.0)
Timing of death												
Antenatal	13 (18.3)	6 (20.0)	28 (26.2)	29 (20.1)	6 (9.5)	14 (23.0)	13 (18.3)	3 (12.0)	8 (44.4)	11 (22.4)	5 (13.5)	3 (18.8)
Postpartum	58 (81.7)	24 (80.0)	79 (73.8)	115 (79.9)	57 (90.5)	47 (77.0)	58 (81.7)	22 (88.0)	10 (55.6)	38 (77.6)	32 (86.5)	13 (81.2)
Days from admission to death, n (%)												
0 to 1	15 (21.1)	10 (33.3)	56 (52.3)	45 (31.2)	33 (52.4)	41 (67.2)	18 (25.4)	12 (48.0)	11 (61.1)	17 (34.7)	11 (29.7)	7 (43.7)
2 to 4	27 (38.0)	9 (30.0)	23 (21.5)	38 (26.4)	17 (27.0)	12 (19.7)	27 (38.0)	5 (20.0)	5 (27.8)	13 (26.5)	11 (29.7)	6 (37.5)
5 to 9	16 (22.5)	5 (16.7)	14 (13.1)	37 (25.7)	8 (12.7)	5 (8.2)	17 (23.9))	5 (20.0)	1 (5.5)	11 (22.4)	10 (27.0)	3 (18.8)
>9	13 (18.3)	6 (20)	14 (13.1)	24 (16.7)	5 (7.9)	3 (4.9)	9 (12.7)	3 (12.0)	1 (5.5)	8 (16.3)	5 (13.5)	0 (0.0)
Gestational age at delivery or death (weeks), n = 602 (%)												
Median (IQR)	31 (28 to 34)	34 (28 to 37)	32 (26 to 36)	31 (26 to 36)	35 (30 to 39)	32 (25 to 38)	32 (28 to 36)	34 (32 to 38)	28 (18 to 35)	31 (25 to -35)	36 (32 to 39)	17 (10 to 26)
<22	4 (6.0)	2 (8.0)	12 (13.6)	4 (3.2)	1 (1.7)	5 (10.8)	6 (9.4)	0 (0.0)	4 (30.8)	6 (14.3)	3 (8.1)	7 (58.3)
22 to 27	11 (16.4)	2 (8.0)	14 (16.0)	33 (26.2)	5 (8.5)	9 (19.6)	10 (15.6)	3 (13.0)	2 (15.4)	7 (16.7)	2 (5.4)	3 (25.0)
28 to 36	43 (64.2)	14 (56.0)	41 (46.6)	60 (47.6)	30 (50.8)	16 (34.8)	34 (53.1)	11 (47.8)	5 (38.4)	19 (45.2)	15 (40.5)	2 (16.7)
>36	9 (13.4)	7 (28.0)	21 (23.9)	29 (23.0)	23 (39.0)	16 (34.8)	14 (21.9)	9 (39.1)	2 (15.4)	10 (23.8)	17 (45.9)	0 (0.0)

IQR, interquartile ranges.

Table 4. Causes of maternal death in HIV-infected and HIV-uninfected women, and women with unknown HIV status (n; %), n = 692

	1997 to 2003			2004 to 2009			2010 to 2012			2013 to 2015		
	HIV-infected (n = 71)	HIV-uninfected (n = 30)	HIV unknown (n = 107)	HIV-infected (n = 144)	HIV-uninfected (n = 63)	HIV unknown (n = 61)	HIV-infected (n = 71)	HIV-uninfected (n = 25)	HIV unknown (n = 18)	HIV-infected (n = 49)	HIV-uninfected (n = 37)	HIV unknown (n = 16)
Non-pregnancy related infections	49 (69.0)	8 (26.7)	11 (10.3)	93 (64.6)	8 (12.7)	9 (14.7)	42 (59.1)	2 (8.0)	2 (11.1)	22 (44.9)	5 (13.5)	0 (0.0)
Obstetric haemorrhage	3 (4.2)	3 (10.0)	20 (18.7)	16 (11.1)	11 (17.5)	13 (21.3)	7 (9.8)	4 (16.0)	2 (11.1)	4 (8.2)	6 (16.2)	1 (6.3)
Pregnancy-related sepsis	3 (4.2)	6 (20.0)	4 (3.7)	11 (7.6)	6 (9.5)	0 (0.0)	5 (7.0)	3 (12.0)	0 (0.0)	6 (12.2)	5 (13.5)	0 (0.0)
Hypertensive disorders	2 (2.8)	7 (23.3)	31 (29.0)	9 (6.3)	18 (28.6)	21 (34.4)	2 (2.8)	5 (20.0)	8 (44.4)	9 (18.4)	9 (24.3)	3 (18.7)
Medical and surgical disorders	2 (2.8)	4 (13.3)	10 (9.3)	3 (2.1)	10 (15.9)	3 (4.9)	10 (14.1)	5 (20.0)	2 (11.1)	4 (8.2)	11 (29.7)	2 (12.5)
Other[a]	9 (12.7)	2 (6.7)	25 (23.4)	12 (8.3)	8 (12.7)	13 (21.3)	3 (4.2)	5 (20.0)	4 (22.2)	3 (6.1)	1 (2.7)	10 (62.5)
Unknown	3 (4.2)	0 (0.0)	6 (5.6)	0 (0.0)	2 (3.2)	2 (3.3)	2 (2.8)	1 (4.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)

[a]Other causes of death included: complications of miscarriages and ectopic pregnancies, anaesthetic deaths and cases of acute collapse that include suspected thromboembolism.

Table 5. Institutional maternal mortality ratios at Chris Hani Baragwanath Academic Hospital, 1997 to 2015

	1997 to 2003	2004 to 2009	2010 to 2012	2013 to 2015
HIV prevalence, %	22.0	29.6	28.5	29.2
Live births, n				
Total live births	121,353	128,150	67,056	62,785
Estimated live births in HIV-infected women	26,698	37,932	19,111	18,333
Estimated live births in HIV-uninfected women	94,655	90,218	47,945	44,452
iMMR (95% CI)				
Overall iMMR[a]	171 (149 to 196)	209 (185 to 236)	170 (140 to 204)	162 (132 to 197)
iMMR in HIV-infected women	267 (208 to 335)	379 (319 to 446)	372 (290 to 468)	267 (198 to 353)
iMMR in HIV-uninfected women	32 (21 to 45)	70 (54 to 89)	52 (34 to 77)	83 (59 to 115)
Cause-specific iMMR (95% CI)[a]				
Non-pregnancy related infections	56 (44 to 71)	86 (71 to 103)	69 (50 to 91)	43 (28 to 63)
All causes of death, excluding non-pregnancy related infections and unknown cause	108 (90 to 128)	120 (101 to 140)	97 (75 to 124)	118 (93 to 148)

[a]Includes maternal deaths with unknown HIV status.

in the iMMR largely related to a decrease in deaths due to non-pregnancy related infections in whom 90% of the women were HIV-infected [6]. In our study, the proportion of maternal deaths with known HIV status increased over time, with an increase in pre-pregnancy diagnosis of HIV infection, but the majority were still diagnosed during pregnancy. While there was a significant increase in ART initiation, the majority of women died without ever starting ART, this in the context of advanced immune suppression. Non-pregnancy related infections remained the leading cause of maternal deaths in HIV-infected women throughout the review period. In the later periods, the characteristics of women with unknown HIV status had become more distinct from those who had tested. HIV unknown women more frequently did not access antenatal care, suffered early pregnancy complications, and died soon after admission to hospital – all reasons for not being tested for HIV.

The majority of women who died had accessed antenatal care, but a high proportion of women with an unknown HIV status had not accessed any care. There was also a trend towards a relative increase in the proportion of maternal deaths known to be HIV-infected who had no antenatal care – almost a third in 2013 to 2015. The latest available figure for antenatal care coverage in South Africa is for 2014, and the reported coverage is 90% [19]. Our finding on rates of antenatal care attendance among HIV-infected women and women of unknown HIV status are hence lower than the national average, but similar to that reported in a review of maternal deaths in South Africa at the early stages of ART roll-out [20]. Black *et al.* [20], in their five-year review of maternal deaths at a tertiary hospital, also found a high rate of nonattendance for antenatal care among the women who died. Our finding of an increase in HIV-infected women not accessing antenatal care in 2013 to 2015 is a reflection of the women who remain at risk of dying. Failure to access antenatal care is of concern as antenatal care remains the cornerstone for detection of HIV infection and identification of obstetric complications. Although antenatal care cannot impact on all causes of maternal mortality, it can have a significant impact in decreasing HIV-related mortality in high HIV prevalence settings, with early diagnosis and treatment of pregnant women identified as HIV-infected [21,22]. In our study, the majority of HIV-infected women were diagnosed during pregnancy and this points to a need to increase routine HIV testing outside of pregnancy to allow linkage to care and early initiation of ART. Preconception ART is associated with a decreased risk of HIV-related maternal deaths [23,24].

There was a fall-off at all stages of the HIV management cascade, from HIV testing to assessment for ART eligibility, to initiation of treatment in those found to be eligible. In 2004 to 2012, with introduction and scale-up of availability of ART, less than half of the women had a CD4 count done to assess for ART eligibility. This highlights deficiencies in provision of services and delays in linkage to care. The number of women who were on ART at the time of death increased over time, but less than a quarter were initiated on ART overall, despite advanced immune suppression where the overall median CD4 count was 136 cells/μl. Even in 2013 to 2015 when all HIV-infected pregnant women were eligible for ART, 38.8% were not on treatment at the time of death. Missed opportunities along the HIV management cascade not only impact on maternal health, but have also been directly linked to the risk of MTCT [25]. In a South African national survey, a third of early infant HIV infections were found to be attributable to missed opportunities along the cascade [25]. Historically, delays in ART initiation during pregnancy were related to complex evaluation processes before starting treatment and the lack of integration of antenatal and ART services [26]. While ART initiation has been simplified, and integration of services has increased the proportion of pregnant women started on treatment, there are still individual and contextual factors that impact on ART initiation and retention in care [26–28].

While a large proportion of HIV-infected women who died presented in the antenatal period, the majority of deaths occurred postpartum, and in most cases the conditions that led to the deaths occurred in the antenatal and intrapartum periods. This finding was similar among HIV-uninfected women and women with unknown HIV status. In our study, the

leading cause of death among HIV-uninfected women and women with unknown HIV status were complications related to hypertensive disorders. Among HIV-infected women, almost two-thirds of maternal deaths were due to non-pregnancy related infections, the majority respiratory infections, including TB. This finding is consistent with data from reports on the Confidential Enquiries into Maternal Deaths in South Africa [6]. There was however a progressive decline in maternal deaths due to non-pregnancy related infections, starting in 2010 to 2012 and coinciding with the increase in CD4 count threshold for ART initiation in pregnant women and a greater proportion initiated on ART through integration of services. Respiratory infections are among the most important non-pregnancy related infectious causes of death among HIV-infected women [22,29]. Physiologic and immunologic changes in pregnancy, and immune suppression related to HIV infection, are all thought to increase susceptibility to infections, including respiratory infections [22]. In our study, no data were available on the use of cotrimoxazole and isoniazid, both effective prophylactic interventions in HIV-infected individuals [30]. Data from South Africa indicate poor uptake of isoniazid preventative therapy among HIV-infected pregnant women [31,32]. There have been concerns about the risk of hepatitis with isoniazid use in pregnancy, but available evidence suggests no increased risk even in pregnant women on ART receiving long-term isoniazid [33].

Among the pregnancy-related causes of maternal deaths, a threefold increased risk of puerperal sepsis has been reported in HIV-infected women, and the risk is said to be even higher, almost six times, following a caesarean section, consistent with our findings where the majority of cases of puerperal sepsis were secondary to caesarean sections [34]. The increased risk of puerperal sepsis has been attributed to the immune suppression associated with HIV infection [34]. Although the median CD4 count among women who died of puerperal sepsis in our study was higher than the median CD4 count overall, less than half were on ART at the time of death. Due to the limited number of published studies, it is not possible to determine the effect of ART on the risk of puerperal sepsis [34]. Data on the association between other obstetric complications and HIV infection are inconsistent [34,35]. There is hence a need for improvements in identification and management of obstetric complications that may be aggravated by underlying HIV infection [11]. There is also a need to address the unmet need for contraception in both HIV-infected and uninfected women as prevention of unintended pregnancies also contributes to the reduction in maternal deaths [2].

It is widely recognised that early initiation of ART needs to be scaled up if we are to see a sustained reversal in HIV-related maternal deaths. At the end of our review period, it was still too soon to see the impact of lifelong ART for all pregnant and postpartum women. As ART programmes are scaled up, there is a need for strategies to increase retention in care, especially postpartum – a period associated with high rates of loss-to-follow-up [28]. Integration of maternal health and ART services, facility- and community-based support programmes, and male partner involvement are all strategies that have been used in improving retention in care [36]. In our study, there was limited information on women who had defaulted ART. Data from Malawi, one of the first countries to introduce Option B+, indicate high rates of loss to follow-up in the first year of starting ART, especially with ART initiation during pregnancy and when there was no maternal indication to start treatment [37].

There are several strengths to our study, and these include a long review period with data spanning almost two decades, starting in the pre-ART era until ART became standard of treatment for all HIV-infected pregnant women. The other strength is the vigilance in storage of records of women who died in our obstetrics unit. A standardised classification for causes of death was also used, minimising the chances of misclassifications of maternal deaths. The main limitation was the absence of HIV status in a large proportion of women who died in the early years of the study period, giving artefactually low estimates of iMMR. In our study, 68% of women who died with a known HIV status were HIV-infected. Hence, the HIV prevalence in women with unknown HIV status could have been anywhere between 29%, the prevalence rate in pregnant women attending antenatal clinics, and 68%, the prevalence rate in women who died. The sensitivity analysis, with its given assumption, gave higher estimates of iMMR, especially for 1997 to 2003, but the significant downward trend for HIV-infected women remained, and appears to be a robust finding. Another limitation is the absence of information on deaths occurring outside the hospital obstetrics unit, but we consider this proportion to be small [7]. Ideally, this study should have included comparative data on the many thousands of HIV-infected women who gave birth at the hospital and survived. Gathering such information was beyond our capacity and mostly impossible, because hospital records were destroyed after five years of storage during most of the study periods.

5 | CONCLUSIONS

With scaling up of ART availability and better integration of antenatal and HIV management services in South Africa, we are starting to see a positive impact on maternal mortality in HIV-infected women. However, the MMR in HIV-infected women remains unacceptably high. Efforts to address drivers of mortality in this group of women, and barriers to accessing ART that still exist, need to be accelerated if we are to see substantial decreases in maternal mortality.

AUTHORS' AFFILIATIONS

[1]School of Clinical Medicine, Department of Obstetrics and Gynaecology, University of the Witwatersrand, Johannesburg, South Africa; [2]School of Public Health, University of the Witwatersrand, Johannesburg, South Africa; [3]SACEMA (DST/NRF Centre of Excellence in Epidemiological Modelling and Analysis), Stellenbosch University, Stellenbosch, South Africa; [4]Wits Reproductive Health and HIV Institute, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [5]International Centre for Reproductive Health, Department of Obstetrics and Gynaecology, University of Ghent, Ghent, Belgium; [6]Anova Health Institute, Johannesburg, South Africa; [7]School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa

COMPETING INTERESTS

The authors report no conflicts of interest.

AUTHORS' CONTRIBUTORS

CNM initiated the study, contributed to the study design and data collection, and was the main investigator responsible for the interpretation of results and drafting of the manuscript. EJB contributed to the study design, data collection

and analysis, and drafting of the manuscript. MFC contributed to the data analysis and drafting of the manuscript. KF contributed to the study design and led the data collection. JAM contributed to the study design and drafting of the manuscript. All authors reviewed, contributed to and approved the final manuscript.

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GAUTENG PROVINCE
REPUBLIC OF SOUTH AFRICA

POLICY, PLANNING AND RESEARCH (PPR)
Enquiries: Dr B Ikalafeng
Tel: +2711 355 3500
Fax: +2711 355 3675 Email:bridget.ikalafeng@gauteng.gov.za

CONTACT DETAILS OF THE RESEARCHER	
Date	23 October 2012
Contact number	
Email	mnyani@anovahealth.co.za
Researcher /Principal investigator (PI)	Dr Coceka Mnyani
Supervisor	
Institution	University of Cape Town, School of Public Health and Family Medicine
Research title	Analysis of routinely collected data from prevention of mother-to-child transmission programmes in the Johannesburg Metro District, Gauteng

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This approval is granted only for a research proposal submitted to GDH by Dr Coceka Mnyani entitled "Analysis of routinely collected data from prevention of mother-to-child transmission programmes in the Johannesburg Metro District, Gauteng"

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za

07 October 2011

HREC REF: 456/2011

A/Prof L Myer
Public Health & Family Medicine

Dear A/Prof Myer

PROJECT TITLE: ANALYSIS OF ROUTINELY COLLECTED DATA FROM PMTCT PROGRAMMES IN THE JOHANNESBURG METRO DISTRICT, GAUTENG.

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

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

Approval is granted for one year till the 28 October 2012.

Please submit a progress form, using the standardised Annual Report Form (FHS016), if the study continues beyond the approval period. Please submit a Standard Closure form (FHS010) if the study is completed within the approval period.

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

Please quote the HREC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

s.thomas

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Mnyani

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M081128**
PROJECT	Experiences with a New PMTCT Programme in Soweto, Johannesburg: Lessons Learned
INVESTIGATORS	Dr C Mnyani
DEPARTMENT	Perinatal HIV Research Unit
DATE CONSIDERED	08.11.28
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 09.01.28 **CHAIRPERSON** .....
(Professor P E Cleaton Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Prof J McIntyre

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Coceka Mnyani

CLEARANCE CERTIFICATE	**M10233**
PROJECT	An Audit of HIV-Infected Children Seen in the Prevention of Mother-to-Child Transmission of HIV Programme in Soweto, Johannesburg
INVESTIGATORS	Dr Coceka Mnyani.
DEPARTMENT	Perinatal HIV Research Unit
DATE CONSIDERED	26/02/2010
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 23/03/2010 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr H Struthers

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
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PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

University
of the Witwatersrand,
Johannesburg

Human Research Ethics Committee (Medical)
(formerly Committee for Research on Human Subjects (Medical)

Secretariat: Research Office, Room SH10005, 10th floor, Senate House • Telephone: +27 11 717-1234 • Fax: +27 11 339-5708
Private Bag 3, Wits 2050, South Africa

03 November 2010

Dr Coceka Mnyani
ANOVA Health Institute
12 Sherborne Road
PARKTOWN
2193

Dear Dr Mnyani

RE: Protocol M10233: 'An audit of HIV-Infected Children Seen in the Prevention of Mother-to-Child Transmission of HIC Programme in Soweto, Johannesburg
Protocol amendments

This letter serves to confirm that the Chairman of the Human Research Ethics Committee (Medical) has reviewed and approved the amendments to the questionnaire on the abovementioned protocol as detailed in your letter dated 01 November 2010.

Thank you for keeping us informed and updated.

Yours sincerely,

Anisa Keshav
Secretary
Human research Ethics Committee (Medical)

R14/49 Dr Coceka Nandipha Mnyani et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M130801

NAME: (Principal Investigator) Dr Coceka Nandipha Mnyani et al

DEPARTMENT: ANOVA Health Institute
Private

PROJECT TITLE: Infant Feeding Practices in HIV-1 Infected and-uninfected Women in Soweto, Johanesburg

DATE CONSIDERED: 30/08/30/13

DECISION:

CONDITIONS:

SUPERVISOR: Prof James McIntyre

APPROVED BY: _____
Professor PE Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 20/08/2013

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

_____ _____
Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Professor E Buchmann

CLEARANCE CERTIFICATE **M120118**

PROJECT Maternal Mortality in the Era of Antiretroviral Therapy at Chris Hani Baragwanath Academic Hospital

INVESTIGATORS Professor E Buchmann.

DEPARTMENT Department Obstetrics & Gynaecology

DATE CONSIDERED 27/01/2012

DECISION OF THE COMMITTEE* Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 27/01/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor :

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

Questionnaire for healthcare workers in the study on assessment of the new PMTCT programme in Soweto, Johannesburg

This questionnaire is part of a study to assess healthcare workers' and clients' experiences with the new PMTCT programme in Soweto, Johannesburg. The programme was rolled out in March 2008, and most facilities have had at least 6 months experience with the new programme. The aim of this study is to assess these experiences, and identify any challenges and shortcomings in the programme.

Any information you give will be treated with confidence, and you may refuse to answer any questions you are not comfortable with.

Questions about self

1. Gender
   - ☐ Female
   - ☐ Male

2. What is your position in the clinic?
   - ☐ Midwife
   - ☐ PMTCT coordinator
   - ☐ PCR sister
   - ☐ Lay counselor
   - ☐ Other, specify_____

3. How long have you been in the current position?
   - ☐ Less than 6 months
   - ☐ 6 months to 1 year
   - ☐ 2 to 5 years
   - ☐ 6 to 10 years
   - ☐ More than 10 years

Questions about the job

4. How many patients do you see everyday?
   - ☐ Indicate number

5. Are you coping with the number?
   - ☐ Yes
   - ☐ No

6. If you are not coping, have you spoken to anyone about it?
   - ☐ Yes
   - ☐ No
   - ☐ Coping

7. If you are not coping, and have spoken to someone, has anything been done to make the situation better?
   - ☐ Yes
   - ☐ No

8. How satisfied are you with these aspects of your job?

1 = not satisfied
2 = only slightly satisfied
3 = satisfied
4 = very satisfied
5 = extremely satisfied

- ☐ Working hours
- ☐ Working conditions
- ☐ Cooperation of coworkers
- ☐ Support from your supervisor
- ☐ Attitude of your supervisor
- ☐ Technical 'know-how' of your supervisor
- ☐ The amount of pay for the work that you do
- ☐ Personal knowledge on PMTCT
- ☐ Personal knowledge on HIV/AIDS
- ☐ The number of clients you see everyday
- ☐ Knowledge of clients about the new PMTCT programme
- ☐ Attitude of clients
- ☐ Ability to manage clients who are HIV-infected
- ☐ Chance to be of service to others
- ☐ Interaction with the community you are working in

Questions on the new PMTCT programme

9. Were you informed about the new programme before it started?
- ☐ Yes
- ☐ No
- ☐ Don't know

10. Do you feel that the information you were given was enough?
- ☐ Yes
- ☐ No
- ☐ Don't know

11. Did you receive any training before the new programme was started?
- ☐ Yes
- ☐ No

12. Do you feel that the training you received was sufficient?
- ☐ Yes
- ☐ No
- ☐ Don't know

13. Except for the training you received, have you had any other opportunities to learn about the new programme?
- ☐ Yes
- ☐ No

14. If you had other opportunities to learn, where were they from?
- ☐ Government guidelines
- ☐ Further training on the programme
- ☐ Media
- ☐ Co-workers
- ☐ Other, specify_____

15. Do you feel confident to manage pregnant women who are HIV-infected?
- ☐ Yes
- ☐ No

16. Is there somebody you can ask if there is an issue you are not sure about in the management of your clients?
- ☐ Yes
- ☐ No

Questions on people's perception about pregnant women with HIV/AIDS.
Please answer strongly agree (SA), agree (A), disagree (D), strongly disagree (SD), don't know (DK)

17. Pregnant women with HIV/AIDS deserve special care
☐

18. Disclosure is still a big issue in pregnant women who are HIV-infected
☐

19. HIV-infected pregnant women face neglect from their partners
☐ .

20. HIV-infected pregnant women face violence from their partners
☐

21. People with HIV/AIDS should not have children
☐

22. HIV-infected women are not compliant on their ART
☐

23. Healthcare facilities are not doing enough to support HIV-infected pregnant women
☐ .

24. The government is not doing enough to support HIV-infected pregnant women
☐ .

25. Women with HIV/AIDS are having too many children
☐ .

26. HIV-infected women are getting pregnant to get grant money
☐

27. Men are involved in the PMTCT programme
☐ .

28. Men should be tested for HIV if their partner is positive

☐

I am going to ask you a few questions about PMTCT

29. Someone who has taken nevirapine in a previous pregnancy cannot take it again in the next pregnancy

☐ Yes
☐ No

30. If she takes Nevirapine a second time, it does not work

☐ Yes
☐ No

31. Nevirapine can be taken more than once in the same pregnancy

☐ Yes
☐ No

32. Taking AZT alone can lead to the development of resistance

☐ Yes
☐ No

33. AZT alone is used to treat HIV even if one is not pregnant

☐ Yes
☐ No

34. All pregnant women should be given HAART regardless of their CD4 count

☐ Yes
☐ No

35. If a pregnant woman gets HIV for the 1st time during pregnancy, chances of infecting the baby are small

☐ Yes
☐ No

36. It is important to know the pregnant woman's partner's HIV status

☐ Yes
☐ No

37. If a woman exclusively breastfeeds, the baby cannot get HIV

☐ Yes
☐ No

38. When a child is more than a year old and the mother is still breastfeeding, chances of the baby getting HIV are smaller than when the child is less than 6 months old

☐ Yes
☐ No

39. Women who are HIV-infected should not use the loop (IUCD) for contraception

☐ Yes
☐ No

Questions on attitudes towards the new PMTCT programme

40. Has the new programme increased your workload?
- ☐ Yes
- ☐ No

41. Do you think you were prepared for the new programme when it started?
- ☐ Yes
- ☐ No

42. Do you think the new programme is helping HIV-infected pregnant women and their children?
- ☐ Yes
- ☐ No

43. Do you think it is a good thing that the programme was started?
- ☐ Yes
- ☐ No

44. Do you think you need more staff to deal with the new programme?
- ☐ Yes
- ☐ No

Questions about the clients' knowledge and attitudes towards the new programme

45. Where you work, do you have a lot of clients, who refuse to take AZT?
- ☐ Yes
- ☐ No

46. Do you think your clients are compliant on AZT?
- ☐ Yes
- ☐ No

47. Do your clients know enough about the new programme?
- ☐ Yes
- ☐ No

48. Do your clients ask a lot of questions?
- ☐ Yes
- ☐ No

49. Do you think most of your clients disclose their status to their partners?
- ☐ Yes
- ☐ No

50. Do you think your clients understand all the information given to them about the PMTCT programme?
- ☐ Yes
- ☐ No

Is there anything that could have been done differently about the new programme?
- ☐ Yes
- ☐ No

If yes, what could have been done differently?

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Is there anything that can be done to improve the programme?

- ☐ Yes
- ☐ No

If yes, what do you think can be done?

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Questionnaire for clients in the study on assessment of the new PMTCT programme in Soweto, Johannesburg

This questionnaire is part of a study to assess clients' and healthcare workers' experiences with the new PMTCT programme that was started in March 2008. Clients who will be interviewed are those who are HIV-infected, pregnant and attending antenatal clinics in healthcare facilities in Soweto, Johannesburg.

History of previous pregnancies:

1. Age ☐☐

2. Parity ☐☐

3. Gravidity ☐☐

4. Gestational age ☐☐ weeks/ ☐☐ months

5. Number of live children ☐☐

6. When did you discover that you are HIV positive?
   - ☐ Current pregnancy
   - ☐ Previous pregnancy
   - ☐ Other time outside of pregnancy

7. If diagnosed in previous pregnancy, did you take nevirapine then?
   - ☐ Yes
   - ☐ No
   - ☐ Don't know

8. If nevirapine was taken, what year was it? ☐☐☐☐

9. Has the baby from that pregnancy been tested for HIV?
   - ☐ Yes
   - ☐ No

10. If tested, what is the baby's HIV status?
   - ☐ Negative
   - ☐ Positive
   - ☐ Don't know

Questions on disclosure of HIV status:

11. Have you disclosed your HIV status?
   - ☐ Yes
   - ☐ No

12. If yes, to whom?
   - ☐ Partner
   - ☐ Parent
   - ☐ Sibling
   - ☐ Friend
   - ☐ Other, specify_____

13. If you have not disclosed to partner, why? (Can choose more than 1 option)
    - ☐ Partner will leave me
    - ☐ Scared that partner will be violent
    - ☐ Partner will accuse me of being unfaithful
    - ☐ Partner will accuse me of infecting him with HIV
    - ☐ Other, specify _____

14. Have you discussed HIV/AIDS with your partner?
    - ☐ Yes
    - ☐ No

15. Do you know your partner's HIV status?
    - ☐ Yes
    - ☐ No

16. If known, what is it?
    - ☐ Negative
    - ☐ Positive
    - ☐ Don't know

Questions about current pregnancy and PMTCT:

17. How far was your pregnancy when you booked? ☐☐ weeks

18. What is your latest CD4 count? ☐☐☐☐

19. Have you started using AZT yet?
    - ☐ Yes
    - ☐ No

20. If yes, how long have you been using AZT for? ☐☐ weeks

21. Why are you using AZT/ why do you need to use AZT if you are HIV-infected and pregnant?
    - ☐ For my own health
    - ☐ To prevent my partner getting HIV
    - ☐ To decrease the chance of the baby getting HIV
    - ☐ All of the above

22. What is the ideal time to start AZT?
    - ☐ 3 months
    - ☐ 5 months
    - ☐ 7 months
    - ☐ 9 months

23. Is AZT taken throughout pregnancy?
    - ☐ Yes
    - ☐ No
    - ☐ Don't know

24. What do you need to take during labour?
- ☐ Nothing
- ☐ Nevirapine only
- ☐ AZT only
- ☐ Nevirapine and AZT
- ☐ Don't know

25. Does the baby get any treatment after being born?
- ☐ Yes
- ☐ No
- ☐ Don't know

26. If yes, what does the baby get?
- ☐ Nevirapine only
- ☐ AZT only
- ☐ Nevirapine and AZT
- ☐ Don't know

27. If the mother took AZT for 2 months in pregnancy, and the baby is given AZT, how much does it get?
- ☐ 1 day
- ☐ 7 days
- ☐ 10 days
- ☐ 28 days
- ☐ Don't know

Questions on infant feeding and testing:

28. What have you decided to give your baby after delivery?
- ☐ Breast milk only
- ☐ Formula only
- ☐ Breast milk and formula
- ☐ Have not decided yet

29. If you have chosen to exclusively breast feed, how long should it be for?
- ☐ 1 month
- ☐ 3 months
- ☐ 6 months
- ☐ 9 months

30. If you have chosen to exclusively formula feed, how long should it be for?
- ☐ 1 month
- ☐ 3 months
- ☐ 6 months
- ☐ 9 months

31. If exclusive breast feeding is the preferred option, what else can be given to the baby?
- ☐ Water
- ☐ Formula
- ☐ Porridge
- ☐ Nothing
- ☐ Don't know

32. If exclusive formula feeding is option chosen, what else can be given to the baby?
- ☐ Water
- ☐ Breast milk
- ☐ Porridge
- ☐ Nothing
- ☐ Don't know

33. Do you think that if you choose to use formula, people will know that you are HIV-infected?
- ☐ Yes
- ☐ No

34. At what age is the baby usually tested for HIV for the 1st time?
- ☐ At birth
- ☐ At 4 or 6 weeks
- ☐ At 3 months
- ☐ At 6 months
- ☐ At 1 year

Questions on counseling:

35. Do you think that the information you are given by sisters and counselors is enough?
- ☐ Yes
- ☐ No

36. How many counseling sessions have you received?
- ☐ None
- ☐ 1 session
- ☐ 2 sessions
- ☐ 3 sessions
- ☐ More than 3 sessions

37. Do you think that the time the counselors/health care workers spend talking to you is enough?
- ☐ Yes
- ☐ No

38. Do you think the counselors/health care workers treat you differently because you are HIV positive?
- ☐ Yes
- ☐ No

39. Are the counselors/health care workers impatient with you?
- ☐ Sometimes
- ☐ All the time
- ☐ Never

40. Do you belong to a support group?
- ☐ Yes
- ☐ No

41. If you belong to a support group, does it help you in any way?

- ☐ Yes
- ☐ No
- ☐ Don't know

42. Is there anything else you would like to say about being HIV positive and pregnant?

_____
_____
_____
_____
_____
_____
_____
_____
_____

43. Is there anything that can be done differently in the antenatal clinics?

_____
_____
_____
_____
_____
_____
_____
_____

Questionnaire for audit study **Study number: ☐☐☐**

Date of interview: __/ __/ __ (dd/mm/yy)

Clinic: _____

Clinic number: ☐☐☐☐☐☐☐☐☐☐

A. Demographics:

1. Age: ☐☐

2. Place of birth:
☐ South Africa
☐ Mozambique
☐ Zimbabwe
☐ Other, specify_____

3. Parity: ☐☐ 4. Gravidity: ☐☐

5. Marital status:
☐ single and not living with partner
☐ unmarried, but living with partner
☐ married
☐ divorced
☐ widowed
☐ other, specify_____

6. Highest level of education:
☐ no formal schooling
☐ junior school (grade 1-7)
☐ senior school (grade 8-11)
☐ matric (grade 12)
☐ tertiary education

7. Employed: ☐ yes ☐ no

8. Source of income:
☐ self only
☐ partner only
☐ self and partner
☐ parents
☐ other, specify_____

9. Dwelling:
☐ house with electricity and water
☐ informal settlement

B. History of positive HIV status:

10. Known HIV positive before last pregnancy: ☐ yes ☐ no

11. If known, for how long? ☐☐ month(s) or
☐☐ year(s)

12. On ART prior to last pregnancy: ☐ yes ☐ no

13. If yes, for how long? ☐☐ month(s) or
☐☐ year(s)

14. Any regimen change since start of ART: ☐ yes ☐ no

15. If yes, reason for regimen change: ☐ side effects
☐ non-adherence
☐ pregnancy
☐ other, specify _____

16. Has a CD4 count ever been done? ☐ yes ☐ no

17. If yes, what is the latest CD4 count? ☐☐☐☐

18. Partner's HIV status: ☐ negative
☐ positive
☐ unknown

19. If partner HIV-infected, on ART: ☐ yes ☐ no ☐ don't know

C. <u>History of previous pregnancies</u>:

20. Previous PMTCT (excluding last pregnancy): ☐ yes ☐ no

21. If yes, how many pregnancies where PMTCT was taken: ☐☐

22. If previous PMTCT, how long ago was it: ☐☐ months ☐☐ year(s)

23. Please give details about previous pregnancies with known positive HIV status:

Year	Type of PMTCT taken	Child's HIV status	If child HIV+, on ART?

Type of PMTCT taken: 1=sdNVP, 2=AZT only, 3=sdNVP and AZT, 4=ART, 5=other, specify

Child's HIV status: 1=negative, 2=positive

D. <u>History of last pregnancy</u>:

24. Planned pregnancy: ☐ yes ☐ no

25. Booked: ☐ yes ☐ no

26. If unbooked, what was the reason: ☐ clinic far
☐ turned away from the clinic
☐ did not know she was pregnant until very late
☐ other, specify _____

27. If booked, facility where antenatal clinic attended: _____

28. Province where antenatal clinic attended:
- ☐ Gauteng
- ☐ Western Cape
- ☐ Eastern Cape
- ☐ KwaZulu-Natal
- ☐ Limpopo
- ☐ Mpumalanga
- ☐ North West
- ☐ Northern Cape
- ☐ Free State

29. Antenatal clinic attended in another country:
- ☐ Zimbabwe
- ☐ Mozambique
- ☐ Other, specify _____

30. Gestational age at booking: ☐☐ weeks

31. Total number of antenatal clinic visits: ☐☐

32. HIV test done antenatally: ☐ yes ☐ no

33. HIV test only done after delivery: ☐ yes ☐ no

34. If HIV test only done after delivery, reason(s) why only done after delivery:
- ☐ unbooked
- ☐ not offered HIV test during pregnancy
- ☐ declined HIV test during pregnancy
- ☐ other, specify _____

If HIV test done antenatally,

35. Gestational age when HIV test done: ☐☐

36. CD4 cell count done at same visit: ☐ yes ☐ no

37. Was CD4 count result given: ☐ yes ☐ no

If given, how long after HIV test were CD4 cell count results collected:
- ☐☐ day(s)
- ☐☐ week(s)

38. If CD4 cell count not done at same visit as HIV test, at what gestation was it done:
- ☐☐ weeks

39. Booking CD4 cell count result: ☐☐☐☐

40. Prophylaxis or ART received during last pregnancy:
- ☐ AZT only
- ☐ AZT 1st, then ART
- ☐ ART
- ☐ nothing

41. If AZT received, gestational age at which started: ☐☐ weeks
Total duration of AZT before delivery: ☐☐ weeks

42. If ART started in last pregnancy, gestational age at which started: ☐☐ weeks
Total duration of ART before delivery: ☐☐ weeks

43. If ART started before last pregnancy, total duration of ART before delivery:
☐☐ weeks
☐☐ year(s)

44. Self-reported adherence to AZT or ART during pregnancy:
☐ very good
☐ good
☐ fair
☐ poor
☐ very poor

E. <u>History of labour and delivery</u>:

45. Date of delivery: __/ __/ __ (dd/mm/yy)

46. Place of delivery:
☐ Chris Hani Baragwanath Hospital
☐ Lenasia South
☐ Lillian Ngoyi
☐ Zola
☐ Itereleng
☐ Stretford
☐ Mofolo
☐ Home
☐ Other, specify _____

47. Gestational age at delivery: ☐☐ weeks
Based on ☐ dates
☐ ultrasound

48. Mode of delivery:
☐ normal vaginal delivery
☐ elective caesarean section, indication _____
☐ emergency caesarean section, indication _____
☐ vacuum
☐ forceps

49. Episiotomy: ☐ yes ☐ no

50. Birth weight: ☐☐☐☐ g

51. Intrapartum and postpartum complications during labour:
☐ none
☐ rupture of membranes more than 4 hours before delivery
☐ labour more than 12 hours
☐ labour augmented
☐ antepartum haemorrhage
☐ baby admitted to neonatal ICU ☐☐ days
☐ other, specify _____

52. Prophylaxis or treatment taken during labour and delivery: ☐ NVP only
☐ AZT only
☐ NVP and AZT
☐ Truvada
☐ ART ☐ nothing

53. If no prophylaxis or treatment taken, what were the reasons:
☐ forgot to take tablets
☐ tablets left at home
☐ declined treatment
☐ other, specify _____

F. <u>Infant prophylaxis given</u>:

54. Infant prophylaxis given after delivery: ☐ sdNVP only
☐ AZT syrup for 7 days
☐ AZT syrup for 28 days
☐ AZT syrup for 6 weeks
☐ NVP syrup for 6 weeks
☐ extended NVP syrup prophylaxis
☐ nothing

55. If infant prophylaxis given, how soon after delivery was the prophylaxis given?
☐ immediately after delivery
☐☐ days after delivery
☐☐ weeks after delivery
☐☐ months after delivery

56. If no infant prophylaxis given, reasons why not given:

☐ not offered
☐ declined infant prophylaxis
☐ other, specify _____

G. <u>Infant feeding option</u>:

57. Counselling given on infant feeding: ☐ yes ☐ no

58. Infant feeding option chosen after delivery: ☐ exclusive breastfeeding
☐ exclusive formula feeding
☐ mixed feeding

59. If exclusive breastfeeding, duration: ☐☐ week(s) ☐☐ month(s)

60. If exclusive formula feeding, duration: ☐☐ week(s) ☐☐ month(s)

61. Source of formula if formula feeding: ☐ local clinic
☐ buys own formula
☐ other, specify _____

62. Has the supply of formula been: ☐ uninterrupted
☐ interrupted

63. Current infant feeding option: ☐ exclusive breastfeeding
☐ exclusive formula feeding
☐ mixed feeding

64. Duration of current feeding option: ☐☐ days
☐☐ weeks
☐☐ months

H. <u>Infant testing and treatment</u>:

65. Age at which baby first tested for HIV: ☐☐ week(s) ☐☐ month(s)

66. Previous admission to hospital: ☐ yes ☐ no

67. If admitted, reason for admission: ☐ gastroenteritis
☐ chest infection
☐ other, specify _____

68. Duration of admission: ☐☐ days ☐☐ weeks

69. Is the baby currently on any of the following:
☐ none
☐ cotrimoxazole
☐ antibiotics
☐ TB treatment
☐ multivitamins
☐ other, specify _____

Infant feeding survey interview guide – antenatal component

The interview guide is for both HIV-infected and –uninfected women

Date of interview: ___/ ___/___ **Interviewer: _____**
dd mm yy

Study number: ☐☐☐☐ **Clinic number: _____**

Number of clinic visits for this pregnancy – 1st, 2nd, 3rd, 4th, other_____
(Circle the one that applies, and include current visit)

A. <u>Demographics</u>:

1. Age: _____ 2. Weeks pregnant _____ (***Get duration of pregnancy from the antenatal card)***

3. Number of previous pregnancies: _____
(Include all pregnancies whether the child/children are alive or not)

4. Marital status: ☐ Single and not living with partner ☐ Single, but living with partner
☐ Married ☐ Divorced ☐ Widowed
☐ Other, specify_____

5. Highest level of education: ☐ Junior school (grade 1-7) ☐ Senior school (grade 8-11)
☐ Matric (grade 12) ☐ Tertiary education ☐ No formal schooling

6. Employed: ☐ Yes ☐ No

7. Source of income: ☐ Self only ☐ Partner only ☐ Self and partner
☐ Parents ☐Other, specify_____

8. Dwelling: ☐ House with electricity and water
☐ Informal settlement, if yes,
A. does it have water? ***(inside)*** Yes ☐ No ☐
B. does it have electricity? Yes ☐ No ☐

9. Total number of people in household: _____

10. Number of children younger than 18 years in household: _____
(Include also those that are not the client's own)

11. Currently living with parents or parent in-laws in household: ☐ Yes ☐ No

B. <u>Details on HIV status</u>

12. HIV status: ☐ Negative ☐ Positive ☐ Unknown

13. Timing of HIV diagnosis: ☐ Before current pregnancy ☐ During pregnancy ☐ Not done
(Current pregnancy)

14. If HIV positive, latest CD4 count: _____
(From the antenatal card)

15. What tablets are you currently taking? ☐ FDC/ART started before current pregnancy
☐ AZT ☐ FDC/ART started during pregnancy
☐ Nothing ☐ Other, specify _____

16. Have you disclosed your HIV status? ☐ Yes ☐ No
(Whether HIV-infected or –uninfected)

If no, why?
_____

17. If you've disclosed, who have you disclosed to? ☐ Partner ☐ Parent ☐ Sibling
☐ Friend ☐ Other, specify_____
(Can choose more than one answer)

C. <u>Infant feeding choices</u>:

18. Have you ever breastfed before? ☐ Yes ☐ No

19. If you've breastfed before, what is the longest time you breastfed for? _____
(Weeks, months, years. If there's more than one child that was breastfed, choose one that was breastfed the longest, and give that answer)

20. What are you planning to feed the baby? ☐ Breast milk only ☐ Formula only
☐ Breast milk and formula ☐ Other, specify _____

21. Did you receive counselling in the clinic on infant feeding? ☐ Yes ☐ No

22. If planning to breastfeed, how long do you plan to breastfeed for?
_____ weeks or _____months or _____years

23. If planning to formula feed, how long do you plan to formula feed for
_____ weeks or _____months or _____years

24. If planning to give breast milk and formula, how long do you plan to give this for?
_____ weeks or _____months or _____years

25. If planning to formula feed, where will you get the money to buy formula from?

☐ Own money ☐ Money from partner ☐ Money from your family

☐ Money from partner's family ☐ Social grant ☐ Other, specify_____
(Can choose more than one)

26. Why have you decided the above?
☐ Information from the clinic ☐ Information from the media, e.g. radio
☐ Decision made with partner ☐ Influence from the family
☐ Information from friends ☐ Other, specify _____
(Can choose more than one)

27. Have you discussed your decision with anyone? ☐ Yes ☐ No
(Infant feeding choice)

28. If yes, who have you discussed it with? ☐ Partner ☐ My family ☐ Partner's family ☐ Friend ☐ Other, specify_____

(Can choose more than one; exclude healthcare workers)

29. If HIV-infected, has your HIV status influenced your infant feeding choice? ☐ Yes ☐ No
Explain,

_____

(Only ask if the woman is HIV-infected)

30. If employed, are you returning to work after delivery? ☐ Yes ☐ No
If returning to work, when? In ☐ 6 weeks ☐ 3 months ☐ 4 months ☐ 5 months ☐ 6 months ☐ other, specify _____

How has this affected your infant feeding choice?

_____

_____

D. <u>Infant Feeding knowledge</u>

Please do not lead clients when asking questions, and don't comment if they give wrong answers. Be careful of your body language also when asking the questions

31. If one chooses to exclusively breast feed, how long should it be for?
☐ 1 month ☐ 3 months ☐ 6 months ☐ 9 months ☐ other, specify _____

32. If one chooses to exclusively formula feed, how long should it be for?
☐ 1 month ☐ 3 months ☐ 6 months ☐ 9 months ☐ other, specify _____

33. If exclusive breast feeding is the option chosen, what else can be given to the baby?
☐ Water ☐ Formula milk ☐ Porridge ☐ Other food ☐ Nothing ☐ Don't know
(Can choose more than one)

34. If exclusive formula feeding is the option chosen, what else can be given to the baby?
☐ Water ☐ Breast milk ☐ Porridge ☐ Other food ☐ Nothing ☐ Don't know
(Can choose more than one)

35. Do you think that if you choose to use formula, people will think that you are HIV-infected?
☐ True ☐ False
36. Do you think most mothers exclusively breastfeed for 6 months?
☐ True ☐ False ☐ Don't know

37. Do you think it is easy for mothers to exclusively breastfeed for 6 months?
☐ True ☐ False ☐ Don't know

38. Enough information is given in the clinics to encourage mothers to exclusively breastfeed
☐ True ☐ False ☐ Don't know

39. Working mothers can easily exclusively breastfeed for 6 months
☐ True ☐ False ☐ don't know

40. When an infant cries it always means that it's hungry
☐ True ☐ False ☐ don't know

41. Breast milk is better than formula milk
☐ True ☐ False ☐ don't know

42. Formula milk is almost as good as breast milk
☐ True ☐ False ☐ don't know

43. Infants who are breastfed are less likely to get infections
☐ True ☐ False ☐ don't know

44. All mothers should breastfeed for up to 2 years
☐ True ☐ False ☐ don't know

Questions 45 to 52 must be answered by both HIV+ and HIV- women

45. Does the HIV-infected mother who is breastfeeding need to take any medication?
☐Yes ☐ No ☐ Don't know

46. If she needs to take medication, what does she need to take?
_____

47. If she takes medication, how long does she need to take it for?
☐ For life ☐ Until 1 week after stopping breastfeeding ☐ It depends on the CD4 count
☐ Don't know ☐ other, specify _____

48. Does the baby need to take medication during breastfeeding?
☐ Yes ☐ No ☐ don't know

49. If the baby needs to take medication, what does it need to take? _____

50. If the baby takes medication, how long does it need to take it for?
☐ 6 weeks ☐ 12 weeks ☐ 6 months ☐ 9 months ☐ It depends on whether the mother is on ART or the FDC and when she started treatment
☐ Don't know ☐ other, specify _____

51. If the mother is HIV-infected, when is the infant first tested for HIV?
At _____ weeks or _____months

52. With the HIV-infected mother, when is the infant tested again after stopping breastfeeding?

After: ☐ 1 month ☐ 6 weeks ☐ 3 months ☐ 6 months ☐ 9 months
☐ Other, specify _____ ☐ don't know

E. <u>Breastfeeding support</u>

53. Not enough information is given in the clinics on exclusively breastfeeding
☐ True ☐ False ☐ don't know

54. Breastfeeding support groups in the clinics would encourage mothers to exclusively breastfeed
☐ True ☐ False ☐ Don't know

55. Breastfeeding support groups in the community would encourage mothers to exclusively breastfeed ☐ True ☐ False ☐ Don't know

56. Cultural factors prevent most mothers from exclusively breastfeeding
☐True ☐False ☐ Don't know

57. Influence from elders in the family prevent most mothers from exclusively breastfeeding
☐True ☐False ☐ Don't know

Comments: _____

_____

_____

Infant feeding survey interview guide – postnatal component

Date of interview: ___/ ___/___ Interviewer: _____

Study number: ☐☐☐☐ Clinic number: _____

A. Demographics:

1. Age: _____ 2. Number of previous pregnancies: _____
(Include all pregnancies whether the child/children are alive or not-include the recent pregnancy)

3. Marital status: ☐ Single and not living with partner ☐Single, but living with partner ☐ Married ☐ Divorced ☐Widowed ☐ Other, specify_____

4. Highest level of education: ☐ Junior school (grade 1-7) ☐ Senior school (grade 8-11) ☐ Matric (grade 12) ☐ Tertiary education ☐ No formal schooling

5. Employed: ☐ Yes ☐ No

6. Source of income: ☐ Self only ☐ Partner only ☐ Self and partner ☐ Parents ☐ Other, specify_____

7. Dwelling: ☐ House with electricity and water
☐ Informal settlement, if yes, does it have water? Yes ☐ No ☐;
Does it have electricity? Yes ☐ No ☐

8. Total number of people in household: _____

9. Number of children younger than 18 years in household: _____
(Include also those that are not the client's own)

10. Currently living with parents or parent in-laws in household: ☐ Yes ☐ No

B. Details on HIV status:

11. HIV status: ☐ Negative ☐ Positive ☐ Unknown

12. Timing of HIV diagnosis: ☐ Before pregnancy ☐ During pregnancy ☐ Not done
(Recent pregnancy)

13. If HIV positive, latest CD4 count: _____ ***(If available)***

14. What tablets are you currently taking? ☐ FDC/ART started before pregnancy
☐ FDC/ART started during pregnancy
☐ Nothing ☐ Other, specify _____

15. Have you disclosed your HIV status? ☐ Yes ☐ No
(Whether HIV-infected or –uninfected)

16. If you've disclosed, who have you disclosed to? ☐ Partner ☐ Parent ☐ Sibling ☐ Friend ☐ Other, specify_____
(Can choose more than one answer)

C. <u>Infant feeding choice</u>:

17. How old is the infant? _____ weeks/months

18. Place of delivery: ☐ Chris Hani Baragwaneth Hospital ☐ Lenasia South

☐ Lillian Ngoyi ☐ Zola ☐ Itereleng ☐Stretford ☐ Mofolo ☐ Home

☐ Other, specify _____

19. Date of delivery: ___/___/___
dd/mm/yy

20. What are you currently feeding the infant? ☐ Breast milk only ☐ Formula only

☐ Breast milk and formula ☐ Breast milk and solids ☐ Formula and solids

☐ Other, specify _____

21. If breastfeeding, how long have you been breastfeeding for?
_____ weeks or _____ months

22. Have you ever breastfed before? ☐ Yes ☐ No

23. If you've breastfed before, what is the longest time you breastfed for? _____
(Weeks, months, years. If there's more than one child that was breastfed, choose one that was breastfed the longest, and give that answer)

24. If formula feeding, how long have you been formula feeding for?
_____ weeks or _____ months

25. If giving breast milk and formula, how long have you been giving this for?
_____ weeks or _____ months

26. If giving breast milk and solids, how long has she been giving this for?
_____ weeks or _____ months

27. If giving formula and solids, how long have you been giving this for?
_____ weeks or _____ months

28. Have you given any of the following: gripe water, traditional medicines, tea, water, juice or any other drinks? (Circle the ones that apply)- ***(Can choose more than one)***

29. If using formula, where do you get the money to buy formula from?

☐ Own money ☐ Money from partner ☐ Money from my family

☐Money from partner's family ☐Social grant ☐ Other, specify

_____

(Can choose more than one)

30. What is your current infant feeding decision based on?

☐ Information from the clinic ☐ Information from the media, e.g. radio or TV

☐ Decision made with partner ☐Influence from the family

☐ Information from friends ☐Other, specify _____

(Can choose more than one)

31. Have you discussed your decision with anyone? ☐Yes ☐ No
(infant feeding choice)

32. If yes, who have you discussed it with? ☐ Partner ☐ Her family ☐ Partner's family
☐ Friend ☐ Other, specify _____

(Can choose more than one; exclude healthcare workers)

33. If HIV-infected, has your HIV status influenced your infant feeding choice? ☐ Yes ☐ No

Explain_____
(Only ask if the woman is HIV-infected)

34. Are you returning to work? ☐ Yes ☐ No

35. If you are returning, when are you returning? ☐ Have returned already

Returning in: ☐ 6 Weeks ☐ 3 Months ☐ 4 Months ☐ 5 Months ☐ 6 Months

☐ Other, specify _____

36. How has this affected your infant feeding choice?

_____

_____

37. If you have chosen to exclusively breastfeed, what have the challenges been?

_____

_____

D. <u>Infant feeding knowledge</u>:

Please do not lead clients when asking questions, and don't comment if they give wrong answers. Be careful of your body language also when asking the questions

38. If one chooses to exclusively breast feed, how long should it be for?

☐ 1 month ☐ 3 months ☐ 6 months ☐ 9 months ☐ Other, specify _____

39. If one chooses to exclusively formula feed, how long should it be for?

☐ 1 month ☐ 3 months ☐ 6 months ☐ 9 months ☐ Other, specify _____

40. If exclusive breast feeding is the option chosen, what else can be given to the baby?

☐ Water ☐ Breast milk ☐ Porridge ☐ Other food ☐ Nothing ☐ Don't know

(Can choose more than one)

41. If exclusive formula feeding is the option chosen, what else can be given to the baby?

☐ Water ☐ Breast milk ☐ Porridge ☐ Other food ☐ Nothing ☐ Don't know

(Can choose more than one)

42. Do you think that if you choose to use formula, people will think that you are HIV-infected?

☐ Yes ☐ No

43. Do you think most mothers exclusively breastfeed for 6 months? ☐ Yes ☐ No ☐ Don't know

44. Do you think it is easy for mothers to exclusively breastfeed for 6 months?

☐ Yes ☐ No ☐ Don't know

45. Enough information is given in the clinics to encourage mothers to exclusively breastfeed

☐ True ☐ False ☐ Don't know

46. Working mothers can easily exclusively breastfeed for 6 months

☐ True ☐ False ☐ Don't know

47. When an infant cries it always means that it's hungry

☐ True ☐ False ☐ Don't know

48. Breast milk is better than formula milk

☐ True ☐ False ☐ Don't know

49. Formula milk is almost as good as breast milk

☐ True ☐ False ☐ Don't know

50. Infants who are breastfed are less likely to get infections

☐ True ☐ False ☐ Don't know

51. All mothers should breastfeed for up to 2 years

☐ True ☐ False ☐ Don't know

Questions 52 to 59 must be answered by both HIV+ and HIV- women

52. Does the HIV-infected mother who is breastfeeding need to take any medication?

☐ Yes ☐ No ☐ Don't know

53. If she needs to take medication, what does she need to take?

_____

54. If she takes medication, how long does she need to take it for?

☐ 1 month ☐ 3 months ☐ 6 months ☐ 9 months ☐ It depends on the CD4 count

☐ Don't know ☐ other, specify _____

55. Does the baby need to take medication during breastfeeding?

☐ Yes ☐ No ☐ Don't know

56. If the baby needs to take medication, what does it need to take?

_____

57. If the baby takes treatment, how long does it need to take it for?

☐ 1 month ☐ 3 months ☐ 6 months ☐ 9 months ☐ It depends on whether the mother is on FDC/ART and when it was started ☐ Don't know ☐ Other, specify

_____

58. If the mother is HIV-infected, when is the infant first tested for HIV? At _____ weeks/months

59. With the HIV-infected mother, when is the infant tested again after stopping breastfeeding?

After: ☐1 month ☐ 6 weeks ☐3 months ☐ 6 months ☐ 9 months ☐ Don't know

D. <u>Breastfeeding support</u>:

60. Not enough information is given in the clinics on exclusively breastfeeding

☐True ☐ False ☐ Don't know

61. Breastfeeding support groups in the clinics would encourage mothers to exclusively breastfeed ☐ True ☐ False ☐ Don't know

62. Breastfeeding support groups in the community would encourage mothers to exclusively breastfeed

☐ True ☐ False ☐ Don't know

63. Cultural factors prevent most mothers from exclusively breastfeeding

☐True ☐ False ☐ don't know

64. Influence from elders in the family prevent most mothers from exclusively breastfeeding

☐ True ☐ False ☐ don't know

Comments: _____

_____

_____

Maternal mortality study data collection tool

File number: _____ Study number: ☐☐☐☐

Background information

Area of residence: _____

Age at time of death: ____ years Parity: ____ Gravidity: ____

Booked: Y/N Booking date: ___/___/___ Gestational age at booking: ____ weeks

Gestational age determined by: LNMP/palpation/ultrasound

Singleton/twins/other, specify _____

☐ ectopic pregnancy ☐ abdominal pregnancy gestational age: ____ weeks

☐ other, specify_____

Booking haemoglobin: _____

At the time of death, was the woman still pregnant? Y/N

If not pregnant, when did she die? ☐ during labour and delivery ☐ postpartum

Details on HIV testing

Timing of HIV test: prepregnancy/antenatal/intrapartum/postpartum/not done

HIV status: negative/positive/unknown

If HIV positive, baseline CD4 count done: Y/N Date of baseline CD4 count: ___/___/___

Baseline CD4 count result: _____

Antenatal AZT initiated: Y/N Date AZT initiated: ___/___/___

Duration of AZT before delivery or death: ____ days/weeks

Preconception ART: Y/N If yes, duration: ____ months/years

ART regimen: ☐ d4T ☐ TDF ☐ 3TC ☐ AZT ☐ NVP ☐ EFV ☐ Aluvia

☐ unknown ☐ other, specify _____

Referred for ART antenatally: Y/N If referred, date referred: __/ __/ __

ART initiated during pregnancy: Y/N If yes, duration of ART before death: ____ weeks/months

ART regimen: ☐ d4T ☐ TDF ☐ 3TC ☐ AZT ☐ NVP ☐ EFV ☐ Aluvia

☐ other, specify _____

Comments: _____

_____

_____

Admission details

Date of admission: ___/ ___/___ Time of admission: ___ h ___

Self-referral: Y/N Referred by: ☐ clinic or ☐ hospital

If referred, referring clinic or hospital: _____

Was the woman still pregnant on admission? Y/N

Gestational age on admission: ____ weeks If still pregnant, was she in labour? Y/N

If in labour, was she in latent/active phase? ☐ latent phase ☐ active phase

Postpartum on admission: Y/N If postpartum, days postpartum: ____ days

Reason(s) for admission : (can choose more than one)

☐ LAP ☐ in labour ☐ rupture of membranes ☐antepartum haemorrhage ☐ BBA
☐ postpartum haemorrhage ☐ abdominal wound sepsis ☐ offensive vaginal discharge
☐ headache ☐ blurred vision ☐ convulsions ☐ collapsed
☐ elevated blood pressure (BP) Admission BP: ____ ☐ proteinuria
☐ pyrexia ☐ cough ☐ shortness of breath ☐ chest pains
☐ abdominal pain ☐ diarrhoea ☐ vomiting other, specify _____

Comments: _____

_____

_____

Underlying medical condition

☐ neurological _____ ☐ respiratory _____ ☐ cardiac _____

☐ renal _____ ☐ abdominal _____ ☐ other _____

On chronic medication: Y/N If yes, specify: _____

_____

Special investigations

Blood results on admission:

WCC _____ Hb _____ Platelets _____ Urea _____ Creatinine _____

Total protein _____ Albumin _____ ALT _____ AST _____

LDH _____ INR _____ PTT _____

Worst blood results: **Date of blood results: ___/___/___**

Hb _____ Platelets _____ Urea _____ Creatinine _____

CD4 count _____

Other: _____

Admission foetal ultrasound done: Y/N

If done, findings on ultrasound: ☐ placenta praevia ☐ abruption placentae

☐ ectopic pregnancy ☐ abdominal pregnancy ☐ RPOC ☐ IUFD

☐ other, specify: _____

Chest X-ray: done/not done **Chest X-ray findings:** ☐ normal ☐ parenchymal infiltrates

☐ pleural effusion ☐ unilobar pneumonia ☐ multilobar pneumonia

☐ military pattern ☐ ground glass pattern ☐ cardiomegaly ☐ pulmonary oedema

☐ hilar lymph nodes ☐ other, specify _____

Sputum results: ☐ AFB positive ☐ AFB negative ☐TB culture positive

☐ other, specify _____☐ not done

Lumbar puncture (LP): done/not done Findings: ☐ normal ☐ bacterial meningitis

☐ TB meningitis ☐ cryptococcal meningitis ☐ other, specify _____

CT brain: Y/N If done, findings:

☐ intracerebral bleed ☐ infarct ☐ space-occupying lesion ☐ oedema

☐ coning ☐ other, specify: _____

Other special investigations and findings: _____

_____

_____

Delivery details

Date of delivery: __/ __/ __ Place of delivery: clinic/hospital/home/BBA

Name of delivery clinic/hospital: _____

GA at delivery: ____ weeks Birth weight: ____ g

Mode of delivery: ☐ NVD ☐ vacuum ☐ forceps ☐ elective C/S ☐ emergency C/S

☐ peri-mortem C/S

Indication for C/S: _____

Pregnancy outcome: ☐ live birth ☐ FSB ☐ MSB ☐ neonatal death ☐ miscarriage

☐ ectopic pregnancy

Comments: _____

_____

_____

_____

_____

_____

Medical management

☐ oral antibiotics ☐ IVI antibiotics ☐ TB treatment ☐ antihypertensives

☐ oral steroids ☐ IVI steroids ☐ tocolytic

☐ misoprostol route of administration ☐ PR ☐ oral ☐ sublingual

☐ total misoprostol dose administered ☐ other, _____

Blood transfusion: Y/N

Surgical interventions

☐ evacuation of the uterus ☐ hysterectomy ☐ laparotomy ☐ other _____

Comments: _____

_____

Details about the death

Date of death: ___/_ __/___ Time of death: ___ h ___

☐ undelivered ☐ delivered If delivered, hours/days postpartum: ____ hours/days

If undelivered, gestational age at death: _____ weeks

Cause of death: please circle one or more causes under each category

☐ **Coincidental cause:**
MVA, other accidents, assault, rape, herbal medicine, other (specify) _____

☐ **Medical and Surgical disorders:**
Cardiac disease, endocrine, GIT, CNS, respiratory, haematological, genito-urinary, auto-immune, skeletal, psychiatric, neoplasm, other (specify) _____

☐ **Non-pregnancy-related infections:**
PCP pneumonia, other pneumonia, TB, endocarditis, UTI, appendicitis, malaria, cryptococcal meningitis, other meningitis, Kaposi's sarcoma, toxoplasmosis, cholera, hepatitis, gastroenteritis, wasting syndrome, complications of anti-retroviral therapy, other (specify) _____

☐ **Ectopic pregnancy:**
<20 weeks, >20 weeks

☐ **Miscarriage:**
Septic miscarriage, haemorrhage (non- traumatic), uterine trauma, GTD, following legal TOP

☐ **Pregnancy-related sepsis:**
Chorioamnionitis with ruptured membranes, chorioamnionitis without ruptured membranes, puerperal sepsis after NVD, puerperal sepsis after c/s, bowel trauma at c/s

☐ **Obstetric haemorrhage:**
Abruption with/without h/t, praevia, other APH not specified, ruptured uterus with/without previous c/s, retained placenta, morbidly adherent placenta, uterine atony, vaginal/cervical trauma, inverted uterus, bleeding during c/s, bleeding after c/s, other PPH not specified _____

☐ **Hyperemesis gravidarum**

☐ **Hypertension:**
Chronic hypertension, proteinuric hypertension, eclampsia, HELLP, liver rupture, acute fatty liver

Final cause of death: ☐ respiratory failure ☐ cardiac failure (pulmonary oedema, cardiac arrest)

☐ renal failure ☐ liver failure ☐ cerebral complications (intracranial haemorrhage, cerebral oedema, brain death following hypoxic event) ☐ haematological (disseminated intravascular coagulation, severe anaemia) ☐ multi-organ failure

☐ **Anaesthetic complications:**
General / epidural / spinal anaesthetic

☐ **Embolism:**
Pulmonary embolus, amniotic fluid embolus

☐ **Acute collapse – cause unknown**

☐ **Unknown:**
Death at home or outside health services, no primary cause found, lack information

☐ other, specify _____

Comments: _____

_____

Post-mortem done: Y/N If done, result: _____

_____

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ORIGINALITY REPORT

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1	Coceka N Mnyani, Eckhart J Buchmann, Matthew F Chersich, Karlyn A Frank, James A McIntyre. "Trends in maternal deaths in HIV-infected women, on a background of changing HIV management guidelines in South Africa: 1997 to 2015", Journal of the International AIDS Society, 2017 Publication	3%
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