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# Coverage of prevention of mother-to-child transmission services in Cape Town, South Africa

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Thesis presented for the degree of Doctor of Philosophy in the School  
of Public Health and Family Medicine, University of Cape Town

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This thesis is presented in fulfilment of the requirements for the degree of Doctor of Philosophy (PhD) in the School of Public Health and Family Medicine, Faculty of Health Sciences, University of Cape Town. The work on which this thesis is based is original research and has not, in whole or in part, been submitted for another degree at this or any other university. The contents of this thesis are entirely the work of the candidate, or in the case of multi-authored published papers, constitutes work for which the candidate was the lead author. The contribution of the candidate to included multi-authored papers is further delineated in the preface to the thesis.

Kathryn Stinson

February 2012

University of Cape Town

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## Preface

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This thesis comprises 5 papers written for publication as per provision 6.7 in the General Rules for the Degree of Doctor of Philosophy (PhD) of the University of Cape Town, and with the approval in 2010 of the University Doctoral Degrees Board. The analysis and drafting of these papers was carried out by the candidate during the period of doctoral degree registration.

The candidate was the lead author on each manuscript and responsible for the study design (of all projects except the first), the data collection, analysis and synthesis of results under the supervision of her doctoral advisor. All co-authors critically reviewed and approved the submitted manuscripts. The following five papers are included as part of the thesis and are presented as self-contained chapters in the following order:

- Stinson, K., Boulle, A., Smith, P., Stringer, E.M., Stringer, J.S.A., Coetzee, D. (2012) Coverage of the prevention of mother-to-child transmission (PMTCT) programme in the Western Cape, South Africa using cord blood surveillance. *Journal of Acquired Immune Deficiency Syndromes*, (in press)
- Stinson, K., Boulle, A., Coetzee, D., Abrams, E.J., Myer, L. (2010) Initiation of highly active antiretroviral therapy among pregnant women in Cape Town, South Africa. *Tropical Medicine and International Health* 2010; 15(7): 825-32.
- Stinson, K., Myer, L. Service delivery approaches for antiretroviral therapy initiation during pregnancy in South Africa (to be submitted for review in 2012 to *PLoS Medicine*)
- Stinson, K., Myer, L. (2012) Barriers to initiating antiretroviral therapy during pregnancy: a qualitative study of women attending services in Cape Town, South Africa. *African Journal of AIDS Research*, (in press)
- Stinson, K., Myer, L. (2012) HIV-infected women's experiences of pregnancy and motherhood in Cape Town, South Africa. *Vulnerable Children and Youth Studies*, (in press)

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## Abstract

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Prevention of mother-to-child transmission (PMTCT) services were established in Cape Town during 1999, and antiretroviral treatment (ART) services for pregnant women with advanced stage HIV were implemented in 2004. This thesis uses a mixed-methods approach to evaluate these services between 2005 and 2008, and describes the challenges to PMTCT programme coverage in this setting.

Five chapters, each submitted for publication, are presented. The first paper presents results from a cross-sectional study utilizing cord blood surveillance to ascertain PMTCT programme coverage in 2007-2008. Cord blood analysis showed that 58% of HIV-infected women received standard of care treatment according to guidelines. Missed opportunities for intervention were found at different stages of the PMTCT care pathway, including failure to test for HIV and sub-optimal regimen adherence during labour. Discrepancies between documented coverage and cord blood coverage suggested a need for strengthened routine data collection and reporting. The second and third papers examine ART initiation in eligible women accessing antenatal services in 2005 and 2008. Three service models are described, defined by the proximity of the antenatal service to the ART service. In these retrospective cohorts, data showed that uptake of ART in pregnancy increased from 51% in 2005 to 52% in 2008. In 2005, there was no difference in uptake between service models. However, the 'integrated' service with outreach staff providing ART in the antenatal facility initiated significantly more women in 2008. In both papers, late antenatal presentation was associated with failed coverage. The fourth paper describes HIV-infected women and service providers' perceptions of challenges to ART initiation in pregnancy, and the final paper discusses women's experience of HIV-positive pregnancy and motherhood. Paper 4 suggests that a triple emotional burden of pregnancy, HIV-positive diagnosis and the requirement to start lifelong therapy, impacts on ART uptake, while Paper 5 suggests that considerable emotional work is undertaken by these women to maintain their social identities as mothers. The thesis concludes that PMTCT coverage remains sub-optimal in this setting. Novel approaches to service delivery which focus on missed opportunities for intervention as well as the needs of women should be explored.

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In high school, the single piece of vocation guidance I was given – by my History of Music teacher – was that I should consider writing a doctorate one day. At the time I had no idea that twenty years after carefully crafting essays on Bach cantatas and Mozart symphonies, I would be submitting a body of work in public health concerning a topic so compelling that it drew me in to the point of obsession. This product of three years of work would not have been possible without the assistance of others. In particular, I would like to thank the following people who have supported me through the process:

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Prevention of mother-to-child transmission of HIV concerns the experience of mothers, their children and their families. Much of the inspiration behind my research was provided by my mother and father, who showed me in childhood that it is possible to embrace life, chronic illness and loss with dignity and fortitude. My children, William and Sophie gave me the time and space required to think and write, when I know that they would have preferred to have had me more present as a mother. This thesis would not have been possible without the unstinting support of my husband, Tom, who acted as a sounding board for ideas, unconditionally provided hours of childcare on weekends and holidays and continued to encourage me to the end. To you all, thank you.

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## Chapter 1 — Introduction

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### 1.1 Background

Antiretroviral (ARV) regimens administered to pregnant women and exposed infants during pregnancy and postpartum have been shown to be highly effective in the prevention of mother-to-child transmission of HIV (PMTCT) and the preservation of maternal health.<sup>1-7</sup>

Paediatric AIDS has been virtually eliminated in resource-rich settings, yet children account for one in six new HIV infections in sub-Saharan Africa daily, the majority of these infections being attributable to mother-to-child transmission (MTCT).<sup>8</sup>

The epidemiology of HIV in children reflects the burden of disease in women, and AIDS is the leading cause of death among women of reproductive age worldwide.<sup>9</sup> HIV has contributed to considerable increases in maternal mortality in sub-Saharan Africa, and has hampered the progress towards meeting Millennium Development Goal (MDG) 5, which aims to improve maternal health.<sup>10,11</sup> HIV-infected women experience greater morbidity and mortality than uninfected women,<sup>12</sup> and initiation of antiretroviral treatment in women during pregnancy may be both lifesaving for women, and impact on the reduction of vertical transmission.<sup>13</sup>

Prevention of mother-to-child (PMTCT) programmes have been implemented across Africa, where the highest proportion of HIV-infected pregnant women live.<sup>11,14</sup> Yet, compared to resource-rich settings and the rapid scale-up of national antiretroviral therapy (ART) programmes in countries with a high burden of disease, progress in the expansion and coverage of PMTCT programmes has for the most part lagged behind expected targets, despite reports that 70% of HIV-infected pregnant women in these settings access antenatal services at least once in pregnancy.<sup>15</sup> Service- and patient-related factors such as poor service integration and resource constraints, programme uptake, poor adherence and loss to follow-

up, limit the public health effectiveness and impact of these programmes.<sup>16</sup> Programme estimates of global PMTCT coverage in 2009 indicated that 53% of HIV-infected pregnant women and 35% of exposed infants received antiretroviral drugs.<sup>17</sup>

Improved approaches to health system delivery of PMTCT programmes and the use of safer and more acceptable treatment regimens with proven effectiveness have been promoted over the past decade.<sup>18</sup> While some ground has been gained in attenuating the impact of HIV infection in children through improved PMTCT programme effectiveness, antiretroviral prophylaxis in pregnancy and postpartum is of little therapeutic benefit to mothers, particularly in women with advanced stage disease. Children of mothers who have died of AIDS have a 3- to 4-fold increased risk of mortality, regardless of HIV status.<sup>19,20</sup> A recent shift in focus from simple pregnancy-based prophylactic interventions to reduce vertical transmission, first demonstrated in the 1990s, to the recognition of the importance of maternal health situated in models of family-based care has resulted in the more comprehensive PMTCT strategy found in current international guidelines.<sup>21</sup> Not only does this approach focus on prevention of paediatric infection, it also incorporates additional elements to target the primary prevention of HIV in women of reproductive age, the prevention of unintended pregnancy in HIV-infected women, and the identification of women who require treatment for their own health, emphasising the need to link them and their families to HIV treatment and care services.<sup>22</sup>

Historically, PMTCT programme interventions in the field have concentrated primarily on the third and fourth elements of the strategy, focusing on women who are identified as HIV-infected and already pregnant.<sup>23</sup> While these approaches have been shown to drastically decrease paediatric infection in resource-constrained settings and improve maternal and child health, challenges remain in the implementation of PMTCT programmes in health systems which are poorly resourced and inadequately integrated to meet the needs of HIV-infected

pregnant women who require a continuum of care in the context of maternal and child health services.<sup>24,25</sup>

In the WHO's commitment to global PMTCT scale-up, integration and the forging of service linkages has been earmarked as an area of focus to promote stronger maternal, infant and child and reproductive health programmes.<sup>21</sup> Pregnancy is a critical time for identifying HIV infection in women for prevention of MTCT, but antenatal services can also identify a cohort of women with advanced stage disease and facilitate opportunities to link them to lifelong antiretroviral treatment (ART).<sup>24,26</sup> Thus, within PMTCT programmes there is the potential to integrate prevention and treatment, two areas of service delivery that are frequently independently defined.<sup>27</sup> Furthermore, recent scientific developments have led to the use of extended ART regimen combinations for maternal treatment and/or mother-infant prophylaxis, to cover the breastfeeding period in order to mitigate postpartum transmission and to increase programme effectiveness by lowering late postpartum transmission risk, and providing women with a broader range of infant feeding options.<sup>1,28-30</sup>

## 1.2 Rationale

This thesis is situated within a larger body of operational research which evaluates the effectiveness of PMTCT programmes in resource-constrained settings. The population under study is drawn from HIV-infected pregnant women attending antenatal services in Cape Town, South Africa, and the research concentrates on PMTCT and ART treatment services for HIV-infected pregnant women within a broader social context of pregnancy and motherhood. Operational research into programme implementation is useful on a local level because it can provide context-specific evidence on the gaps and weaknesses which may affect service uptake and programme effectiveness. As a result, programmatic improvement can be effected by addressing missed opportunities that are identified through service-based evaluation.<sup>23</sup> Little is known about PMTCT programme coverage, and more specifically, the

availability of ART services for women in pregnancy within the Cape Town service setting. Furthermore, the challenges faced by HIV-infected women in initiating ART during pregnancy have not been investigated in this population. Overall, there is a paucity of research which documents the lived experience of HIV-positive motherhood in resource-constrained settings.

Historically, PMTCT programmes have highlighted the weaknesses of health services in resource-constrained settings but at the same time, have presented an opportunity for health systems strengthening.<sup>9</sup> The starting premise of this thesis is based upon the argument made elsewhere<sup>15,23,25-27</sup> that the transfer of scientific progress in PMTCT research to resource-constrained settings has not been optimized, and a gap remains between efficacy of PMTCT interventions and the operational effectiveness of these programmes. Within ten years of publication of the first trial results that demonstrated the efficacy of PMTCT regimens in 1994, MTCT had been virtually eliminated in well-resourced countries.<sup>27</sup> In the United States and the United Kingdom, the early identification of HIV-infected women in pregnancy through universal opt-out HIV screening; the administration of effective antiretroviral regimens to women who require it for their own health or for prophylaxis; the use of caesarean section and the complete avoidance of breastfeeding through the use of safe replacement feeding, has led to vertical transmission rates of 1-2%.<sup>31</sup> A call has been made for resource-constrained settings to work towards the virtual elimination of paediatric HIV.<sup>32,33</sup> Yet PMTCT programmes in these contexts continue to lag behind in their coverage, due to a higher burden of disease, poor health system infrastructure, cost implications a lack of service integration as well as social and structural factors which influence demand for PMTCT.<sup>34</sup>

### 1.3 Aim

The aim of this thesis is twofold. First, it documents and evaluates the coverage of the PMTCT programme in terms of prophylactic interventions and ART for women in Cape Town who require it for their own health during pregnancy. In the context of this thesis, coverage is defined as the proportion of the at-risk population who successfully access and utilize the intervention, excluding those not accessing antenatal care, or accessing antenatal care privately or outside the public health setting. Second, the thesis investigates the barriers to maternal ART initiation in pregnancy and describes the experience of HIV-positive motherhood. The real-world population effects of a programme are a product of intervention efficacy and coverage, and hence effectiveness is synonymous with programme impact. While this thesis does not address PMTCT outcomes directly, through the synthesis of these findings, it draws inferences on factors which may compromise programme effectiveness. Five research questions are employed to achieve these aims:

- What proportion of HIV-infected pregnant women who access antenatal care in Cape Town are identified by services as requiring PMTCT interventions, and receive standard of care regimens by delivery?
- What proportion of women who present at antenatal services and are subsequently identified as eligible to initiate lifelong ART, have started treatment by the time they deliver?
- Is there a difference between selected service models for delivering ART to HIV-infected pregnant women with advanced disease in Cape Town, and have there been changes in ART coverage within these service models since the inception of the programme?
- What are the perceived challenges which compromise ART initiation by HIV-infected women in the context of pregnancy?

- How do HIV-infected women - pregnant and 6-month postpartum - experience HIV-infection during pregnancy, and furthermore, how do they manage HIV-positive motherhood?

Based on the synthesis of the findings of this thesis, the concluding chapter discusses why programme coverage in this setting is suboptimal and makes recommendations for future service improvement.

#### 1.4 Outline

A mixed methods approach has been applied to answer these research questions. Three research projects were undertaken to collect primary data used in this thesis (Table 1.1).

**Table 1.1 Summary of research projects, their outcomes and primary methodology, used in the preparation of the thesis**

| Project | Chapter | Publication title  | Outcome   | Methodology  |
|---------|---------|--|---|--|
| 1       | 3       | Coverage of the prevention of mother-to-child transmission programme in the Western Cape, South Africa using cord blood surveillance       | PMTCT coverage                                  | Cross sectional survey using clinical folders and cord blood specimens |
| 2       | 4       | Initiation of highly active antiretroviral therapy among pregnant women in Cape Town, South Africa   | ART initiation in pregnancy                     | Retrospective cohort study using service registers and folders         |
|         | 5       | Service delivery approaches for antiretroviral therapy initiation during pregnancy in South Africa   | ART initiation in pregnancy (follow up)         | Retrospective cohort study using service registers and folders         |
| 3       | 6       | Barriers to initiating antiretroviral therapy during pregnancy: a qualitative study of women attending services in Cape Town, South Africa | Challenges to ART initiation                    | In-depth interviews  |
|         | 7       | <b>HIV-infected women's experiences of pregnancy and motherhood in Cape Town, South Africa</b>   | The lived experience of HIV-positive motherhood | In-depth interviews  |

The first entailed cord blood surveillance in the Western Cape, which formed a sub-study to the PEARL Study, conducted in four African countries between 2007 and 2010.<sup>35</sup> The PEARL Study was a two-part evaluation of the effectiveness of PMTCT services at both the community and facility level. The second comprised two evaluations of ART initiation in

three different service delivery models in Cape Town services in 2005 and 2008. The third was a qualitative study among health care providers and HIV-infected pregnant or postpartum women, which investigated the barriers to ART initiation in pregnancy and the experience of HIV-positive motherhood.

The projects' outcomes, which pertain to retrospective service data from 2005 to the end of 2008, are reported in five self-contained chapters that have been prepared for publication during the period of registration for the PhD. Chapter 2 reviews the literature and places the research within the broader context of PMTCT implementation research. The first research project is described in Chapter 3, and concerns the evaluation of PMTCT programme coverage. This chapter entails an analysis of a cord blood surveillance exercise at three Cape Town antenatal services during 2007-2008. Overall coverage is analysed and comparisons are drawn between the documentation of interventions dispensed and their presence in cord blood. Through the analysis of the PMTCT cascade, missed opportunities for prevention are identified.

The second research project is described in Chapters 4 and 5, and concerns ART initiation in Cape Town. These two chapters present an evaluation of ART initiation among eligible pregnant women during the early stages of the programme in 2005, and in a follow-up study conducted in 2008. Three service delivery models are compared in terms of the proportion of eligible women who initiate ART before delivery, in order to provide insight on the optimal model for ART provision for pregnant women within Cape Town health services.

While these two projects present quantitative service-related data, the third project qualitatively examines the challenges to initiating ART in pregnancy and women's lived experience of HIV infection, pregnancy and motherhood. Chapters 5 and 6, which are based on the results of this project, present the results of in-depth interviews with service providers and HIV-infected pregnant or 6 month postpartum women. In order to gain insight into the

factors that compromise treatment coverage, Chapter 5 examines the barriers to ART initiation described by women who were identified as eligible for lifelong treatment in pregnancy. Chapter 6 explores women's perceptions of HIV infection in pregnancy, and how women manage HIV-positive motherhood. Since much evidence on the experience of HIV-positive motherhood emanates from resource-rich settings, this chapter uses developed country discourse to compare and contrast the experiences of HIV-positive mothers in the context of the South African HIV epidemic.

The final chapter synthesises the results from the three research projects into an account of factors that influence PMTCT programme effectiveness in this setting. Conclusions are drawn about programme coverage, which according to the data presented in the thesis, is suboptimal. While these results are in keeping with findings from other African settings discussed in the literature review, the possible reasons for compromised programme effectiveness, and proposed interventions for improvement, are discussed in the context of both the evidence presented in each paper and current international trends in PMTCT. The overall limitations of the thesis and potential avenues for future research are described.

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## Chapter 2— The development of PMTCT programmes: a literature review

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This review establishes the background to, and the conceptual framework for, this thesis. It covers the development of PMTCT interventions and the successes and failures resulting from their implementation in field settings over the past 20 years. Specific evidence pertaining to the establishment and expansion of the South African PMTCT programme is presented in order to provide the context for the rest of the thesis. While this thesis does not cover the impact of infant feeding on MTCT, the final part of the review focuses on current international scientific trends that address postpartum transmission, and are emerging as increasingly important challenges. These scientific advancements, which provide the basis for future operations research, are discussed in the concluding chapter of this thesis.

This literature review is structured around themes which are pertinent to the empirical research conducted in the ensuing chapters. In order to lay the ground work for the rest of this thesis, Section 2.1 of this literature review provides an account of the first decade of PMTCT programme implementation. After briefly outlining the risk factors for MTCT, this section describes the transfer of evidence from clinical trials to the field, and the evidence for early successes and failures of simple drug regimens introduced to resource-poor contexts. Since this thesis concerns a South African setting, evidence from sub-Saharan Africa is afforded particular weight here.

Sections 2.2 and 2.3 follow chronologically from Section 2.1, by documenting the emergence of ART for pregnant women in resource-poor contexts. The idea of service linkage between ART and antenatal care is introduced in Section 2.3 and early evidence for the feasibility of integrated ART and antenatal services is discussed. The published literature from other African settings is described here, in light of the challenges to linkages to care.

This section provides the background for the content of Chapters 4 and 5 of the thesis, which evaluate different service delivery models for ART initiation in pregnancy, these models varying in terms of the proximity of antenatal care to ART services.

While the abovementioned sections situate the thesis within a broader context of PMTCT programme development, Section 2.4 reviews the literature on challenges to PMTCT coverage and ART initiation. This section covers cross-cutting themes pertinent to all the chapters, including late antenatal presentation (Chapters 4, 5 and 6); reluctance to test for HIV in pregnancy, leading to unknown HIV status (Chapter 3); psychosocial aspects of HIV-positive pregnancy and motherhood (Chapter 7) and challenges to the initiation of ART and adherence during pregnancy and postpartum (Chapter 6). Other themes, including access and service-related barriers to PMTCT and counselling and testing in the peripartum are also discussed as important barriers to PMTCT coverage, however, are only indirectly associated with the empirical research in this thesis.

Section 2.5 provides the background to the research setting of this thesis, through the documentation of the PMTCT programme from inception in 1999 to 2011 in the Western Cape and other parts of South Africa. This provides local context for the data presented in this thesis, which range from 2005 to 2008. Section 2.5 also documents evidence of poor routine data collection within the PMTCT programme which compromises the reporting of programme progress.

Although beyond the scope of this thesis, infant feeding is emerging as an important challenge to prevention of postpartum vertical transmission. Section 2.6 covers some of the major findings from postpartum prevention studies and interventions reported around 2009, which have shaped the current WHO PMTCT guidelines (2010).<sup>36</sup> The presentation of this evidence leads into Section 2.7, which focuses on the call for the elimination of paediatric HIV and current PMTCT policy in South Africa. Section 2.8 concludes with a synthesis of the main themes of the literature review.

## 2.1 Prevention of mother-to-child transmission: the first decade

### 2.1.1 *Risk factors for MTCT*

MTCT accounts for the majority of paediatric infections worldwide, and can occur during pregnancy, labour and delivery or postpartum during breastfeeding.<sup>37</sup> In non-breastfeeding populations, transmission risk ranges between 15-30% , this risk being increased to 20-45% in breastfeeding populations.<sup>9</sup> Other host characteristics include maternal immune factors, including neutralising antibodies; breast milk immune factors and fetal or newborn immune response.<sup>38,39</sup> Genetic factors such as the foetal HLA type and maternal-foetal HLA concordance may increase risk of MTCT, due to limited effectiveness of the foetal immune response against maternal HIV.<sup>39</sup> Certain viral characteristics have been associated with transmission, and one or very few viral variants are reported more commonly than multiple variants in infected infants. The evidence on HIV subtype differences in vertical transmission, however, is mixed.<sup>39</sup>

There is a strong relationship between high maternal viral load, low CD4 cell count and elevated transmission risk.<sup>40</sup> Perinatal MTCT risk can be reduced to around 2% with the use of antiretroviral regimens and the complete avoidance of breastfeeding.<sup>3,4,7,41</sup> Elective caesarean section and the avoidance of prolonged rupture of membranes have also been shown to reduce transmission risk.<sup>42,43</sup> Recent evidence supporting the use of antiretrovirals administered to mothers and/or infants in the postpartum period can reduce the risk of MTCT to 5% in breastfeeding populations.<sup>44</sup>

### 2.1.2 *Evidence from clinical trials*

In 1994, the ground-breaking Pediatric AIDS Clinical Trials Group (PACTG) protocol 076 demonstrated marked reductions in vertical transmission through the administration of antepartum azidothymidine (AZT) from 14 weeks gestation, intrapartum and to the newborn for 6 weeks postpartum. This regimen showed a 67.5% relative reduction in MTCT at 6

weeks in non-breastfeeding women.<sup>2</sup> In the United States and other well-resourced countries, immediate changes were made to public health policy to implement this intervention, frequently in conjunction with caesarean section.<sup>45</sup> The complexity and cost of this regimen prevented its wide-spread use in Africa until results from trials in Thailand and, later, Côte d'Ivoire demonstrated the efficacy of shorter course oral AZT, which targeted the antenatal and peripartum period, reducing transmission risk by around 50% and 44% respectively.<sup>46,47</sup> To account for breastfeeding populations, DITRAME/ANRS 0049a reported a reduced MTCT risk of 38% in Burkina Faso and Côte d'Ivoire at 6 months postpartum,<sup>48</sup> while later the addition of lamivudine (3TC) to increase antiviral potency in combination with AZT to mother ante-, peri- and postpartum to the mother and infant demonstrated a reduction in transmission risk of 61% at six weeks.<sup>49</sup> However, little impact was found for AZT on transmission risk during breastfeeding.<sup>27</sup>

Around the same time, the efficacy of single dose nevirapine (sdNVP) was demonstrated in a breastfeeding population in Uganda.<sup>50</sup> Based on the assumption that a single dose intervention targeted at the neonate and ingested by the mother at the onset of labour, followed by an infant dose within 72 hours of delivery, would be sufficient to reduce vertical transmission risk, HIVNET 012 reported a 47% efficacy between 14 -16 weeks.<sup>51</sup> As a nonnucleoside reverse-transcriptase inhibitor (NNTRI) with a long half-life, sdNVP was deemed simple to administer and inexpensive to use in resource-constrained settings and it was heralded as a breakthrough for PMTCT where medical infrastructure is inadequate, not least because sdNVP could be used in breastfeeding populations with poor access to antenatal care.<sup>9,18</sup> However, protection was not sustained in breast feeding populations with infections being reported from 56 days to 18 months follow up.<sup>51,52</sup> As the fifth trial to be reported among breastfeeding populations, the South African Intrapartum Nevirapine Trial (SAINT) compared regimens from the PETRA and HIVNET trials, notably multiple dose AZT/LMD and sdNVP, and found that both regimens had similar efficacy and safety.<sup>19,53</sup> In

2000, in order to take into consideration local context and country-level programme capacity, the WHO and UNAIDS recommended three options for PMTCT including short course AZT or AZT/LMD, sdNVP and exclusive breastfeeding with early weaning in resource-constrained settings, depending on feasibility, efficacy, acceptability and cost.<sup>54</sup>

### **2.1.3 *Field effectiveness of early PMTCT programmes in resource-constrained settings***

These successes paved the way for a series of pilot projects for the provision of PMTCT services in resource-constrained countries.<sup>18,55</sup> In 2001, targets of reducing the proportion of vertically infected children by 20% by 2005 and by 50% by 2010 were set by the United Nations General Assembly in the Declaration of Commitment on HIV/AIDS.<sup>56</sup>

UNAIDS/UNICEF, WHO and the World Bank launched projects focusing on short course AZT in Botswana, Burundi, Cote d'Ivoire, Honduras, India, Kenya, Rwanda, Tanzania, Uganda, Zambia, and Zimbabwe. United Nations agencies and global funding initiatives, such as the Global Fund and PEPFAR, as well as pharmaceutical companies supported the expansion of sdNVP interventions.<sup>57</sup> These efforts were also supported from as early as 1999 in 11 countries in sub-Saharan Africa, Russia and Thailand by the Elizabeth Glazer Pediatric AIDS Foundation's (EGPAF, through support of the Gates Foundation and other private donors) "Call to Action".<sup>14,58,59</sup> With the goal of expanding access to PMTCT programmes in these settings, EGPAF projects focussed on the integration of PMTCT within existing maternal and child health services, the training and re-deployment of staff to deliver the services, and the promotion of new cadres of staff such as lay health workers, community workers and traditional birth attendants to assist with programme strengthening. To assist with programme uptake, these countries also applied different counselling and testing approaches incorporating opt-out counselling and rapid HIV testing. Choice of ARV regimen was determined by country on the basis of large scale feasibility and cost, with most countries opting for sdNVP, with the selective piloting of dual regimens and ART.<sup>58</sup>

#### 2.1.4 *Early evidence of missed opportunities for PMTCT coverage*

Optimal PMTCT programme coverage is reliant on the completion of a series of interventions through pregnancy and after birth, including access of antenatal/PMTCT services; offer and acceptance of HIV testing and if HIV-infected, receipt and ingestion of antiretrovirals before, during and after delivery and through breastfeeding. This sequence of steps is known as the PMTCT cascade.<sup>60</sup> After 2000, several African countries published early results from evaluations of their PMTCT pilot programmes. These reports highlighted some of the successes and also several challenges in early programme implementation, which were later to be found in other settings to lead to suboptimal programme coverage. For example, in Zambia, the feasibility and cost effectiveness of sdNVP was demonstrated in the first year of programme operations (2001), with a 72% HIV testing uptake and 57% and 40% of women and babies receiving NVP respectively, leading to a PMTCT rate of 65 children per 1 000 identified infected mothers.<sup>61</sup> Lower uptake was reported in Zimbabwe, where despite universal testing uptake, the first pilot programme demonstrated that only 74% of women returned to collect their test results and 24% of infected women and children received sdNVP.<sup>62</sup> Return for HIV test results and low uptake of peripartum AZT were also a challenge in Côte d'Ivoire. In Abidjan, 80% of women opted to undergo testing and 71% of HIV-negative women returned for their results. Fewer infected women (60%) returned for their results and 64% of women received AZT up to delivery.<sup>63</sup> Another effectiveness study in Abidjan (ANRS 1201/1202 Ditrane Plus), commencing in 2000, suggested uptake among one third of women who had been identified for a dual regimen package in pregnancy.<sup>64</sup> These reports were among the first to reveal missed opportunities for prevention and service gaps which led to suboptimal PMTCT programme coverage.

Field efficacy of MTCT was reported to vary widely across settings as the first outcomes from these early field studies were released. In Kenya, a perinatal transmission rate of 18% at 14 weeks was documented with the use of sdNVP, suggesting a limited reduction

in effect from 21%.<sup>65</sup> Another effectiveness study in this country which compared the sdNVP regimen from HIVNET 021 to the Thailand study comprising AZT from 36 weeks and during labour, reported higher MTCT among those who received sdNVP (22%) versus those who received the AZT protocol (9%).<sup>66</sup> In a prospective cohort of two clinics in Lusaka, Zambia, the 6-week transmission rate was reported to be 11%.<sup>67</sup> In Cameroon, an early effectiveness study of NVP reported 10% of children infected with HIV at 6 to 8 weeks, similar to the results found in the SAINT trial NVP arm.<sup>53,68</sup>

Operational issues that emerged as challenges in these settings included the need to adjust patient flow and accommodate nurse training in PMTCT for the purpose of scale-up and integrating PMTCT within antenatal services. Adequate staffing and district level support were seen to be integral to programme expansion, and community mobilization demonstrated increased service coverage in Zimbabwe.<sup>69</sup> Patient adherence was a challenge in Zambia and Kenya, with the latter country reporting that male partner notification and partner support increased adherence in pregnancy.<sup>66,67</sup> Most countries reported challenges to testing and the return for HIV results, even in the context of rapid testing, citing stigma and fear of partner abuse as contributory reasons.<sup>23,61,63</sup> In Côte d'Ivoire, poor uptake in the ANRS 1201/1202 Ditrane Plus study was associated with lower educational level and living with a partner. The authors suggested that more community awareness could assist women with a better understanding of the PMTCT programme as well as create wider awareness of the benefits of HIV testing and programme uptake among women and their families.<sup>64</sup>

### **2.1.5      *The emergence of drug resistance***

Although not covered in this thesis, drug resistance induced by short course regimens resulting in incomplete suppression of HIV, was a widespread concern from 2000. This shaped much of the literature on PMTCT and became an issue for policy change. It was evident that the long half-life and potency of NVP that contributed to the success in

reducing vertical transmission was also a limitation, particularly among women with advanced-stage disease who had high plasma HIV RNA levels and low CD4+ cell counts.<sup>70</sup> Both HIVNET 012<sup>50</sup> and the SAINI<sup>53</sup> trials showed rapid selection of NVP-resistant HIV after one and two doses of NVP for up to 18 months and 13 months postpartum respectively in both women and children.<sup>71-75</sup> Resistance was not limited to NVP, but was also reported for other short course regimens that did not fully suppress HIV, including 3TC and AZT, the probability of resistance increasing with higher plasma HIV RNA levels and regimen duration.<sup>76,77</sup>

At the time, scientists considered whether resistance was clinically meaningful and if so, what the implications of antiviral agents for exposed women in subsequent pregnancies would be. Also, little was known about the management of women who required NNRTI-based highly active antiretroviral (HAART, referred to here as ART) regimens for their own health post sdNVP exposure, and the consequences thereof.<sup>27,78</sup> Evidence from the results of the Perinatal HIV prevention Trials group (PHPT-2) trial in Thailand by Lallemand *et al.*, which demonstrated that the use of sdNVP to mother and infant in addition to short course AZT (from 28 weeks) led to an 80% reduction in transmission in formula-fed infants at one month.<sup>79</sup> This marked the beginning of a second generation of less expensive, feasible combination regimens for resource-constrained contexts.<sup>80</sup> However, in subsequent follow-up analyses of these data, Jourdain *et al.* confirmed that women who had previous exposure to sdNVP were less likely to attain virologic suppression (<50 copies/ml) than those who were NVP naïve. Nevertheless clinical improvements and CD4 cell counts were comparable in the two groups.<sup>81</sup> Again, resistance from intrapartum dosing was notably more prevalent among women with high plasma HIV-1 RNA levels and low CD4 cell counts, who would have benefited from ART in pregnancy. This fuelled further debate around strategies to optimize the benefits of PMTCT for women who required prophylaxis as well as those who required antiretroviral therapy for their own health in resource-constrained settings.<sup>81,82</sup>

Critics of the PMTCT programme voiced concerns about the lack of attention paid to maternal health outcomes in light of the increasing maternal mortality attributed to AIDS and argued that the focus of PMTCT needed to be extended beyond the prophylactic benefit to the foetus. It was highlighted that women had little access to antiretroviral therapy for themselves, and that child outcomes were prioritised over maternal health and survival.<sup>83,84</sup> There was need to seek affordable and safer combination regimens which could be used in resource-poor settings.<sup>85</sup>

### *2.1.6 The introduction of combination drug regimens for PMTCT in Africa*

Since the release of the PACTG 076 results, evidence from other trials and observational cohorts demonstrated that antiretroviral agents including ART, together with caesarean section delivery, lowered MTCT risk to around 2%.<sup>3,4,7,86</sup> Guidelines recommending extended duration of ART in pregnancy combined with caesarean section and the avoidance of breastfeeding had been implemented rapidly in the United States, Europe and Brazil for all women.<sup>80,87-89</sup> The combined use of these prolonged, effective regimens and the rapid mobilization of public health services; the availability of good sanitation and the cultural acceptability of replacement feeding contributed to dramatic decreases in MTCT reported around 2002-04 in these settings.<sup>19,90</sup>

By contrast, the widening gap between resource-rich and resource-poor contexts was conspicuous: while there were 124 new infections among children under 13 years in the United States in 2005,<sup>91</sup> at the same time vertical transmission in low and middle-income countries was increasing unabated, with an estimated 1800 infants becoming infected per day.<sup>92</sup> While sdNVP reduced MTCT, scientists argued that there was a 'moral imperative' to improve MTCT rates in resource-constrained settings.<sup>78</sup>

By the late 1990s, triple-drug regimens were already widely available as prophylaxis for women in the United States and Europe.<sup>93</sup> Yet more complex, efficacious regimens in

resource-constrained settings required sufficient service reach and delivery to be effective. Since 2001, unprecedented public health mobilization towards stemming the HIV epidemic has occurred. While countries were committed to reducing the proportion of infected infants by 20% by 2005, in 2005 only 7 out of 71 countries were on track to meet this target.<sup>94</sup>

In 2004, revised guidelines for resource-constrained settings were published by the WHO in response to new scientific evidence on regimen safety and efficacy which were to be implemented in the context of the scale-up of PMTCT programmes.<sup>95</sup> Several clinical approaches were described in these guidelines: women who did not have indications for ART were to receive either AZT from 28 weeks of pregnancy together with sdNVP during delivery and sdNVP and a week of AZT for the infant. Recognizing that combination regimens could be burdensome on both services and pregnant women and hence neither feasible nor acceptable, these guidelines made provision for alternative regimens based on AZT alone, short-course AZT/3TC or sdNVP alone.<sup>95</sup> The importance of maternal health in resource-constrained settings was highlighted, and for the first time, it was recommended that women who required treatment for their own health were to receive it during pregnancy.<sup>95</sup>

With the efficacy of the second generation PMTCT regimens for resource-constrained settings involving short course combination treatments clearly demonstrated in the PHPT-2 trial,<sup>79</sup> study results from Côte d'Ivoire and Botswana showed further reduction in transmission rates, suggesting that reducing MTCT to below 5% in Africa was possible.<sup>80</sup>

Dual regimens were shown to be effective in a trial in Côte d'Ivoire. In this study, maternal AZT from 36 weeks and infant dose for 1 week postpartum, as well as sdNVP to mother and infant peripartum led to a transmission rate of 6.5% (95% CI: 3.9-9.1%) at 6 weeks, a 72% reduction in transmission risk when compared to AZT alone. Importantly, however, this study reported that although ART regimens were not widely available for women at the time of the study, MTCT rates decreased with regimen complexity in ART-

eligible women: 23% with AZT alone, 13% for AZT and sdNVP, and 9% for AZT, 3TC and sdNVP. While these results were not statistically significant, the authors reported that the dual regimen was particularly effective in settings where access to ART was not available, yet they expressed concern over the residual transmission risk among these women for whom ART would be more effective.<sup>96</sup>

More promising findings were reported in Botswana around the same time. In this study, women were randomized to receive sdNVP or placebo in labour in addition to AZT from 34 weeks gestation (all infants received sdNPV and AZT for one month). One-month transmission rates of 4.3% (95% CI:  $\pm 2.3\%$ ) were reported for the intervention and 3.7% (95% CI:  $\pm 2.2\%$ ) in the placebo arm, although these results were not statistically different. In 2002 while the trial was underway, ART was introduced for women with advanced disease (CD4 cell count  $\leq 200$  cells/ $\mu$ /L) in Botswana, and 2.8% of women on ART transmitted HIV to their infants.<sup>97</sup> For the first time, vertical transmission rates below 5% had been demonstrated in Africa.

## 2.2 The emergence of ART for pregnant women in resource-constrained settings

During a technical consultation concerning the drafting of the 2004 WHO guidelines, which recommended treatment for women with indications for ART in pregnancy for the first time,<sup>95</sup> it was acknowledged that antenatal services provided an opportunity to identify and link women with advanced stage disease to lifelong ART treatment and care, preventing residual vertical transmission at the same time.<sup>98</sup> Yet these recommendations, based on successes in Europe and America, were proposed for programmes which were already burdened with poor uptake of simple regimens. There was virtually no evidence at this time to suggest the efficacy or safety of ART in resource-poor contexts and there was concern for the feasibility of ART initiation in pregnancy, given the challenges associated with PMTCT uptake reported in early effectiveness studies.<sup>98</sup>

ART had been shown to be effective in Brazil where it had been used since 1998,<sup>89</sup> however, the first results of ART use in a resource-constrained African setting were reported from Côte d'Ivoire among women on the MTCT-Plus Programme. Early results showed that of 69 live births to women who started ART at 30 weeks gestation, there was one case of MTCT.<sup>99</sup>

Around this time, the Drug Resource Enhancement against AIDS and Malnutrition (DREAM) programme, run in several African countries, enrolled women on triple regimens, regardless of CD4 cell count threshold during pregnancy, continuing for 6 months postpartum for prevention and lifelong therapy for women with advanced stage disease.<sup>100</sup> DREAM in Mozambique demonstrated strong programme uptake and 80% completion of the treatment protocol and transmission rates in Mozambican (across all CD4 cell counts) to be 3%.<sup>101</sup> Limitations of this study may have contributed to this favourable outcome: the sample size was small (n=985) and selection bias may have occurred as selected Mozambican facilities were used.

The preliminary evidence from the MTCT-Plus programme in Côte d'Ivoire was released around the time of the Abuja Call to Action in December 2005, which underscored the move towards the elimination of HIV in infants and young children.<sup>102</sup> Following this, the WHO released revised recommendations for PMTCT in 2006. The purpose of these guidelines was to align PMTCT programmes with increasing international commitment to universal access to HIV prevention, treatment and care.<sup>103</sup> The guidelines comprised a two-tier strategy for the provision of standardized regimens as described in the 2004 guidelines. However, a public health approach was stressed within the context of human and financial resource constraints. The primary focus of the updated guidelines was the integration and streamlining of PMTCT within maternal and child health services to increase service utilization and broaden the reach of PMCT programmes. Not only were PMTCT programmes to be placed within maternal and child health, but pathways to link women to

HIV services for lifelong ART were seen as critical for increasing programme effectiveness.<sup>104</sup>

2.3 Integrating ART for pregnant women within antenatal services  
Within PMTCT programmes there is the potential to integrate prevention and treatment, two areas of service delivery that are frequently independently defined.<sup>27</sup> Pregnancy provides a valuable but time-limited opportunity for identifying HIV infection in women for the purpose of prevention of MTCT. Yet antenatal services can also identify a cohort of women with advanced stage disease and facilitate opportunities to link them to lifelong treatment and care.<sup>24,26</sup> The treatment and care of pregnant women with advanced stage disease, as well as the extension of these services to their families has been incorporated in PMTCT strategy since 2002,<sup>105</sup> this being further entrenched in the 2006 WHO PMTCT guidelines. In the WHO's 2010 commitment to global PMTCT scale-up, integration and the forging of service linkages has been earmarked as an ongoing area of focus to promote maternal, infant and child and reproductive health programme strengthening.<sup>21</sup>

### 2.3.1 *The development of linkages between antenatal and ART services*

Service linkage is a term often used loosely and interchangeably with the term 'integration'<sup>106</sup> and more recently, it also extends to the concept of 'continuum of care', which refers to the promotion of linked services to minimise patient attrition. In this thesis, the investigation of service linkages is central to the analysis of Chapters 4 and 5, where service models for ART initiation in pregnancy are discussed, and the question regarding the optimal model of service delivery is posed.

Service linkage across different programmes in primary health care settings was first applied to the management of the elderly<sup>107</sup> and then expanded to include among others, the integration of sexual and reproductive health services for women in maternal health care and linkages between family planning services and HIV/STI services in the 1990s, as a response

to the need for disease control through existing mainstream services for women.<sup>108,109</sup> The rationale behind integration is to meet a broader range of client needs and to have greater population reach, thus improving the efficiency and effectiveness of health service delivery.<sup>110</sup> Since the ideology behind service linkage is very much the same, there is little consensus on the definition and interpretation of integrated versus linked services and hence the use of these terms varies within the literature.<sup>111</sup>

The literature on service integration concedes that service linkages can be successful in terms of outcomes and impact under certain conditions, yet in some instances it is neither feasible nor beneficial.<sup>112</sup> The latter is frequently attributed to incompatibility between policy and service levels: if policy guidelines are drawn up at an administrative level within a verticalised management framework (i.e. with separate programme directorates), the implementation of integrated programmes at the service level may be compromised. Similarly, separate funding streams for discrete programmes can add complexity to integrated service implementation. Health care provider training or experience, capacity and attitudes will influence success of integration, as will patients' level of understanding and attitudes towards disease.<sup>109</sup>

The integration of services to manage maternal and child health and services to treat HIV illustrates the potential effectiveness of a comprehensive service delivery approach through a continuum of care from the time of preconception through to postpartum and beyond. From as early as 2002, a four-prong strategy for PMTCT was devised to incorporate the prevention of primary infection of women of reproductive age; the prevention of unintended pregnancies among women living with HIV; the prevention of MTCT and the provision of appropriate treatment, care and support for HIV-infected mothers and their children and families.<sup>105</sup> The third and fourth prongs are the focus of most programmes in the field and programme reporting, due to the complexity of monitoring and reporting on data on prongs one and two.<sup>17,113</sup>

As described above, evidence from early field effectiveness studies suggested that PMTCT interventions using simple short course regimens in resource-constrained countries could be successfully integrated into antenatal services. PMTCT guidelines were easily incorporated into antenatal service delivery and had the potential for widespread coverage. Both PMTCT and antenatal services involved care of mothers and infants and sufficient cross-over in skills between staff at primary health care level.<sup>114</sup> Antenatal services across sub-Saharan Africa were well attended and sdNVP and short course regimens which were limited to pregnancy and the peripartum were simple to administer by nurses or midwives. In particular, sdNVP did not require multiple antenatal visits nor laboratory monitoring and could be initiated in labour.<sup>80</sup> While these simple combination regimens were shown to be feasible in resource-constrained settings, researchers raised concerns about residual transmission attributable to women who required ART for their own health.<sup>96</sup> Furthermore, sdNVP may have been more complex programmatically in rural areas with fewer infrastructural and staff resources to ensure complete coverage. There was growing recognition of the missed opportunity to address the health concerns of these women in the context of antenatal care, among whom the greatest impact of MTCT prevention could be achieved.<sup>83,115</sup>

### **2.3.2 Antenatal services as a gateway to lifelong maternal ART**

HIV care and treatment services for women with advanced stage disease have more often been established as stand-alone services, which could threaten the continuity of care during pregnancy, postpartum and beyond in these women. As a result, scientists have suggested that the aim of a comprehensive approach to PMTCT programmes - that is, to combine prevention and treatment of HIV - may be compromised.<sup>24</sup> Pregnancy is episodic, requiring progression from antenatal services to delivery services and postnatal baby care. In contrast, HIV requires ongoing longterm care. Given the separate administration of services, in some cases distinct funding streams and capacity of services in terms of specialised training and

expertise, it has been suggested that programme linkages to forge a continuum of care, rather than integration of services may be less complex to engineer.<sup>24</sup>

With the efficacy of PMTCT regimens proven and early evidence that ART initiation in resource-constrained contexts was feasible and effective, the focus of efforts to strengthen and scale up PMTCT programmes has moved to operations and implementation research since the release of the 2006 WHO PMTCT guidelines.<sup>104</sup> There was new interest in appropriate models of care which facilitate ART initiation through linkages to care in eligible pregnant women, despite poor health services infrastructure and other challenges in resource-constrained contexts.<sup>116</sup> It was this interest in models of care which provided the rationale to undertake the research presented in Chapters 4 and 5, in order to shed light on different approaches in a South African setting.

Several demonstration projects were initiated to test the acceptability and feasibility of providing much needed ART to women who were identified as eligible in pregnancy. MTCT-Plus (referred to above) was developed as a multi-country five-year demonstration project in 2003 which took established PMTCT services one step further by building on the existing programme and providing treatment and care packages.<sup>26</sup> In addition to supplying short course prophylaxis, MTCT-Plus provided ART and treatment for opportunistic infections to women with advanced stage disease, family planning, and psychosocial and nutritional support. This was one of the first projects to test the implementation of ART services for pregnant women in multiple settings and it served as a model for future PMTCT programmes.<sup>117</sup> Emphasising linkage to care, the objective of the MTCT-Plus model was to incorporate a family-based care approach that recognised the opportunity to link women and their partners and children to HIV services. The model focus was on a multi-disciplinary team approach, which provided staff at various levels of service to manage patients. The model was adapted to each setting's needs.<sup>26</sup>

Using PMTCT services as a gateway to lifelong treatment of women was extended in the MTCT –Plus programme, which placed the HIV-infected pregnant woman in the pivotal role of facilitating the testing and treatment of family members.<sup>118</sup> MTCT-Plus also developed support structures for women and their families in the form of community outreach, a treatment ‘buddy’ system for adherence support and support groups for psychological wellbeing. In services poorly resourced with data monitoring and evaluation tools, MTCT-Plus designed and implemented monitoring systems for patients in care.<sup>24,26</sup> Country outcomes from the MTCT-Plus programme suggested successful MTCT prevention, with a 12-month transmission rate in Côte d’Ivoire of 2.3% among women who initiated ART in pregnancy versus 16.1% in women who received short course regimens.<sup>119</sup> MTCT-Plus demonstrated the effectiveness of the two-tier approach, advocated by the WHO, and offered dual therapy to women who did not require treatment for their own health. Reporting on data from Côte d’Ivoire between 2003 and 2005, overall transmission at 4 weeks was 2.2% (95% CI: 0.3-4.2%) and cumulative transmission at 12 months was 5.7% (95% CI: 2.5-9.0%) in the MTCT-Plus cohort. Infant HIV-free survival was 95.7% (95% CI: 1.7-7.0%). These findings were most promising, and suggested that the two-tier approach in a resource-constrained setting was feasible, safe and highly effective.<sup>120</sup>

Two further papers produced from the MTCT-Plus cohorts highlighted both successes and challenges of the programme. In Côte d’Ivoire, around half of women enrolled in the programme disclosed their HIV status to their partners, 30% of whom came forward to be tested. Of the men who were found to be HIV-infected, 78% enrolled in the programme, while 10% of exposed children were brought for HIV testing.<sup>118</sup>

Another two studies from the MTCT-Plus consortium reported adherence to ART declining over time among women who had initiated in pregnancy in Uganda, and poor adherence 12 months after initiation among women who had received short course PMTCT in pregnancy and who had initiated ART postpartum in Côte d’Ivoire.<sup>121,122</sup> These challenges

to adherence highlighted the need to enhance long-term continuum of care strategies – often not required in other primary health care packages – in order to improve patient retention and health outcomes.<sup>115</sup>

In building on this evidence-base, further research from other countries on different approaches to offering ART to HIV-infected pregnant women emerged. In Zambia, Killam *et al.* showed that an intervention which provided an integrated ART service once to twice weekly within the antenatal service, doubled the uptake of ART within 60 days of delivery, compared to uptake among pregnant women accessing separate antenatal and ART services (32% in the intervention group versus 14% in the control group). Interestingly, the intervention did not have any effect on the time to initiation, which was at least 10 weeks for both groups. Furthermore, retention in care measured at 90 days was not significantly different between the two groups (87.8% in the intervention group versus 91.3% in the control group).<sup>123</sup>

In Rwanda, two models of care were evaluated in the context of guideline change from single drug regimens to dual and triple therapy between 2006 and 2008. The results showed that women who attended antenatal sites which offered an integrated, full package of care including dual therapy and ART were almost twice as likely to be enrolled in ART services, compared to women who attended stand-alone antenatal and ART services. However, there were no significant differences between the two models in terms of initiation of ART, which was 83% between 2007 and 2008 overall. This suggests that the integrated service may have assisted with treatment referral, but it failed to demonstrate an effect on treatment uptake. The authors note that several innovative interventions may have contributed to the high uptake of ART. These included focused psychosocial support; the presence of patient escorts to ensure that referral to ART services occurred; and a patient tracking system utilized by social workers to trace defaulting pregnant women. These interventions were feasible due to the small proportion of HIV-infected women who were eligible for ART.<sup>124</sup>

Another study evaluated a delivery model to forge linkages between ANC and ART services in Johannesburg, South Africa. This intervention placed health workers from the ART service once per week in the ANC to identify and assist ART eligible pregnant women with referral to participating ART services. Adherence counselling and treatment preparation took place within the ANC before referral. The results of this before-after study found that the median time to treatment initiation was reduced from 56 days (prior to the intervention) to 37 days after the intervention was implemented. Although the coverage of ART in pregnancy was not reported for the period prior to the intervention, ART initiation in eligible women was 75.4% during the intervention.<sup>125</sup>

While these studies demonstrate the feasibility of integrating ART within ANC services, their results also suggest challenges to rapid uptake of interventions before delivery and suboptimal treatment coverage of ART in pregnancy. This is consistent with an observational study in Botswana that showed that 37% of women who were eligible for ART in pregnancy initiated treatment. Women who presented at ANC services at 20 weeks gestation or more were less likely to initiate ART. Although the authors do not describe the procedures of referral of women from ANC to ART services, they suggest that referral between services may have contributed to low uptake.<sup>126</sup>

A South African study reported that late presentation was a challenge to timely ART initiation in an integrated service in pregnancy, with the mean gestational age of initiation being 27 weeks. High postpartum loss to follow up was also suspected at this service.<sup>127</sup> Pregnancy provides a limited period to optimize treatment initiation, and the risk of vertical transmission in utero and the peripartum is decreased with every week of antenatal ART.<sup>128</sup> These findings suggest that in spite of service linkages or integration, barriers to optimal ART coverage and timely treatment initiation persist.

## 2.4 Challenges to PMTCT uptake and ART initiation in pregnancy

The results of the abovementioned studies illustrate what has been an ongoing concern for the past decade, notably a potential ‘efficacy-effectiveness’ gap between the successes of PMTCT trials in reducing MTCT and the limited impact of these programmes in operational settings, particularly in resource-constrained contexts.<sup>19,27</sup> While the risk factors for MTCT are universal, women in resource-constrained settings may not have access to interventions available to their Western counterparts, for example, sophisticated drug regimens, caesarean section or safe alternatives to breastfeeding.<sup>60</sup> Despite this, simplified drug regimens have proven to be feasible and as effective in the field, and it is programme coverage - which impacts on effectiveness – that has emerged as an ongoing health systems challenge.

Progress towards universal coverage of PMTCT programmes has been made; however, it has occurred at a slow pace. In 2009, it was estimated that 26% of HIV-infected women received an HIV test, an increase from 7% in 2005. Only half of these women were assessed for ART eligibility in the same year and 53% (range: 40%-79%) of HIV-infected women received antiretrovirals in pregnancy for PMTCT, an increase from 15% (12%-18%) in 2005.<sup>17</sup>

It has been suggested that poor PMTCT coverage may be neither due to a lack of political will nor the absence of technical support alone, because even settings with mature services continue to fall short of universal coverage. It is more likely a result of a combination of barriers which include service and patient driven factors that impact on the uptake of both PMTCT programmes and initiation of lifelong ART in pregnancy.<sup>23</sup> Much research into the reasons for suboptimal PMTCT programme coverage is concerned with evaluating the attrition at each step of the PMTCT cascade, which comprises a sequence of events required to deliver antiretroviral interventions to HIV-infected women and their exposed children. HIV counselling, testing and CD4 cell count testing is required to identify women for the administration of appropriate and opportune treatment during antenatal care, delivery and postpartum. Exposed infants need to be identified by services for peripartum or

late postpartum ART, if tested and found to be infected. Modelling exercises have shown that even 5% attrition at each step of the cascade compounds sufficiently to result in 86% antiretroviral coverage, this proportion falling dramatically with successively lower coverage of each step of the cascade.<sup>129</sup> The success of each consecutive step of the cascade is dependent on the coverage of the previous step. To illustrate, an HIV-infected woman who is unaware of her status may access comprehensive and high quality antenatal services, yet remain at risk of MTCT and avoidable death as a result of undiagnosed HIV.<sup>114</sup> Hence each aspect of the PMTCT package of interventions is integral to ensuring uptake and missed opportunities at any step will negatively impact on coverage. It is under these conditions that mothers are lost to care and that the proven efficacy from trial conditions cannot be realised in operational settings.<sup>129</sup>

Many studies have investigated the reasons for poor coverage of PMTCT programmes. Most of this research is setting specific and while lessons can be learned from these evaluations, they may not be broadly applicable. This is because variation in the burden of maternal HIV disease, health service capacity, HIV awareness and community attitudes and social context may influence programme success. Yet, through local level health system evaluation, insights can be gained into the inherent patient- and service-related factors which contribute to programme success or failure.<sup>23</sup> Much of this literature reports on challenges to PMTCT programme coverage without distinguishing between the specific barriers to short course and lifelong drug regimen uptake. This is likely due to the fact that all HIV-infected women begin at the antenatal clinic where their status is identified, hence there is commonality in the first few steps of the PMTCT cascade regardless of CD4 cell count. Barriers and challenges to PMTCT uptake as found in this body of literature are thematically presented below.

#### **2.4.1 Access and service-related barriers**

Coverage of PMTCT services can be compromised in settings where antenatal care is either difficult to access or where there is insufficient infrastructure to provide PMTCT interventions. After initiating several pilot programmes in resource-constrained settings, PMTCT services were expanded to many countries in Africa due to aid from the Elizabeth Glazer Pediatric AIDS Foundation (EGPAF), the US President's Emergency Fund for AIDS Relief (PEPFAR) and other organizations including the Bill and Melinda Gates Foundation.<sup>14</sup> Service coverage increased over time and by 2006, 108 countries representing 99% of women with HIV in low and middle-income countries were reporting on PMTCT programme data, suggesting substantial progress in scale-up of services.<sup>130</sup> However, HIV counselling and testing coverage for pregnant women was reported to be 35% in sub-Saharan Africa in 2009.<sup>17</sup> Service-level challenges to the access of PMTCT programmes include poor health service infrastructure, limited service capacity, staffing shortages, competing health priorities and lack of prioritization of maternal and child health services, all of which compromise service delivery.<sup>34,131-135</sup>

#### **2.4.2 Late antenatal presentation**

Many women in sub-Saharan Africa, including South Africa, present at late gestational age for antenatal care<sup>136-140</sup> and there may be little time for women who are diagnosed with HIV in pregnancy to consider the effect that a lifelong chronic illness may have on motherhood. Late presentation in pregnancy is a prevalent theme in Chapters 4 and 5, where it is shown to impact on ART initiation directly, as well as suboptimal duration of ART prior to delivery. This finding is re-iterated by service providers in Chapter 7.

Late entry into antenatal care is a barrier to effective PMTCT coverage because it limits the opportunity for timely uptake of treatment. As already mentioned, late presentation has been associated with poorer uptake and sub-optimal duration of ART in

pregnancy. Early evidence also reported that women who presented late in pregnancy were more likely to be HIV-infected,<sup>141</sup> and fewer antenatal care visits have been shown to predict poorer postnatal care seeking behaviour.<sup>142,143</sup>

The WHO antenatal care guidelines recommend a minimum of four antenatal visits for women in resource-constrained settings. Research into the preferences and behaviour of women seeking antenatal care has provided some insight into the factors that influence late presentation, although these factors vary between settings. In a review of factors affecting the utilization of antenatal care in resource-constrained settings, Simkhada *et al.* suggested that earlier antenatal care access was reported in different studies to be associated with being married, educated or of a higher socio-economic status, while multiparous women were on occasion less likely to seek early antenatal care. The authors reported a possible association between age and parity: older women of low parity may seek earlier antenatal care.<sup>144</sup> In a study of South African women, qualitative data indicated that access to antenatal care was compromised due to the travel required. Needing to be convinced of a pregnancy through physical symptoms was also an important motivator for seeking antenatal care.<sup>139</sup>

### **2.4.3 Reluctance to test for HIV during pregnancy**

The cord blood surveillance paper presented as Chapter 3 finds that unknown HIV status through the failure to test in pregnancy is a contributory factor to missed opportunities for PMTCT coverage. The emotional cost of screening tests has been well documented and screening uptake has been shown to be successful if patients believe that the benefits of testing outweigh the risks.<sup>145</sup> This has been reported in industrialized countries with strong health systems which have sufficient resources to offer HIV-infected women.<sup>146</sup> However, questions concerning informed consent for HIV testing in the context of pregnancy were raised in the early stages of PMTCT programme implementation. Voluntary counselling and testing guidelines were originally developed for use in mainstream HIV services and sexual

and reproductive health programmes for individuals seeking HIV testing.<sup>147</sup> Hence it is thought that antenatal HIV testing may be perceived differently from selective HIV screening conducted in mainstream HIV services in that the former may be strongly motivated by the desire to protect the unborn child.<sup>23</sup>

Debates emerged around the appropriateness of incorporating HIV testing as a routine component of antenatal screening,<sup>148</sup> particularly at a time when the introduction of routine HIV testing in pregnancy in the USA and other resource-rich countries early on in the HIV epidemic demonstrated substantial success in the identification of HIV-infected women for treatment.<sup>149</sup> Despite this, the benefits of knowledge of HIV status outweigh the risks in light of the efficacy of drugs to treat infection and calls to re-evaluate HIV testing models in pregnancy in order to facilitate greater uptake of PMTCT have been made.<sup>147</sup>

In contrast, however, routine testing has been slower to be implemented in most parts of Africa, where historically voluntary counselling and testing (VCT), or opt-in approaches have been adopted. Despite this, studies have provided evidence of routine testing acceptability and impact on increased PMTCT coverage in countries including Botswana, Zimbabwe, and Malawi.<sup>14,146,150,151</sup> In South Africa, opt-in counselling approaches (VCT) were used in PMTCT guidelines with a policy shift to provider-initiated counselling and testing (PICT) 'opt-out' approach in 2009-10.<sup>152</sup> One study from Mpumalanga has reported increased testing coverage in pregnancy with the introduction of PICT, where testing coverage increased from 69% in 2007/08 to 81% in 2009. Common reasons for not testing included knowing one's status already, fear of stigma, concerns around provider confidentiality.<sup>153</sup>

Testing in pregnancy is advantageous because it creates awareness of HIV risk in HIV negative women, who consequently may be better equipped to manage sexual risk during pregnancy and postpartum. An HIV-positive diagnosis in pregnancy may assist with the management of the diagnosis in terms of referral for psychosocial support, assistance with

decisions around disclosure and infant feeding options and care as well as providing an opportunity to seek early treatment.<sup>154</sup> Women who acquire awareness about PMTCT prior to pregnancy, or who have tested previously, are more likely to accept testing in pregnancy.<sup>155-157</sup> In several countries, barriers to uptake of testing were found to include fear of an HIV-positive test result.<sup>113,158-161</sup> Other reasons for test refusal among Côte d'Ivoirian women include requiring permission from their partners to test or wanting to make a decision later at home on whether to undergo testing.<sup>159</sup> In some settings, being married has increased the likelihood of uptake of testing.<sup>157</sup> Reports on the acceptability of VCT among Nigerian pregnant women were favourable. Fears of stigmatization due to lack of confidentiality in disclosure of the test result were a barrier to uptake in this study, this also being found in a study of Ghanaian women.<sup>162,163</sup> In Sudan, older women, primigravids and women of Muslim faith were more likely to follow through with an HIV test after initially agreeing to it. Authors suggested that possible barriers to uptake included service fees and long waiting times in this setting.<sup>164</sup>

Concern about disclosure of HIV status is a well-documented challenge to testing uptake in pregnancy, and is linked to the perceived stigma associated with infection. Disclosure of HIV status is advocated by both the WHO and CDC as a means to decrease anxiety, garner social support and to decrease risk of transmission through uptake of preventive interventions and behavioural change. Disclosure may also facilitate partner testing and access to family-based HIV care.<sup>165</sup> In a review of rates and barriers to disclosure in pregnancy, Medley *et al.* document that fear of abandonment, discrimination and rejection by partners or family members were the most commonly cited barriers to disclosure of HIV status in pregnancy. Fear of partner rejection was of particular concern to women who were economically dependent on their partners.<sup>147</sup> A recent study of women from Tshwane, South Africa, described that women balanced the risk of abandonment with the desire for support

and to raise transmission risk awareness within their intimate relationships. Few women experienced adversity as a result of disclosure, as has been documented elsewhere.<sup>147,166</sup>

#### **2.4.4      *Counselling and testing in the peripartum***

The barriers cited above underscore complex factors which may result in a woman completing a pregnancy without the knowledge of her HIV status, consequently leading to a missed opportunity for antenatal PMTCT intervention. Missed opportunities for treatment further extend to those women who either have few antenatal visits, hence minimizing the opportunity for offering HIV counselling and testing, and those who present for the first time in labour. The proposal for implementation of counselling and testing for women who present in labour with no or few antenatal care visits, or for women with undocumented HIV at the time of delivery was raised in the USA soon after the guidelines for dispensing AZT for PMTCT were implemented in the late 1990s. Drawing comparisons with congenital syphilis transmission, it was thought that women with minimal or no antenatal care would be the most likely to transmit HIV.<sup>167</sup> This was confirmed in results from the Mother-Infant Rapid Intervention at Delivery (MIRIAD) Study, which showed that more than 60% of the women who had tested HIV-positive in labour had received no antenatal care and that 75% of HIV-positive women had attended 3 or fewer antenatal visits. This study demonstrated the acceptability and feasibility of perinatal consent and rapid testing, and also highlighted the need to support women from marginalized groups who for economic or psychosocial reasons did not access early antenatal care.<sup>168,169</sup> Testing in labour wards was recommended for implementation by the CDC in 2004 and set the example for resource-constrained settings to follow suit with rapid point-of-care testing in labour wards.<sup>170,171</sup> Testing in labour or during delivery is also considered important in the management of women who seroconvert in pregnancy. These women are a high risk of MTCT, as incident infection is associated with viraemia in the first few weeks of HIV infection.<sup>172</sup> Due to their early prior

HIV-negative status, these women will most likely not receive nor follow interventions to reduce MTCT risk.

The field effectiveness of testing in labour in resource-constrained settings was recently demonstrated in a study in Swaziland, the results of which showed significant differences in the uptake of testing during delivery and prophylaxis coverage among women who attended health facilities where nurses had received training in an intervention to identify and offer testing women in labour with unknown or negative HIV status.<sup>173</sup>

Seroconversion in this study was 4% among women who had tested HIV-negative earlier in pregnancy and 15% of all HIV-positive specimens were attributed to women whose HIV status was unknown at time of arrival. In a South African study, 66% of women accepted intrapartum HIV testing and all women who were found to be HIV-infected accepted prophylaxis before delivery.<sup>174</sup> While this suggests the feasibility of peripartum testing in this setting and current guidelines recommend the testing of women in latent labour, there are no data to support evidence of feasibility and acceptability in routine service provision.

In South Africa, reported rates of seroconversion in pregnancy vary. In Chapter 3, the cord blood surveillance study shows that a small proportion of women (0.7%) were found to have seroconverted in pregnancy. Around the start of the millennium, seroconversion at Chris Hani Baragwanath Hospital was reported as 5%<sup>175</sup> and 2% in KwaZulu-Natal.<sup>176</sup> However, in a small study in the Western Cape, no seroconversion was found in a sample of 532 pregnant women.<sup>177</sup> Moodley *et al.* documented in a cross-sectional study nested within a PMTCT programme that the incidence of HIV was four times as high in HIV-negative women who retested between 36-40 weeks gestation than found in a survey of the general population.<sup>178</sup> This underscores the importance of repeat testing in late pregnancy. Repeat testing has been advocated for any subsequent visit of women who refused a test at a previous visit, and at 32 weeks for women who previously tested HIV-negative in early

pregnancy since 2008, however, it is not known how well repeat testing is utilized in services.<sup>178</sup>

#### *2.4.5 Psychosocial aspects of HIV-positive pregnancy and motherhood*

It is well documented that women undergo severe emotional stress when receiving an HIV-positive test result.<sup>179</sup> Furthermore, pregnancy is a life event accompanied by hormonal changes. As with HIV diagnosis, these changes may place women at heightened risk of depression.<sup>180</sup> It has been reported from African settings that HIV-infected women suffer greater levels of psychological distress than non-infected women during pregnancy<sup>181</sup> hence women who are diagnosed with HIV during pregnancy may be more at risk of depressive and somatic illness than women of known HIV status who become pregnant.<sup>182</sup> A high background prevalence of depressive disorders associated with unplanned pregnancy and poor socio-economic circumstances has been documented among South African rural women enrolling for PMTCT services, regardless of HIV status.<sup>183</sup> Hence it is possible that a woman diagnosed HIV-positive in pregnancy takes on a further emotional burden regarding the acceptance of her illness and the need to protect her child when she may already be experiencing psychological distress.

In most parts of Africa, motherhood is highly valued, this being true in South Africa where childbearing is considered the norm among married and co-habiting couples.<sup>184-186</sup> Motherhood carries heavy social meaning, with reproduction being a strong component of the female role and social identity.<sup>187,188</sup> Yet the social construction of maternal identity is thought to be determined by greater political processes.<sup>189</sup> High social value is attached to pregnancy, yet HIV is associated with stigma and deviance.<sup>190,191</sup> As a result, it has been suggested that HIV-infected women are at risk of negative attitudes towards motherhood, as a result of the internalized conflict between social constructs of motherhood and the stigma associated with HIV infection.<sup>192</sup> Representations of HIV-positive motherhood extend to the

social stereotype of the deviant or ‘bad’ mother – as a mother who fails to protect her child from danger.<sup>193</sup> Hence discourse on HIV-positive motherhood suggests that HIV infection places these mothers in a ‘double-bind’ such that while social expectations dictate reproduction, so society condemns HIV-positive motherhood.<sup>190,191</sup> This paradox is often observed in the decision-making processes of HIV-infected pregnant women and mothers. Frequently their anxiety concerning the avoidance of vertical transmission during pregnancy and in the postpartum entails counterbalancing the social risks of HIV infection with the benefits of motherhood for these women.<sup>194</sup> This is explored in Chapter 7, where the lived experience of HIV-positive motherhood is documented in the Cape Town setting. This chapter also describes a typology of ‘work’ associated with the preservation of maternal identity – that of a ‘good’ and protecting mother.<sup>195-197</sup>

#### **2.4.6 *Challenges to the initiation of ART and regimen adherence during pregnancy and postpartum***

Acceptance, treatment initiation and adherence to antiretroviral regimens in pregnancy are crucial to maximise viral suppression in order to reduce the risk of MTCT. There is little evidence which describes the specific challenges to treatment initiation in pregnant women who are eligible for ART, and this theme is examined in detail in Chapter 6 through a qualitative study of service providers and ART-eligible pregnant or 6 months postpartum women. The findings of this study suggest that women often presented late in pregnancy, as discussed previously, and they experienced stages of denial and acceptance of diagnosis, which delayed treatment initiation. Fear of treatment side effects and difficulty in accepting lifelong treatment are also pertinent themes documented in Chapter 6. Results from a qualitative study among pregnant women accessing ART in Uganda suggest both logistics, service-related factors and psychosocial challenges impact on ART initiation in pregnancy. Poor service access due to transport or financial restraints; long waiting times at the services; poor quality provider-patient interactions, as well as fear of disclosure and stigma were

highlighted as barriers to treatment initiation.<sup>198</sup> A study from Soweto, South Africa, among non-pregnant, ART-eligible adults suggested that ART refusal was associated with feelings of wellbeing, despite these patients meeting the criteria to initiate ART.<sup>199</sup>

Most studies which examine the behavioural aspects of adherence to lifelong ART for the benefit of individual health do so in non-pregnant populations. This research commonly reports adherence as a series of thresholds of complete adherence (100%), and incomplete adherence ( $\leq 95\%$ ).<sup>200</sup> A small body of research specifically focuses on adherence to short course regimens during pregnancy in resource-constrained settings. In a study from the United States, adherence to ART during pregnancy was 65%, this dropping in subsequent postpartum months, including among women who were on lifelong ART. Factors associated with adherence in the previous 4 days included less advanced disease, favourable mood and the absence of marijuana use.<sup>201</sup>

Botswanan women attending services in Francistown recalled missing doses of AZT due to being away from home, running out of treatment or forgetting to take it on time. Some mentioned that they prioritized other activities and some avoided taking treatment due to fear of side effects, while others suggested that they did not have food to take with the treatment.<sup>131</sup> In an effectiveness study based in Lusaka, Zambia, it was reported that 57% of women who tested HIV-positive at participating antenatal services were documented to have acquired a NVP tablet.<sup>61</sup> In a study of Zimbabwean women in Bindura, non-adherence to sd-NVP and infant NVP was associated with lack of maternal secondary education and home delivery, while increased maternal adherence was associated with previous maternal PMTCT exposure and taking the NPV tablet home. A limitation of this study is recall bias because it was based on self-reported behaviours.<sup>202</sup> Evidence from sub-Saharan Africa suggests that supportive male partner involvement in pregnancy is associated with improved adherence to PMTCT regimens.<sup>203</sup> Male partner involvement is an aspect of PMTCT prevention which is

currently being investigated and promoted as an intervention in resource-constrained settings.<sup>204</sup>

## 2.5 Prevention of mother-to-child transmission in South Africa

### 2.5.1 *The development of PMTCT services in the Western Cape Province, 1999*

The first South African antenatal prevalence survey was conducted in 1990, the results of which showed that HIV seroprevalence among women attending antenatal services was 0.8%.<sup>205</sup> In 1993, the National AIDS Coalition of South Africa was formed and by 1994 this body had drafted the first National AIDS Plan, which included a recommendation for voluntary counselling and testing (VCT) of pregnant women at antenatal clinics and the provision of prophylaxis.<sup>206</sup> However, progress in implementation of the plan in the first four years was slow.<sup>207</sup> In 1998, antenatal seroprevalence had increased to 22.8%,<sup>208</sup> and a rise in infant mortality was attributed to the increase in MTCT.<sup>209</sup> In the same year, in response to evidence from the Thailand<sup>46</sup> trial on the efficacy of AZT, the Gauteng Department of Health proposed the implementation of PMTCT programmes at five pilot sites. However, support for these sites was withdrawn by government soon after, for reasons of affordability.<sup>210,211</sup>

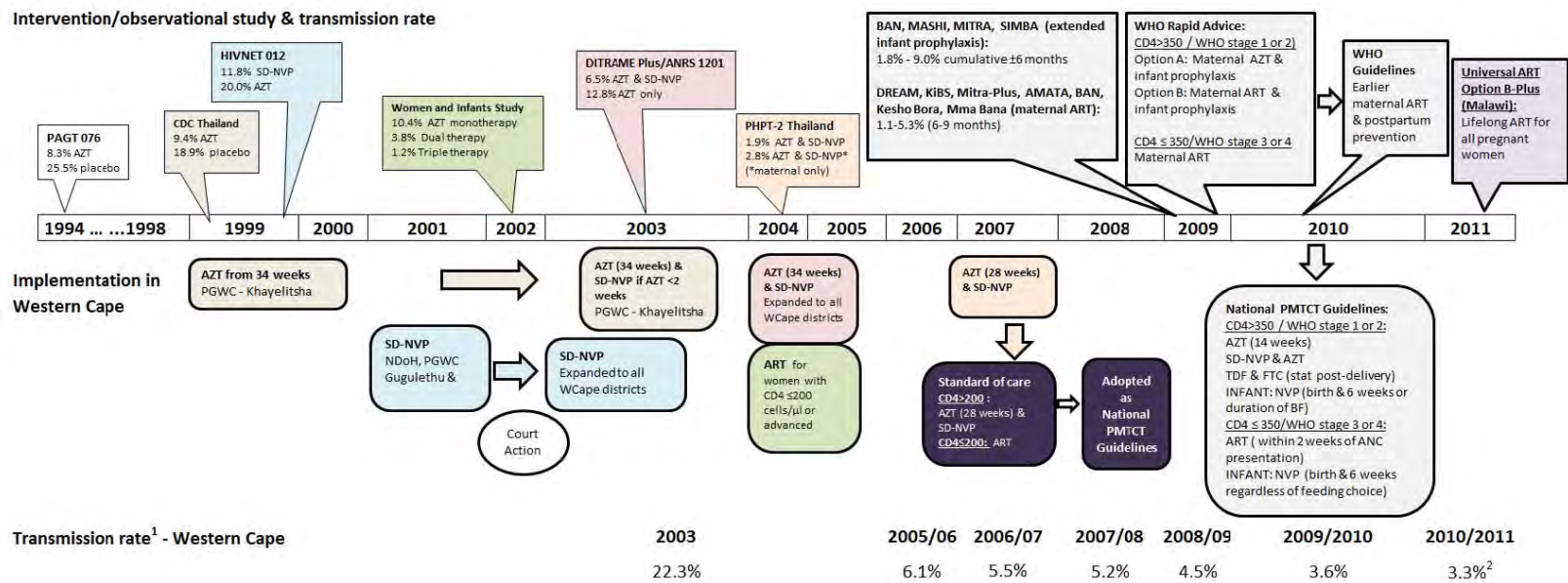
Future progress on the use of AZT in pregnancy was for the most part thwarted in the majority of provinces by government until 2008, when it was incorporated in national PMTCT guidelines as a part of new recommendations for dual regimens and triple therapy for pregnant women, replacing the sdNVP regimen which had been implemented since the commencement of the National PMTCT Pilot Programme in 2001-2002.<sup>212,213</sup>

The time line of the development of the PMTCT programme in the Western Cape province (from which the data for this thesis are drawn), is illustrated in Figure 2.1. The Western Cape was the only province to provide the Thai regimen from January 1999, where

the flagship PMTCT programme was implemented in two midwife obstetric units (MOUs) in Khayelitsha, outside Cape Town. Provision was made for VCT services within the MOU, AZT dispensation and follow up services in nine postnatal clinics which provided formula milk for those who elected to replacement feed.<sup>214,215</sup> By 2004, the PMTCT programme had been expanded throughout the Western Cape as a nurse-driven service which offered dual therapy, as well as CD4 count testing to determine women with indications for HAART and PCR testing for infants at 14 weeks.

At this stage, VCT coverage was 96% and seroprevalence was 11.8% by 2004.<sup>216</sup> The field efficacy of the programme was tested in 2003-2004 among 535 mother-infant pairs. The study reported PMTCT coverage to be 77% with the MTCT rate being 8.8%. The results of this study demonstrated the feasibility and effectiveness of the PMTCT programme in this setting.<sup>217</sup> As a partnership between the Provincial Government of the Western Cape (PGWC) and Médecins Sans Frontières (MSF), three primary health care (PHC) sites were set up in Khayelitsha in 2000 to offer HIV services and ART was made available to those who were eligible according to WHO guidelines in 2001.<sup>218</sup>

**Figure 2.1 Time line of the development of the PMTCT programme in the Western Cape in response to international evidence and policy recommendations.**



<sup>1</sup> Transmission rate among babies accessing PMTCT programme around 6 weeks, reported in routine data (Western Cape Provincial Government Annual Reports)

<sup>2</sup> South African PMTCT Evaluation, 4-8weeks postpartum (Medical Research Council)

Experience gleaned from the implementation of the PMTCT programme in the Western Cape paved the way for the development of ART services for adults and children in this province. As with the PMTCT programme, the ART services relied on partnerships and the outsourcing of counselling to the NGO sector. Starting with an ART site administered by MSF in 2001 in Khayelitsha, more sites were set up in Khayelitsha, Langa, Gugulethu and a number of secondary and tertiary facilities by 2003. The ART programme was rolled out in earnest following the government's commitment to the national provision of ART in 2004.<sup>214,215</sup> In the same year, the Western Cape PMTCT protocols were redrafted to include referral of pregnant women who were identified as ART-eligible to ART sites.<sup>214</sup> Satellite clinics were set up within the MOU or in close proximity to the MOU to facilitate referral.<sup>219</sup>

Also in 2004, McCord hospital in KwaZulu-Natal implemented the WHO guidelines of 2004, with financial assistance from EGPAF. Dual regimens for prophylaxis and ART for maternal health were made available for women accessing services. Data from an 18-month observational cohort in this setting reflected 91% testing coverage with 26% of women eligible for ART according to CD4 cell count result. Of the 97% of women who received ARV regimens, 44% received ART (including short course ART among 60% of women who had a CD4 cell count  $>200$  cells/ $\mu$ L). Overall transmission at 6 weeks was low at 2.9%, being highest among women who received sdNVP (8.2%) and lowest among those who received ART (1.8%). This evidence demonstrated the operational effectiveness of more complex regimens in this setting, yet the outcomes are subject to some limitations. Since McCord is a fee-paying hospital, there may have been selection bias in terms of the socio-economic and educational status of those enrolled in the cohort. Women may choose to refer elsewhere to free services closer to home, impacting on the loss to follow up, which may in turn, affect the estimated transmission rates.<sup>220</sup>

### 2.5.2 *Slow progress in national PMTCT programme scale-up, 1999-2007*

While the Western Cape had scaled up PMTCT services and other isolated sites within South Africa were implementing policy guidelines which were on a par with the 2004 WHO recommendations for resource-poor settings, other provinces lagged behind. In 2001, the Department of Health acted on the evidence from the HIVNET 012 study and implemented PMTCT programmes in 18 pilot sites across South Africa. With two sites in each province, the intervention comprised voluntary HIV counselling and testing to all women presenting for their first antenatal visit and sdNVP for women and their infants intrapartum. Replacement feeding in the form of free formula milk was offered for 6 months and children were offered testing at 12 months.<sup>221</sup> An evaluation of the pilots reported that approximately 9% of pregnant women made use of the PMTCT services at the pilot sites in 2001 and 2002 respectively and the HIV testing uptake rate among these women increased from 51% in 2001 to 56% in 2002. National scale-up commenced after a judgment passed by the Constitutional Court in July 2002,<sup>210</sup> ordering that the government make NVP universally available to HIV-infected pregnant women. The first national PMTCT programme offered voluntary counselling and testing in antenatal services, with NVP to mother and child per HIVNET 012, as well as free infant formula for 6 months postpartum, co-trimoxazole for infants up until 12 months, by which time HIV testing was offered to determine infection status.<sup>222</sup>

In 2000, the government had estimated that 75 000 children were born with HIV in South Africa, given the antenatal prevalence of 24%.<sup>211,223</sup> During the early years of the PMTCT programme, there were limited national routine data on programme outcomes, due to the slow roll-out of the programme.<sup>224</sup> Early outcomes from the national pilot programme reported a total of 1907 infants born to HIV-infected mothers and transmission was documented as 18%. However, due to 50% attrition in this sample, this rate was an unreliable indicator of programme effectiveness.<sup>213</sup> Several small scale studies also provided

'snapshot' evidence of effectiveness at the time within operational settings.<sup>225</sup> Results from a programme at Coronation Hospital in Johannesburg in 2003 reported 15% consent to HIV testing and high sdNVP uptake rates (>95%) at delivery. Transmission rates were 8.7% at 6 weeks and 8.9% at 3 months, with more than 70% of children lost to follow up by 4 months.<sup>222</sup>

Another study conducted between 2002-2004 documented late postpartum transmission in children at 36 weeks from three sites in the Western Cape, KwaZulu-Natal and Eastern Cape. Cumulative transmission or death by 36 weeks was 16% (95% CI: 10-23%); 26% (21-32%) and 35% (28-43%), with maternal viral load being the most significant risk factor of HIV transmission or death, followed by low birth weight and breastfeeding. Furthermore, the authors attributed high transmission to poor health system performance, cautioning that any future availability of dual and triple therapy for pregnant women could be compromised by operational challenges.<sup>226</sup> Evidence from the Eastern Cape between 2003 -2004 highlighted these operational challenges, suggesting a lack of PMTCT integration with antenatal services; poor management systems including a dearth of monitoring tools to evaluate effectiveness; a lack of infrastructure and limited support structures and supervision for staff contributed to poor coverage of the programme. Community stigma, traditional postpartum birth customs and cost of transport to facilities were patient-related barriers which prevented programme uptake.<sup>227</sup> At the same time in the Western Cape, interviews of staff at different levels of health service provision elicited similar responses regarding operational barriers to the uptake of PMTCT services. Limited training opportunities for counsellors and staff; poor co-ordination and staff shortages were highlighted as service-related barriers, while stigma, lack of knowledge, fear of denial and disclosure were cited as patient-related barriers to care.<sup>228</sup>

In 2005, 240 000 children under 15 years of age were estimated to be HIV-infected in South Africa,<sup>229</sup> while the national prevalence from antenatal service data was estimated to

be 30.2% for the same year.<sup>230</sup> South Africa was reported to be one of ten countries to account for two-thirds of all vertical transmission in 2005.<sup>94</sup> In the previous year, the Minister of Health declared during the International AIDS Conference in Bangkok that despite the South African Medicine Control Council's recommendation for the use of dual therapy, sdNVP would continue to be provided in public health sector facilities.<sup>231</sup> Limited data on the coverage and impact of the PMTCT programme were available. In one South African study at this time, it was estimated that the risk of vertical transmission ranged between 19.4% (formula only and exclusively breast fed infants) and 26.1% (mixed feeding practices) at 6 months postpartum.<sup>232</sup>

By 2006, the Department of Health reported that an estimated 302 000 pregnant women were HIV-positive. With 85% antenatal service coverage, it was reported that 73% of women were identified and enrolled on the PMTCT programme.<sup>233</sup> Yet sdNVP was still the only drug available for use throughout most of South Africa, despite the 2006 WHO recommendation of dual regimens and ART for eligible HIV-infected pregnant women.<sup>104</sup> It became clear that while maternity and obstetric services were succeeding in providing appropriate ante- and perinatal care on many levels, the suboptimal management of HIV in pregnancy was regarded as a significant failure by these services to manage the epidemic and HIV was a major threat to maternal and infant survival.<sup>234</sup> According to the Saving Mothers Report for 2002-2004, the gains made in reducing maternal mortality through the management of several direct causes of maternal death such as hypertension and abortion were reversed due to the rise in non-pregnancy related infections, including HIV.<sup>235</sup> HIV-infected pregnant women in South Africa were more likely than their HIV-negative counterparts to develop pregnancy complications and experience adverse outcomes, including anaemia, pregnancy-induced hypertension, lower maternal weight, urinary tract infections, premature delivery and in utero growth restriction.<sup>236</sup> Guidelines on the management of HIV in pregnancy were available but not universally implemented.<sup>237</sup>

Antiretroviral therapy scale-up had begun in 2004, and approximately 190 000 South Africans were receiving treatment by the end of 2005.<sup>238</sup> However, it was estimated that less than 10% of pregnant women were receiving ART and 14% of women were receiving prophylaxis through the PMTCT programme.<sup>237</sup> While antenatal services provided VCT for the identification of HIV-infected women, integration of ART services within maternity care was uncommon. A major challenge to initiation in pregnancy was the verticalisation of programmes, with poor linkage between maternal services and ART services.<sup>237,239</sup>

With sparse routine data available on the PMTCT programme, there was an overriding concern about the significant numbers of HIV-infected children admitted to South African health facilities.<sup>240</sup> In KwaZulu-Natal, cumulative PMTCT effectiveness was measured among infants in combination with reported maternal sdNVP ingestion. The MTCT rate at 4-8 weeks was 20% (95% CI: 17-23%), leading to an HIV prevalence of 7% in infants around 6 weeks, suggesting poor coverage of the PMTCT programme.<sup>241</sup> These poor outcomes were ascribed to a failure to adopt more successful scientific approaches to PMTCT, as well as a failure to address programme weaknesses. Furthermore, while sdNVP may have initially provided the impetus for PMTCT programme expansion in the late 1990s, it was argued that its impact on vertical transmission was clearly no longer having sufficient effect.<sup>242</sup>

At the time, another evaluation from KwaZulu-Natal suggested suboptimal PMTCT service coverage, with high attrition at each step of the PMTCT cascade. A hospital audit of data from women recently postpartum in 2007 reported that 84% of women had had access to testing, of whom 91% accepted. Antenatal NVP was dispensed to 87% of identified HIV-infected women and 76% were administered sdNVP in labour. Documentation of CD4 cell count testing was found in 45% of women, of whom only 46% received their results. Of the women eligible for ART, 47% initiated treatment.<sup>243</sup>

### 2.5.3 *2008 and beyond: International policy translated into improved national PMTCT strategy*

By 2007, the Interagency Task Team (IATT) on Prevention of HIV Infection in Pregnant Women, Mothers and their Children, comprising world experts, scientific and funding bodies as well as national role players, reported on strategies to improve the scale-up and implementation of PMTCT in resource-constrained environments. In order to strengthen PMTCT programmes, IATT called for increased governmental leadership and accountability; the delivery of a standard package of care; the use of provider-initiated testing and counselling in antenatal and postnatal services; the institutionalization of longitudinal care for mothers and children, increasing the linkages between and access to ART for eligible pregnant women and their families; strengthening infant feeding support and nutrition in the context of HIV care; forging links between PMTCT services and sexual and reproductive health services and developing community-based links and empowerment.<sup>15</sup>

By 2006, the WHO had released updated guidelines recommending ART initiation in women with stage 4 disease, irrespective of CD4 cell count; women in stage 1 or 2 with CD4 cell counts of  $<200$  cells/ $\mu\text{L}$  and women with stage 3 disease and CD4 cell counts of 200-350  $\mu\text{L}$ , as well as AZT prophylaxis from 28 weeks' gestation and sdNVP during delivery.<sup>103</sup> While adopting selected recommendations set by IATT and the WHO guidelines of 2006, South Africa released new PMTCT guidelines in early 2008 - the first revision since 2003 - which included the addition of AZT from 28 weeks' gestation to the standard sdNVP package; ART for women with stage 3 or 4 disease and/or a CD4 cell count  $\leq 200$  cells/ $\mu\text{L}$ . Formula milk continued to be offered at no cost to HIV-infected women attending PMTCT services for 6 months, as per the original guidelines, and exclusive breastfeeding for 6 months was also to be encouraged.<sup>212</sup> Although acknowledged to be a long-awaited improvement on the 2003 guidelines, the new guidelines were criticized by experts and civil society for falling short of addressing NVP resistance; the use of sub-optimal ART regimens;

and advocating a low threshold for initiating ART. Furthermore, the failure to address the poor linkages between antenatal and ART services was cited as an ongoing barrier to women who needed ART in pregnancy, this being compounded by the prerequisite that doctors, and not nurses or midwives, initiate and prescribe treatment.<sup>244</sup>

Evidence from South African settings which reported on the effectiveness and feasibility of ART initiation in antenatal contexts, as well as the service-related challenges to implementation at this time has been discussed above in context of the implementation of service integration.<sup>125,127</sup> In these evaluations, which demonstrated that initiating ART in pregnancy was possible, coverage in ART-eligible women was cited as an ongoing challenge. Included in this thesis is a publication which suggests that during the first years of ART availability within Cape Town antenatal services, overall coverage in women eligible for treatment was 51%. Facilities which provided ART within the MOU were not significantly more likely to initiate women than facilities which referred women to separate ART services (Chapter 3).<sup>245</sup> While coverage improved slightly in a follow-up study, the integrated approach to care did demonstrate more favourable coverage (Chapter 4).

As reported nearly a decade beforehand, uptake of PMTCT interventions rather than the efficacy of the drugs themselves, remained a crucial factor which influenced programme effectiveness. Evidence from the PEARL cord blood surveillance study in four African countries (2007-2008), which measured perinatal uptake of NVP prophylaxis in mothers and infants reports that country-adjusted coverage (evidence of NVP in cord blood and record of direct observation of infant administration) was 51%. Failed coverage was associated with fewer antenatal visits (1 or fewer) and younger maternal age (20-25 years), while one in four women who were dispensed sdNVP did not ingest it.<sup>35</sup> Even in light of more complex protocols, optimizing coverage remained an ongoing challenge: in a sub-analysis of this study, Western Cape cord blood antiretroviral coverage showed that 58% of women had

standard of care regimens (defined as AZT and sdNVP or LMD, indicating ART), this being lower than reported in accompanying service data (Chapter 2).

#### 2.5.4 *Continued challenges: the reporting of South African PMTCT coverage through routine data*

Despite these suboptimal results, coverage of ARVs for prophylaxis and maternal health estimates provided by UNICEF,UNAIDS and the WHO for sub-Saharan Africa continued to improve each year from 35% (95% CI: 29-44%) in 2007 to 45% (37-57%) in 2008 and 53% in 2009.<sup>11,17</sup> Increases in the availability of routine data, including disaggregated data were noted, and 35% of women who tested HIV-positive were reported to have been assessed for ART, either according to CD4 cell count testing or clinical staging.<sup>11</sup>

By December 2009, routine data from South Africa reported by the WHO were suggesting a testing rate greater than 95% in antenatal services and antiretroviral intervention coverage greater than 80%.<sup>17</sup> The annual report by the National Department of Health of the same year reported HIV testing rates of 92%, with 91% of infants receiving sdNVP and 77% of women eligible for ART being initiated in pregnancy. This report, however, acknowledged that data collection of dual therapy regimens was compromised and no coverage figures could be produced. An estimated 56% of infants were tested for HIV, but the transmission rate was not published.<sup>246</sup>

Few evaluations on the reporting of routine programme data for PMTCT exist, however, Mate *et al.* reported poor accuracy and completeness in these data from 316 services KwaZulu-Natal in 2007.<sup>247</sup> Their findings suggested huge variations in the quality of the data collected between the sites. Overall, data elements were only reported 50% of the time, and they were reported accurately only 12% of the time.<sup>247</sup> Similar inconsistencies have been found in other published reports of PMTCT routine data,<sup>248,249</sup> and the cord blood surveillance reported in Chapter 3 suggests that inaccurate service reporting may explain in

part the discrepancy between documented dispensation of PMTCT regimens and exposure to regimens as found in the cord blood results.

Another limitation of routine data is that they fail to account for the true services coverage by excluding women of unknown HIV status who do not test in pregnancy, as well as those who may be documented as receiving PMTCT interventions, but who fail to ingest them.<sup>35,61</sup> This weakness provides the rationale for cord blood surveillance, as described in Chapter 3.

Laboratory data may offer an alternative source for data on PMTCT effectiveness. Data from the National Health Laboratory Services reported an estimated 5.8% transmission rate at 2 months of age. Yet a limitation of these data is that they were based on early infant diagnosis coverage of 45%.<sup>250</sup>

At the same time the Western Cape reported that 85% of women presenting in antenatal services tested for HIV. Documented sdNVP uptake was 98% among women presenting in labour, and 22% of HIV-infected women delivering in facilities were on ART. However, this does not indicate the proportion of those who were eligible for ART who received it. Vertical transmission was reported to have decreased from 4.5% in 2008-2009 to 3.6% in 2009-2010 among children identified on the PMTCT programme.<sup>251</sup>

Impressive decreases in early vertical transmission were confirmed in mid-2011, when the Medical Research Council released preliminary results of a national facility-based HIV prevalence survey among infants between the ages of 4-8 weeks. Early vertical transmission ranged between 6.2% (4.5-6.9%) in Mpumalanga and 3.3% in the Western Cape (2.9-4.1%). Selection bias in the study may have arisen through the exclusion of hospitals where acute cases of HIV are more likely to present and recall bias and social desirability bias may have led to inaccurate self-reporting of HIV status in pregnancy.<sup>252</sup>

## 2.6 Transmission through infant feeding

While gains were being made in perinatal prevention, it was acknowledged that infant feeding transmission was becoming one of the most difficult aspects of PMTCT strategy faced by scientists, clinicians and HIV-infected mothers in resource-constrained settings.<sup>253</sup> Ante- and intrapartum regimens targeted perinatal transmission, but subsequent high risk of postnatal transmission remained a challenge.<sup>28</sup> Exclusive breastfeeding for the first six months of life is advocated for all infants for optimal growth and development, as well as for infant health and the immunological benefits of protection against childhood illness.<sup>254</sup> In resource-constrained settings, breastfeeding practices, incorporating exclusive and mixed feeding, may account for up to between one third to one half of late postpartum transmission.<sup>9</sup> In a meta-analysis of individual patient data, 42% of HIV-infected infants were reported as HIV-infected at or after four weeks of age.<sup>255</sup> While transmission risk is constant throughout the breastfeeding period, length of exposure has been associated with elevated risk.<sup>256</sup> Women who have recently seroconverted are at twice the risk of vertical transmission due to high viral load.<sup>172</sup>

In resource-rich settings, complete avoidance of breastfeeding is recommended and attained through safe formula feeding. This has also been achieved in several less-resourced settings, including Brazil, Thailand and parts of Africa where there is sufficient infrastructure and support to promote affordable, feasible, acceptable, safe and sustainable replacement feeding, as recommended by the WHO in 2004.<sup>98,242,257</sup> Updated feeding guidelines recommended exclusive breastfeeding for HIV-infected women in the absence of safe replacement alternatives, for the first six months of life.<sup>258</sup> These were based on evidence regarding the challenges to replacement feeding include poor access to safe water supplies or formula and low acceptability of replacement feeding due to stigma.<sup>34</sup> It is argued that in poorly-resourced countries, the reductions in MTCT afforded by formula feeding are frequently at the cost of competing risks of mortality from other infectious diseases, resulting

in no net benefit of replacement feeding. Hence prevention strategies to modify breastfeeding practices have been examined over recent years to make them safer.<sup>253</sup>

Exclusive breastfeeding has been shown in different country settings to be feasible, and is associated with lowered risk of vertical transmission compared to mixed feeding practices.<sup>232,259-264</sup> While this suggests that exclusive breastfeeding may provide a promising alternative to replacement feeding for women in resource-constrained settings, these studies have shown that it does not eliminate transmission risk.<sup>34</sup> Evidence from trial and observational settings from 2006 onwards has reported that the use of extended antiretroviral prophylaxis in infants substantially reduces the risk of postpartum MTCT in breastfeeding populations, with early postnatal infection rates ranging between 0.8% and 2.5% and 0.8%-4.4% for late postnatal transmission (4-6 weeks to 6-9 months) where data collected and were comparable.<sup>1,34,265-269</sup> Furthermore, maternal ART administered during breastfeeding has also shown promising results. Early postnatal transmission rates from studies assessing the effectiveness of maternal ART reported early postnatal transmission ranging between 0% and 5% (4-6 weeks).<sup>270-274</sup> Late postnatal transmission in these maternal studies, as well as the DREAM and the Breastfeeding, Antiretroviral and Nutrition (BAN) study were also under 5%.<sup>1,100</sup> The BAN study demonstrated a seven month transmission rate of 6.4% in the control arm, 3.8% in the maternal ART arm and 1.8% in the infant NVP arm. The difference between the maternal and infant interventions was not significant, and the study was not powered to detect this difference.<sup>1</sup>

Several limitations to this evidence were noted particularly with respect to the variation between studies in duration of antenatal and postnatal regimen exposure, the rates of exclusive breastfeeding and the duration of feeding practices, the availability of the data available on perinatal vertical transmission, as well as the different CD4 cell count thresholds at which maternal regimens were administered.<sup>28</sup> Maternal ART was administered at moderate to high CD4 cell counts in several studies, provoking concern about induced

resistance and the safety of repeated courses of ART in subsequent pregnancies in women not requiring ART for their own health.<sup>253,275</sup> However, these studies yet again underscored the importance of lifelong ART as the most critical component of managing maternal health and preventing MTCT, showing the greatest impact in women with advanced disease who were on ART in pregnancy.<sup>253,276</sup>

## 2.7 Towards the elimination of paediatric HIV

Following the successful outcomes of these studies, the call for the global elimination of paediatric HIV was made in 2009 and PMTCT recommendations were revised in order to reflect the promotion of more effective programme interventions between 2009 and 2010.<sup>21,44</sup> The primary approach to these guidelines was again a two-tiered strategy comprising prophylaxis for PMTCT and lifelong ART for women who required it for their own health. However, the rationale behind the changes was to ensure a higher proportion of women received treatment for their own health from earlier in pregnancy, in order to optimise maternal and children outcomes. The need for a continuum of care between antenatal and postnatal services was emphasised to underscore the need to address MTCT transmission through breastfeeding.<sup>21</sup>

A number of priority areas for revision included recommendations for earlier prophylactic treatment starting in pregnancy at 14 weeks gestation, as well as earlier initiation of ART in eligible pregnant women. Furthermore, extended mother or infant regimens to cover the period of breastfeeding to reduce postpartum transmission were recommended.<sup>44</sup> Based on the variations in combination therapy used in the postpartum studies, several treatment options were included in these guidelines which could be adapted to different service settings. Maternal ART was recommended for women with clinical indications of advanced disease or a CD4 cell count of  $\leq 350$  cells/ $\mu\text{L}$ . In addition, infants of mothers on ART were to receive either daily NVP or twice-daily AZT for 4-6 weeks of age.

Two options for women who did not require ART for their own health were proposed, to be chosen at country level according to feasibility, acceptability, safety and cost. Option A recommended twice daily AZT from 14 weeks gestation, with the addition of sdNVP in labour and twice daily AZT and LMD for 7 days postpartum to prevent resistance. Daily administration of NVP to infant who are breastfeeding was recommended from birth to one week after cessation of breastfeeding, or for a minimum of 4-6 weeks if breastfeeding is stopped before 6 weeks. In non-breastfeeding populations, the same antenatal regimens were recommended with infant NVP or sdNVP and twice daily AZT, to be administered for 4-6 weeks postpartum. Option B advocated ART for pregnant women who did not require it for their own health, from 14 weeks gestation until delivery, or until a week post-cessation of breastfeeding, coupled with NVP or twice daily AZT to the infant until 4-6 weeks of age.<sup>21</sup>

Other important changes to these recommendations included the move away from more toxic triple therapy regimens towards the use of safer, fixed-dose regimens. The expansion of laboratory settings for the monitoring of CD4 cell counts was also emphasised. Furthermore, with the introduction of extended prophylaxis during the postpartum, countries were urged to assess infant feeding in the context of optimising infant survival.<sup>21</sup>

Concern was expressed for the capacity of middle- and low-income countries to implement the new guidelines rapidly in light of resource constraints and competing health priorities and the need for supported scale-up was highlighted.<sup>277</sup> Following the release of the guidelines, the WHO's PMTCT strategy for 2010-2015<sup>21</sup> underscored the importance of country-level leadership, much like the IATT report of 2007.<sup>15</sup> Furthermore, emphasis was placed on the quality of care for women and children and the integration of maternal and child services; HIV treatment and care and sexual and reproductive health services within a strengthened health system that made appropriate provision for performance measurement.<sup>21</sup>

In the most recent developments towards the virtual elimination of paediatric HIV by 2015, a schema entitled "The Global Plan towards the elimination of new HIV infections

among children by 2015 and keeping their mothers alive, 2011-2015” was devised through a consultative process between UNAIDS, country leaders and a high level task team.<sup>278</sup> The Plan targets middle- and low- income countries, with the intention to assist with the mobilization of efforts towards the virtual elimination of MTCT. There is particular focus on the 22 countries with the highest estimate of HIV-infected pregnant women, of which South Africa is one. Based on the premise that although treatment coverage has improved over recent years, the report suggests that a substantial proportion of women still do not receive required interventions due to missed opportunities within services. The report poses country-level challenges for increased leadership and accountability through better management of resources and services as well as the development of appropriate monitoring and evaluation systems to assess progress. The Plan advocates for the revitalization of national strategies to address the epidemic as well as the strengthening of linkages between maternal and child health services and ART services, enhanced supply of human resources and increased community involvement through improved communication.<sup>278</sup>

The National Department of Health revised the 2008 PMTCT guidelines to incorporate the WHO recommendations of 2010, using Option A for women who did not require treatment for their own health.<sup>279</sup> In support of baby-friendly initiatives in health services, the Department of Health has recommended the withdrawal of free formula milk from all public health facilities. The proposal to increase the support of mothers who wish to breast feed will include the supply of community health promoters and promotion of workplace feeding support as well as tighter regulation of the sale of breast milk substitutes, in an attempt to promote exclusive breastfeeding within the context of the revised 2010 guidelines.<sup>280</sup> These changes have been received with mixed reactions, which are centred around the debate concerning which options have the maximum impact on child survival and not only HIV transmission.<sup>281,282</sup>

Recent policy development in Malawi incorporates “Option B-Plus”, which allows for lifelong universal ART for all HIV-infected pregnant women. This initiative was instigated in order to overcome obstacles in CD4 cell count testing, due to limited resources, and to increase PMTCT coverage in the context of prolonged breastfeeding and high fertility rates. Additional benefits are expected: early ART initiation will reduce the burden of opportunistic infection, sexual transmission of HIV and the risk of drug resistance through treatment interruption.<sup>283</sup> Besides the considerable gains to be made in programme coverage and prevention of vertical transmission, model estimates suggest that huge reductions in maternal mortality in sub-Saharan Africa could be achieved if universal maternal ART were implemented in sub-Saharan Africa.<sup>284</sup> Based on these benefits, this approach should be considered for future incorporation into South African PMTCT policy, yet implementation would require considerable planning around the optimal approaches to delivering universal ART to pregnant women.

## 2.8 Conclusion

This literature review has presented the scientific development of PMTCT programmes and how they have been translated into clinical practice in operational settings. While factors including political will, ample resources and low HIV antenatal prevalence have ensured the success of these programmes in resource-rich settings, the same is not true for resource-constrained settings, which continue to carry the largest burden of paediatric HIV.

In South Africa, as with other middle- and low- income countries, challenges to PMTCT programme strengthening are multiple, encompassing both patient- and service-related factors. The delay in the implementation of new and more effective regimens has proved to be a critical factor which has compromised effectiveness in the past. Furthermore, the poor integration of ART services within maternal health is an ongoing challenge to improving PMTCT coverage in this setting. These issues are investigated in Chapters 4 and 5

in the context of Cape Town services providing PMTCT and ART for pregnant women between 2005 and 2008.

Weaknesses in programme monitoring have been identified across resource-constrained contexts. This is true for South Africa where historically assessment of the PMTCT programme was based on sparse data and much of the evidence on PMTCT progress was reliant on isolated research projects which were not necessarily generalizable. Furthermore, there is evidence to suggest that routine data need to be interpreted in light of challenges to accuracy and completeness, as well as their capacity to reflect true coverage among women of unknown status. This is discussed in light of the findings in Chapter 3.

Despite these challenges, service-based research since 2008 has suggested improvements in programme coverage and early PMTCT outcomes, possibly attributable to the changes to PMTCT guidelines in 2008 and the scale-up of services. Updated guidelines from 2010 may address late postpartum vertical transmission, however, little is known at this stage of their effectiveness in the South African context.

As discussed, there is an international shift in focus towards treatment for prevention, and an increasing proportion of HIV-infected pregnant women will be eligible to initiate ART at earlier stages in pregnancy. Of the small body of literature on the psychosocial issues concerning HIV diagnosis, treatment initiation in pregnancy and women's perceptions of HIV-positive motherhood, most evidence pertains to resource-rich contexts where it is possible that different social and structural forces are at play. Chapters 6 and 7 examine HIV diagnosis, the barriers to treatment initiation and women's views on HIV-positive motherhood in order to provide insights on these issues in a South African setting.

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## Chapter 3

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Paper 1: Coverage of the prevention of mother-to-child transmission programme in the Western Cape, South Africa using cord blood surveillance

Stinson, K., Boule, A., Smith, P., Stringer, E.M., Stringer, J.S.A., Coetzee, D. Coverage of the prevention of mother-to-child transmission (PMTCT) programme in the Western Cape, South Africa using cord blood surveillance. *Journal of Acquired Immune Deficiency Syndromes*, (in press)

University of Cape Town

## **Abstract**

### **Background**

The effectiveness of prevention of mother-to-child of HIV (PMTCT) programmes depends on the successful coverage of a series of interventions through pregnancy, intrapartum and postpartum. Routine monitoring systems based on service data and limited to women on the PMTCT programme may overestimate intervention coverage at multiple points along this cascade.

### **Methods**

Cord blood specimens with individually linked anonymous demographic and pregnancy data were collected from three delivery services in the Western Cape Province, South Africa, and screened for HIV. Seropositive specimens were tested for the presence of antiretrovirals. Comparisons were drawn between documented service data and cord blood findings for HIV seroprevalence and antenatal antiretroviral coverage.

### **Results**

A total of 3 034 specimens were tested for HIV, 507 (16.7%) of which were HIV seropositive. Of these, 470 (92.7%) were tested for the presence of antiretrovirals, of whom 58.1% had evidence of a standard of care maternal antiretroviral regimen, and 73.6% some form of antenatal antiretroviral prophylaxis. Cord blood antiretroviral coverage was lower than that reported by service data. Incomplete antenatal HIV testing accounted for an estimated 46.2% of missed opportunities for transmission reduction.

### **Discussion**

Even in this well-resourced setting, HIV screening and ensuring antenatal compliance with prescribed regimens were the most immediate priorities for reducing vertical transmission. Cord blood surveillance offers a unique opportunity to explore missed opportunities using methods not currently possible from routine antenatal and PMTCT programme reporting.

### 3.1 Background

Mother-to-child transmission of HIV (MTCT) remains the primary route of HIV infection in children. Transmission risk can be dramatically reduced through the use of ante-, intra-, and postpartum antiretroviral (ARV) regimens.<sup>7</sup> Recent reports of declining infant mortality in South Africa may be due in part to the effectiveness of the PMTCT programme and survival of infected mothers on ART.<sup>285,286</sup> Yet antenatal seroprevalence remains high, having increased to 30.2% in 2010,<sup>287</sup> from 29.3% in 2008, when this study was conducted.<sup>288</sup> New national prevention of mother-to-child transmission (PMTCT) guidelines based on 2010 WHO recommendations<sup>36,279</sup> are being implemented throughout public health services and preliminary results from a recent national survey suggest that early MTCT may currently be as low as 3.5%.<sup>252</sup> The elimination of paediatric HIV, however, still requires committed and sustained efforts to achieve high PMTCT programme coverage and a continuum of care that also identifies women at risk of incident infection in pregnancy and postpartum vertical transmission.<sup>17,34,114,289</sup>

The effectiveness of PMTCT programmes is contingent on a cascade of critical steps which include HIV testing in pregnancy and the provision of, and adherence to, antepartum, intrapartum and postpartum ARV regimens.<sup>60</sup> Epidemiological modelling of programme effectiveness has shown that the use of more effective ARV drug combinations could have limited impact on transmission if adequate service coverage of all the steps of the PMTCT programme is not achieved.<sup>129</sup> This highlights the importance of identifying and reducing the missed opportunities in programme coverage.

Effective monitoring and evaluation of PMTCT programmes is hence crucial for the identification of missed opportunities in service delivery along the PMTCT cascade. Since 2001, PMTCT programme coverage in South Africa has been reported through indicators routinely collected and aggregated from service data. However, there is uncertainty about the

quality of data due to incomplete and inaccurate reporting.<sup>247,249</sup> In addition, these data reflect coverage in women attending antenatal care and further document dispensing of PMTCT prophylaxis rather than actual ingestion.<sup>290</sup>

In 2007, the PEARL (PMTCT Effectiveness in Africa: Research and Linkages to Care) study consortium explored a new approach to the evaluation of PMTCT programme coverage through cord blood surveillance of HIV status and nevirapine (NVP) concentration in four African countries.<sup>35</sup> The study was expanded in the Western Cape Province of South Africa to document the effective administration of azidothymidine (AZT) and combined antiretroviral therapy (cART), which were at the time available as standard of care to HIV-infected women with CD4 cell counts above and below 200 cells/ $\mu$ l respectively. Our aim was to describe true standard of care PMTCT coverage using cord blood surveillance of HIV infection and the presence of ARVs. We further sought to compare these outcomes to programme reporting and examine missed opportunities for preventing vertical transmission in the Western Cape PMTCT programme,<sup>219,291,292</sup> which started in 2002 and was considered at the time to be effective based on routine reporting.<sup>219</sup>

### 3.2 Setting

HIV prevalence in the Western Cape among pregnant women 15-40 years was 16.1% in 2008, ranging between subdistricts from 9.3% to 17.9%.<sup>288</sup> Two delivery services in the metropolitan area and one rural area were randomly selected from 32 sub-districts in the province.

At the time of this study, PMTCT services were integrated into primary health care antenatal services, with the exception of cART provision to eligible women, which was provided by a separate programme within the same facility at the antenatal service at all three sites. At the first antenatal visit all women received group HIV counselling followed by individual counselling if they agreed to HIV testing. At the same time a CD4 cell count was

requested. In 2007-8, the standard of care for HIV-infected pregnant women with a CD4 cell count  $>200$  cells/ $\mu\text{l}$  comprised AZT from 28 weeks gestation in combination with single dose NVP to the mother and exposed infant at time of delivery, and three-hourly AZT during labour to the mother. If a woman had a CD4 cell count  $\leq 200$  cells/ $\mu\text{l}$  she was referred to a separate service to initiate cART.<sup>212</sup> Vertical transmission proportions according to these treatment guidelines were reported to be 3.5% among infants who were tested around 6 weeks in immunisation services in 2009 in the Western Cape.<sup>251</sup>

### 3.3 Methods

The study methodology has been described in detail elsewhere.<sup>35</sup> To ascertain cord blood HIV seroprevalence and ARV coverage, consecutive umbilical cord blood specimens were drawn at the study sites between December 2007 and May 2008. A sample size was calculated for the four country study, whereby the number of specimens required was ascertained based upon an assumed PMTCT programme coverage of 55% (95% CI 0.52-0.58). An estimated target of 800 specimens was required from each country, however, in order to make this sample size a function of HIV seroprevalence, this specimen target was divided by the estimated seroprevalence of each country at the time of the study.<sup>35</sup> In some sites there were more deliveries and the study was completed within 6 weeks whereas in others completion took up to 6 months to complete. Anonymous HIV prevalence testing was performed, using a rapid immunoassay (Determine HIV1/2, Abbott Laboratories, Chicago, Illinois). High performance liquid chromatography and tandem mass spectrometry were used to extract and qualitatively detect the presence of maternal NVP, AZT and lamivudine (3TC) on all seropositive specimens.<sup>293</sup> In order to draw comparisons between cord blood outcomes and PMTCT programme reporting, linked anonymous surveillance data were extracted from patient-held antenatal records and service registers at the time of specimen collection. Information collected included demographic details, antenatal and

obstetric data and recorded maternal and infant PMTCT regimen administration (Appendix 1)

The primary study outcomes were maternal HIV seroprevalence and ARV coverage, defined as the proportion of women who had at least NVP and AZT or cART (ascertained through the presence of 3TC) detected in cord blood specimens at delivery. Cord blood HIV seroprevalence and ARV coverage were then compared with HIV seroprevalence and ARV coverage data extracted from service records. In the service data, standard of care was assumed to be any documentation of AZT in combination with single dose NVP, or cART, regardless of duration. A series of proportions for each step of the PMTCT cascade was constructed from the extracted services data and cord blood specimen results. Kappa statistics were calculated to measure the agreement beyond chance between the presence of antiretrovirals in the cord blood and reported antiretroviral provision. Maternal-infant coverage was also determined through combined cord blood ARV coverage and documented administration of infant NVP and/or AZT from service records. Twin deliveries were treated as singleton deliveries for the purposes of analysis, as each set of HIV-exposed twins (n=4) received the same infant prophylaxis. Factors associated with PMTCT coverage were determined using a multivariable logistic regression model. The modelled impact of missed opportunities for maternal prophylaxis was assessed by assuming differential vertical transmission based on standard of care interventions,<sup>212</sup> sub-optimal prophylaxis, no prophylaxis and seroconversion during pregnancy. Model estimates were based on assumed probabilities of 0.04 (AZT and NVP), 0.02 (cART), 0.12 (NVP only), 0.07 (AZT only), 0.20 (no intervention) and 0.35 (seroconversion) reported by Johnson *et al.* in a model for paediatric HIV in this setting.<sup>294</sup>

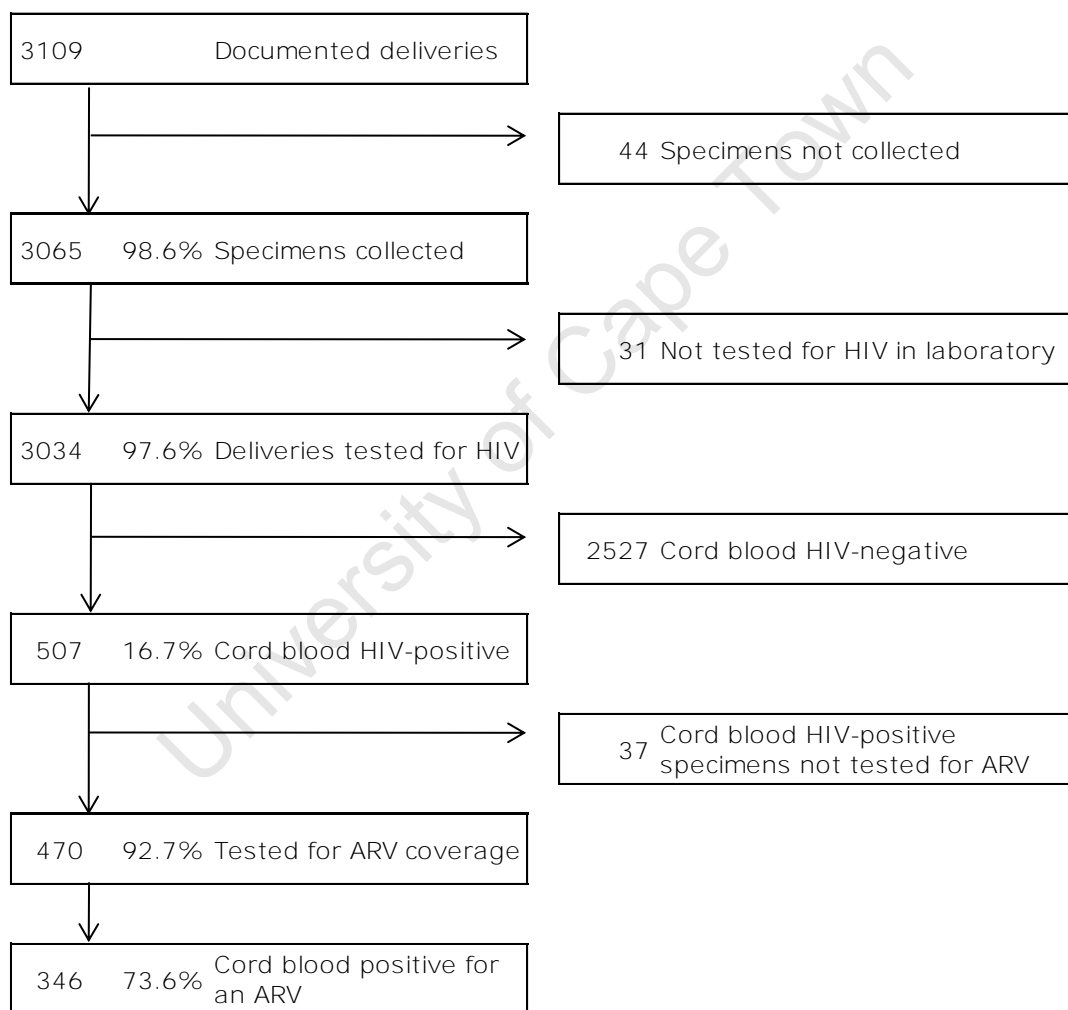
Ethical approval was granted by the institutional review boards of the United States Centers for Disease Control and Prevention; the Health Sciences Faculty Human Research Ethics Committee, University of Cape Town; the Health Department of the Provincial

Government of the Western Cape and the University of Alabama at Birmingham (Appendix 2).

### 3.4 Results

Between December 2007 and May 2008, 3109 women delivered at the 3 sites and 3065 (98.6%) cord blood specimens were collected.

**Figure 3.1 Cord blood specimen collection cascade, 2007-08**



Specimens were not collected from women who delivered before arrival or in instances where it was not possible to retrieve blood from the umbilical cord (cord snapped or unhealthy), or accidental specimen spillage. In total, 3034 specimens (97.6%) were tested

for HIV. Of the HIV-infected specimens (n=507), 470 specimens (92.7%) were tested for the presence of ARV regimens (Figure 3.1).

The median maternal age of women was 24 years (Interquartile range[IQR]: 21-28 years) and 37.4% of women were primigravid. The median number of antenatal visits was 4 (IQR: 3-5 visits), with 21.2% of women having 2 or fewer visits and 8.2% of women having had no antenatal visits. Overall, 10.5% of women had caesarean sections. Four infants were stillborn and were excluded from the maternal-infant coverage analyses. The median birth weight of infants was 3100 grams (IQR: 2800-3400 grams), and 10.8% weighed 2500 grams or less (Table 3.1).

**Table 3.1 Sociodemographic, maternal and child characteristics, 2007-08**

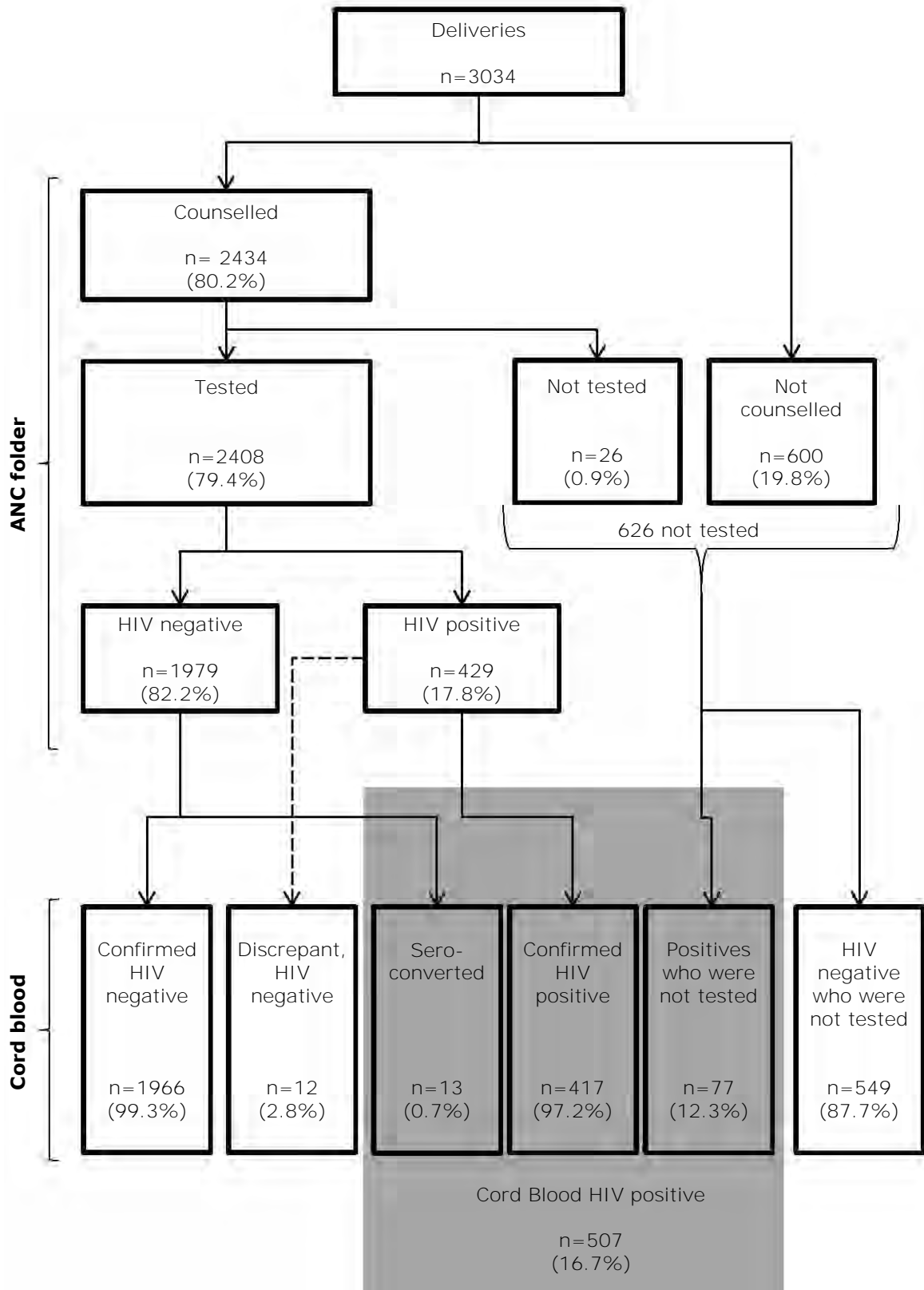
|  | N    | n        |                  |
|--|------|----------|------------------|
| All deliveries   | 3109 |          |                  |
| Deliveries with complete laboratory HIV test                                   |      | 3034     |                  |
| Deliveries with complete HIV and maternal antiretroviral coverage test results |      | 2997     | 96.4%            |
| Primigravid  | 2979 | 1115     | 37.4%            |
| No antenatal visits  | 2995 | 244      | 8.2%             |
| Caesarean section  | 2976 | 313      | 10.5%            |
| Median age at delivery   | 2981 | 24 years | IQR: 21-28 years |
| Median number of antenatal visits  | 2724 | 4 visits | IQR: 2-5 visits  |
| Median birthweight   | 2849 | 3100g    | IQR: 2800-3400g  |

#### 3.4.1 Documented antenatal HIV testing and HIV seroprevalence versus maternal cord blood HIV seroprevalence at delivery

Documented antenatal HIV testing coverage was 79.4% (n=2408, Figure 3.2) and antenatal HIV prevalence among these women was 17.8% (n=429). Cord blood HIV seroprevalence among all women who delivered was similar at 16.7% (n=507, p=0.53).

Among women who did not have an antenatal HIV test, 12.3% (n=77/626) had an HIV seropositive cord blood result. Based on documented antenatal HIV status versus cord blood status at delivery, there were 13 seroconversions (0.7%) and 12 specimens (2.8%) that were reported as HIV seropositive in pregnancy were cord blood HIV seronegative (Figure 3.2).

**Figure 3.2 PMTCT cascade showing HIV status by antenatal record and cord blood result, 2007-08**



### 3.4.2 Documented dispensed antiretroviral prophylaxis and cord blood antiretroviral coverage

Table 3.2 shows that among the women who were documented to be HIV seropositive in service records, 65.8% (n=275) received AZT and NVP; 16.9% (n=71) AZT only; 2.4% (n=10) NVP only, and 7 women were documented to have received no intervention.

Although CD4 cell counts were not extracted from the antenatal data and eligibility for cART could not be ascertained, a further 13.2% (n=55) of women were documented by patient record to be on cART. Hence according to service records, documented ARV coverage for receiving the standard of care including cART was 78.9% (n=330/418), and documented ARV coverage for all women who received any form of ARV drug was 98.3% (n=411/418).

**Table 3.2 ARV regimen coverage per antenatal record and cord blood specimen, 2007-08**

|                                     | Recorded ARV coverage   |      | Cord blood ARV coverage                     |      |                             |      |
|-------------------------------------|-------------------------|------|---|------|-----------------------------|------|
|                                     | Known HIV-positive      |      | Known HIV-positive, confirmed on cord blood |      | All cord blood HIV-positive |      |
|                                     | n                       | %    | N   | %    | n                           | %    |
| AZT <sup>1</sup> & NVP <sup>1</sup> | 275                     | 65.8 | 215   | 55.4 | 217                         | 46.2 |
| cART <sup>1</sup>                   | 55                      | 13.2 | 55  | 14.2 | 56                          | 11.9 |
| AZT                                 | 71                      | 16.9 | 34  | 8.2  | 35                          | 7.4  |
| NVP                                 | 10                      | 2.4  | 37  | 9.7  | 38                          | 8.1  |
| Standard of care                    | 330                     | 78.9 | 270   | 69.6 | 273                         | 58.1 |
| Any                                 | 411                     | 98.3 | 341   | 87.9 | 346                         | 73.6 |
| None                                | 7                       | 1.7  | 47  | 12.1 | 124                         | 26.4 |
| <b>Total</b>                        | <b>418</b> <sup>2</sup> |      | <b>388</b>                                  |      | <b>470</b>                  |      |

Notes: 1: AZT: zidovudine; NVP: nevirapine; cART: Combined antiretroviral therapy

2: Recorded prophylaxis was not available in any record for 11 of 429 women known to be HIV-infected

In comparison, of the 470 HIV seropositive women for whom cord blood specimens were available, 46.2% (n=217/470) had AZT and NVP in their cord blood; 15.5% (n=73/470) had either AZT or NVP, and 11.9% (n=56/470) had 3TC, indicating that they were on cART. A further 26.4% (n=124/470) of HIV seropositive cord blood specimens had no trace of any antiretroviral regimen. In summary, 58.1% (n=273/470) of women confirmed to be HIV seropositive by cord blood had evidence of a standard of care regimen

(dual therapy or cART), while 73.6% (n=346/470) of women were found to have received some form of ARV prophylaxis (Table 3.2).

### **3.4.3 Accuracy of routinely recorded coverage data**

When restricting the analysis to women who were documented by the services to be HIV seropositive, as well as cord blood HIV seropositive and in whom documented coverage could therefore be verified on cord blood (complete results on n=388), estimates of coverage were lower for dual therapy and AZT monotherapy, but higher for NVP on its own (55.4% vs. 65.8%, 8.2% vs. 16.9% and 9.7% vs. 2.4% respectively, Table 3.2).

Combined estimates for standard of care regimens or any regimen were consequently lower on cord blood analysis than reported by the services (69.6% vs. 78.9% and 87.9% vs. 98.3% respectively, Table 3.2).

Kappa statistics measuring agreement beyond chance among the mothers for whom data was available from both sources for cART, AZT and NVP were 0.60, 0.14 and 0.32 respectively, indicating reasonable agreement for cART, but limited agreement for the individual drugs, especially AZT. Of 242 mothers with AZT detected in their cord blood and for whom clinical record data were available, 236 (97.5%) had this recorded in their charts, whereas there was no evidence of AZT in the cord blood of 61/297 (20.5%) of mothers who were reported to have received AZT antenatally. Discrepancies between those reported to have received NVP peripartum and the detection of NVP in cord blood were comparable in both directions, with 15.3% (39/255) of those recorded to have received NVP not having it detected in their cord blood, and similarly 14.6% (37/253) of those with evidence of NVP in their cord blood not having any record of having received this (Table 3.3).

Five out of 72 women who were documented as not having tested and who were cord blood HIV seropositive had evidence of antiretrovirals in their cord blood, whereas none of

the 12 women who were documented as being HIV seropositive but were HIV seronegative on cord blood testing were evaluated for antiretrovirals in their cord blood.

**Table 3.3 Measure of agreement between recorded ARV dispensing and cord blood specimen, 2007-08**

| <b>AZT</b>    |     | Dispensed |            | <b>TOTAL</b> |               |        |
|---------------|-----|-----------|------------|--------------|---------------|--------|
|               |     | No        | Yes        |              |               |        |
| In Cord Blood | No  | 9         | 61         | <b>70</b>    | Agreement:    | 0.7853 |
|               | Yes | 6         | 236        | <b>242</b>   | E(Agreement): | 0.7491 |
| <b>TOTAL</b>  |     | <b>15</b> | <b>297</b> | <b>312</b>   | Kappa:        | 0.1440 |

| <b>NVP</b>    |     | Dispensed |            | <b>TOTAL</b> |               |        |
|---------------|-----|-----------|------------|--------------|---------------|--------|
|               |     | No        | Yes        |              |               |        |
| In Cord Blood | No  | 33        | 39         | <b>72</b>    | Agreement:    | 0.7662 |
|               | Yes | 37        | 216        | <b>253</b>   | E(Agreement): | 0.6585 |
| <b>TOTAL</b>  |     | <b>70</b> | <b>255</b> | <b>325</b>   | Kappa:        | 0.3152 |

| <b>cART</b>   |     | Dispensed  |           | <b>TOTAL</b> |               |        |
|---------------|-----|------------|-----------|--------------|---------------|--------|
|               |     | No         | Yes       |              |               |        |
| In Cord Blood | No  | 293        | 16        | <b>309</b>   | Agreement:    | 0.9030 |
|               | Yes | 19         | 33        | <b>52</b>    | E(Agreement): | 0.7593 |
| <b>TOTAL</b>  |     | <b>312</b> | <b>49</b> | <b>361</b>   | Kappa:        | 0.5972 |

#### 3.4.4 Documented and cord-blood comparison of combined maternal-infant ARV coverage

Two infants born to HIV seropositive women were stillborn, and these mother-infant pairs were removed from this sub-analysis. According to service records, 68.6% (n=293) of infants born to HIV seropositive mothers (n=427) received ARV prophylaxis and 58.3% (n=249) mother-infant pairs received combined maternal standard of care and infant prophylaxis. When examining documented infant prophylaxis coverage among women with an HIV seropositive cord blood specimen (n=468), 62.6% (n=293) of infants were reported to have received ARV prophylaxis, and combined mother–infant coverage (seropositive cord blood and documented infant coverage) was 54.7% (n=256). More than two thirds of the

exposed newborns who did not get ARV prophylaxis were missed because their mothers had not tested for HIV in pregnancy (72/175, 41.1%).

### 3.4.5 Factors associated with maternal coverage

In multivariable analysis that included maternal age, facility location as metropolitan or peri-urban, and mode of delivery as possible confounders based on *a priori* assumptions, having five or more antenatal clinic visits was the only measured association with maternal coverage (defined as receiving either dual prophylaxis or cART, adjusted odds ratio [AOR] 2.47; 95% CI 1.19-5.15, Table 3.4).

**Table 3.4 Multivariable model of predictors of being on the standard of care at delivery, 2007-08**

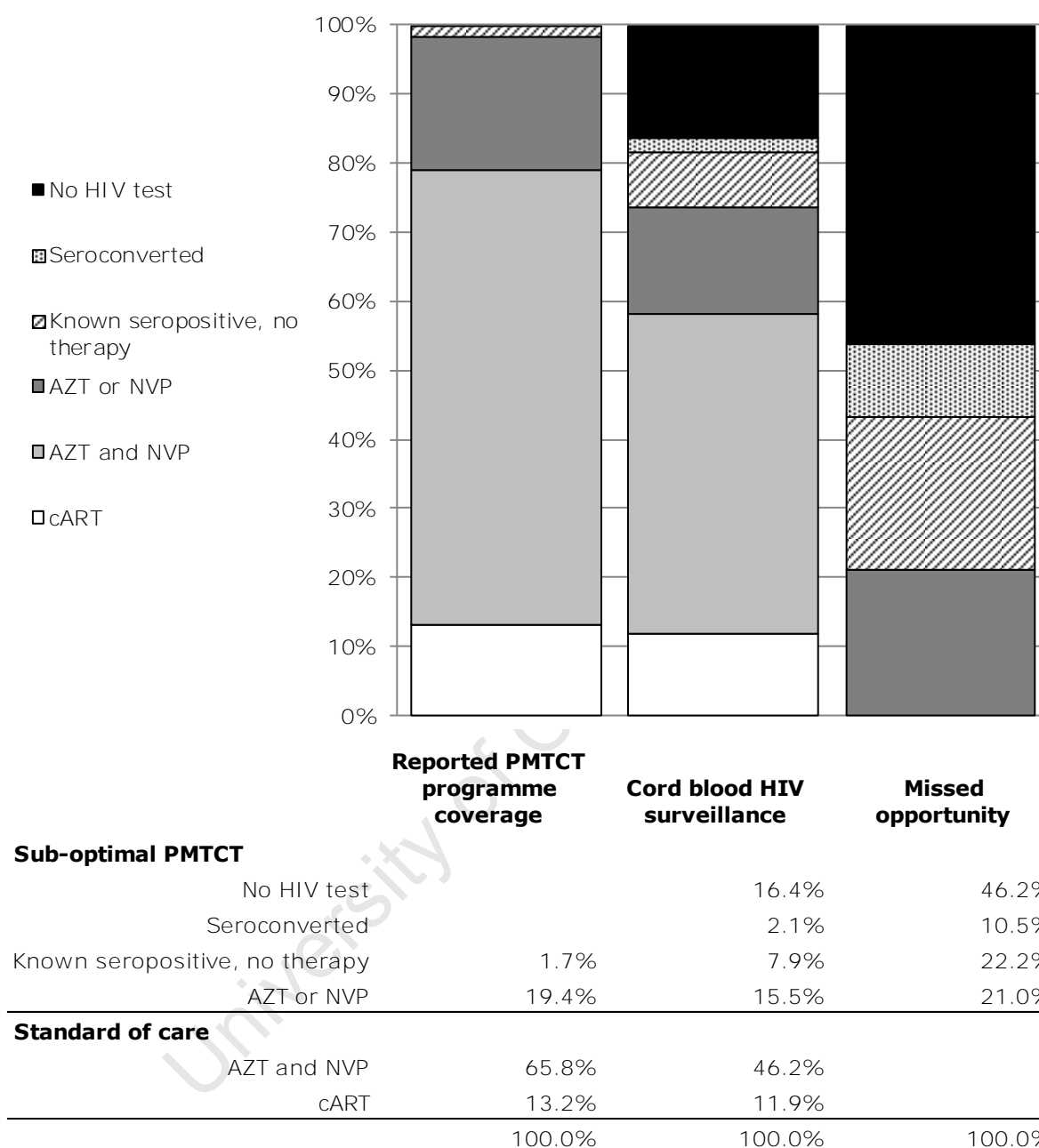
|                                    | Maternal coverage <sup>1</sup> | OR   | 95% CI      | AOR  | 95% CI      |
|------------------------------------|--------------------------------|------|-------------|------|-------------|
| Maternal age (n=466)               |                                |      |             |      |             |
| 15-19 years                        | 13/24                          | 1    |             | 1    |             |
| 20-24 years                        | 90/156                         | 1.15 | (0.49-2.74) | 1.15 | (0.43-3.03) |
| 25-29 years                        | 93/155                         | 1.27 | (0.53-3.01) | 1.22 | (0.46-3.25) |
| 30 years or more                   | 75/131                         | 1.13 | (0.47-2.72) | 1.06 | (0.40-2.83) |
| Facility location (n=470)          |                                |      |             |      |             |
| Metropolitan                       | 189/339                        | 1    |             | 1.00 |             |
| Peri-urban                         | 84/131                         | 1.42 | (0.94-2.15) | 1.24 | (0.78-1.96) |
| Number of antenatal visits (n=414) |                                |      |             |      |             |
| 1 or fewer                         | 19/39                          | 1    |             | 1.00 |             |
| 2-4 visits                         | 147/234                        | 1.78 | (0.90-3.52) | 1.73 | (0.87-3.45) |
| 5 or more visits                   | 98/141                         | 2.40 | (1.16-4.94) | 2.47 | (1.19-5.15) |
| Mode of delivery (n=466)           |                                |      |             |      |             |
| Caesarean section                  | 33/58                          | 1    |             | 1.00 |             |
| Vaginal                            | 238/408                        | 1.06 | (0.61-1.85) | 1.46 | (0.80-2.64) |

Note: <sup>1</sup> Number of women receiving the standard of care or cART/Total number of women with an HIV-positive cord blood specimen

### 3.4.6 Missed opportunities

Based on these results, PMTCT coverage appears near-complete in programme reporting, although 19% of women received only single therapy and 1.7% received nothing (Table 3.2).

**Figure 3.3 Missed opportunities for testing and antiretroviral coverage, 2007-08**



However, Figure 3.3 shows that, according to cord blood surveillance, a substantial proportion of mothers (16.4%) identified as cord blood HIV seropositive did not receive prophylaxis because they had not tested for HIV (Figure 3.3, black shading). A further 7.9% (Figure 3.3, diagonal-lined section) of known HIV seropositive mothers had no ARVs detectable in their cord blood. Assuming differential vertical transmission for mothers seroconverting in pregnancy compared to those already HIV seropositive receiving no

intervention (0.35 versus 0.20)<sup>294</sup> and for mothers receiving standard of care (0.04 for dual therapy and 0.02 for cART) versus other maternal ARV prophylaxis: 0.12 for NVP and 0.07 for AZT<sup>294</sup>), the most frequent missed opportunities for preventing transmission were the result of incomplete antenatal HIV testing and failure to administer any prophylaxis or to ensure adherence in women known to be HIV seropositive.

### 3.5 Discussion

As the international focus shifts towards the global elimination of paediatric HIV, effectively monitoring the coverage of PMTCT programmes is imperative to determine their strengths as well as to address the missed opportunities for identifying HIV infection and for delivering treatment during pregnancy. Our results show that just over half of women identified as cord blood HIV seropositive received the standard of care (dual therapy or cART), and about three quarters of women testing cord blood HIV seropositive had received some form of ARV. Maternal cord blood ARV coverage was significantly lower than that suggested by maternal coverage in routine data. Identifiable programme gaps included incomplete HIV testing and a failure to administer ARVs or ensure adherence.

#### 3.5.1 *Concordance of reported versus cord-blood maternal HIV seropositivity*

Compared to other studies, seroconversion in this study was low (0.7%), assuming that all were true seroconversions and not documenting or reporting errors. Another study in the Cape Town metropole found no seroconversions among 532 pregnant women in 2004.<sup>177</sup> With an estimated transmission probability of 0.35,<sup>294</sup> seroconversion in pregnancy may account for a small, yet significant proportion of transmission in many settings. As programme coverage improves, so the relative contribution of seroconversion will increase, supporting the strategy of repeat testing close to delivery to identify acute infection.<sup>295</sup>

### 3.5.2 *Concordance of routine versus cord-blood maternal ARV prophylaxis coverage*

Results from the cord blood analysis suggested appreciably lower maternal ARV coverage than the near-complete coverage suggested by service data, even when restricted to patients who were definitively known by the services to be HIV seropositive. The largest discrepancy was found between reported and cord blood AZT coverage. Due to the short plasma half-life of AZT and reported variability in concentrations between subjects elsewhere,<sup>296-299</sup> we cannot assume that all women without AZT in their cord blood did not receive any AZT prior to delivery. However, guidelines at the time of this study recommended AZT from 28 weeks gestation as well as 3-hourly during labour. Evidence from other settings has demonstrated the presence of therapeutic concentrations of AZT in cord blood when oral doses were administered within three hours of delivery.<sup>300</sup> Hence in our setting, AZT concentrations should have been reflected in those women who received PMTCT according to protocol during labour. Furthermore cord blood results of AZT coverage at delivery cannot be extrapolated to infer adequate antenatal coverage.<sup>301</sup> There is also a possibility that regimens may not have reflected in women who delivered too quickly after presenting in labour.

### 3.5.3 *Missed opportunities*

Our results show that one in five women did not test for HIV in pregnancy and 12% of these women were HIV seropositive at delivery. Several studies have shown regional variation in antenatal testing coverage in South Africa,<sup>302,303</sup> with the national antenatal testing average estimated to be 92.7%.<sup>246</sup> This is thought to be an overestimate, as testing coverage is reported to be over 100% in some health districts.<sup>248</sup> Routinely collected data from the sites at the time of this study report testing coverage to range between 77-100%, suggesting that HIV screening in pregnancy could be improved. Modelling exercises have shown that failure to achieve near universal testing has a greater impact on vertical transmission than attrition

further along the PMTCT cascade.<sup>129</sup> This analysis supports the importance of initial antenatal testing coverage as the single largest contributor to missed opportunities for preventing transmission, but further highlights substantial missed opportunities, as a result of no prophylaxis being taken by women known to be HIV seropositive, suboptimal prophylaxis and seroconversion during pregnancy.

#### **3.5.4 Limitations**

A limitation of this study is the absence of CD4 cell count data which would have assisted in the further disaggregation of the standard of care. There is also concern about record keeping: clerical errors, antenatal false-positive tests or cord blood false-negative tests could have given rise to the 12 women who tested HIV seropositive in pregnancy and had a seronegative cord blood specimen at delivery. All antenatal HIV seropositive tests are routinely confirmed by a second rapid test in South African service settings, and in our laboratory, the same protocol was performed, with an additional 10% of tests being tested blind for quality assurance. Our specimen collection rate was high at the sites (98.5%), however, logistical challenges resulted in the random loss of 7% of cord blood seropositive specimens which could not be tested for regimen coverage. Furthermore, the small sample size, particularly reflected by the small proportion of HIV seropositive women may account for the lack of statistical power of the reported ARV coverage outcomes.

#### **3.5.5 Conclusion**

Our results show that even in a well-resourced setting, improving HIV screening coverage and ensuring compliance with guidelines for antenatal prophylaxis were the most immediate priorities for reducing vertical transmission. As increasing resources are invested in the rapid expansion of HIV prevention and treatment programmes there is a need for the strengthening of monitoring and evaluation of the effectiveness of these programmes.<sup>304</sup>

Accurate collection and reporting of PMTCT process and outcome indicators remains a

challenge because the interventions at each step of the PMTCT cascade occur sequentially through pregnancy and involve more than one service and provider, as well as crucial delivery of treatment at different points in pregnancy. This study, along with evidence from other settings<sup>305</sup> shows the value of cord blood surveillance as a feasible tool for confirming both antiretroviral provision and regimen adherence. Cord blood surveillance could be used to assist in the interpretation of programme data to improve programme effectiveness.

University of Cape Town

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## Chapter 4

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### Paper 2: Initiation of highly active antiretroviral therapy among pregnant women in Cape Town, South Africa

Stinson K, Boulle A, Coetzee D, Abrams E.J, Myer L. (2010) Initiation of highly active antiretroviral therapy among pregnant women in Cape Town, South Africa. *Tropical Medicine and International Health* 2010; 15(7): 825-32.

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## **Abstract**

### **Objective**

To investigate highly active antiretroviral therapy (HAART)<sup>1</sup> initiation among pregnant women and the optimum model of service delivery for integrating HAART services into antenatal care.

### **Methods**

We analysed clinic records to reconstruct a cohort of all HIV-infected pregnant women eligible for HAART at four antenatal clinics representing three different service delivery models in Cape Town, South Africa. To assess HAART coverage, records of women determined to be eligible for HAART in pregnancy were reviewed at corresponding HIV treatment services.

### **Results**

Among 13,208 pregnant women tested for HIV, 3,498 (26%) were HIV-infected and 516 (15%) were HAART-eligible based on a CD4 cell count of  $\leq 200$  cells/ $\mu$ l. Among eligible women, 51% initiated HAART before delivery, 27% received another prevention of mother-to-child (PMTCT) intervention and 22% did not receive any antiretroviral intervention before delivery. The proportions of women initiating HAART between the different service delivery models were comparable. The median gestational age at first presentation was 26 weeks and early gestational age at first presentation was the strongest predictor of being on HAART by delivery. Of the women who did not initiate HAART in pregnancy, 24% started treatment within two years postpartum.

### **Conclusions**

In this setting with clear PMTCT and HAART protocols, services failed to prioritize and initiate a high proportion of eligible pregnant women on HAART. The initiation of HAART in pregnancy requires strengthened antenatal and HIV services which target women with advanced stage disease.

<sup>1</sup>This paper was published using the term, 'HAART', because at the time of this study, it was the term used for antiretroviral therapy. Hence in order to reflect the publication, no changes have been made to this chapter. In all other chapters, the term 'ART' is used, because this term has replaced 'HAART'.

## 4.1 Background

The use of antiretroviral (ARV) prophylaxis during pregnancy and labour can dramatically reduce the risk of vertical transmission of HIV infection. Highly active antiretroviral therapy (HAART) has the greatest efficacy in reducing mother-to-child transmission (MTCT) of HIV and has significant direct benefits for maternal health.<sup>7</sup> Results from recent studies of improved regimen combinations, earlier treatment start in pregnancy and continued ARV support for mother and infant during breastfeeding in the postpartum period have led to significant changes in the recommendations for managing pregnant HIV-infected women.<sup>30,306-308</sup> In light of new evidence, WHO recently released revised guidelines for the management of HIV-infected women in pregnancy which recommend initiating lifelong HAART earlier in pregnant women, and raising the eligibility criteria from a CD4 cell count threshold of  $\leq 200$  cells/ $\mu\text{l}$  to  $\leq 350$  cells/ $\mu\text{l}$  or WHO clinical staging 3 or 4, irrespective of gestational age.<sup>44</sup>

Despite the importance of HAART during pregnancy, there are significant patient- and service-related challenges to the implementation of HAART services as part of antenatal care. In many settings, high HIV seroprevalence among women of reproductive age results in a sizeable proportion of HIV-infected pregnant women accessing limited antenatal and HIV care services<sup>60</sup>. Patient-driven barriers include lack of knowledge of serostatus prior to conception; reluctance to test in pregnancy; fear of disclosure and denial post-diagnosis, and under-utilization of antenatal care during pregnancy.<sup>16,24,25,309</sup> Service delivery approaches impact on the accessibility and availability of treatment services for HIV-infected pregnant women. Prevention of mother-to-child transmission (PMTCT) services for women who do not have advanced HIV disease, but who require short course prophylactic regimens, are generally integrated within routine antenatal health services managed by midwives. Presently there are few such integrated services for pregnant women who are eligible for HAART.<sup>310</sup>

As a result, these women may need to access antenatal care and stand-alone doctor-driven HAART services that may be geographically separate. The integration of HAART into antenatal services has been proposed and is underway in selected settings, yet little is known about the operational experience of different models of service delivery in resource-constrained contexts.<sup>24</sup>

Cape Town health services were among the first in the region to offer both PMTCT (1999) and HAART (2001), with protocols providing for universal access to HAART for eligible pregnant women since 2003.<sup>219,291</sup> A number of service models for delivering HAART to pregnant women developed during this period, providing an opportunity to explore the relationship between these models and the uptake of HAART. Although HAART has been available for eligible HIV-infected pregnant women in Cape Town since 2003, little is known about HAART coverage in pregnancy. The objectives of this study were to describe HAART coverage in a cohort of eligible women accessing antenatal services and to evaluate different service models for providing HAART.

## 4.2 Methods

### 4.2.1 *Study setting*

This study evaluated three different service models for HAART referral and initiation in pregnancy at four primary care antenatal clinics in Cape Town during 2005. The sites were selected to highlight the differences in the proximity of the ARV service to the antenatal site and the service model offered. One antenatal clinic incorporated an “integrated” HAART service, offered once per week by two outreach doctors. The second antenatal clinic referred eligible women to a stand-alone ARV service in a separate building on the same premises, a “proximal” model of care. The third, the “distal” model constituted two antenatal clinics, and eligible women were referred to ARV services within a five kilometre radius, accessible by foot or public transport.

All four clinics operated according to identical midwife-driven care protocols with the same procedures for all aspects of antenatal care<sup>311,312</sup> including PMTCT. At each antenatal clinic, HIV counselling and opt-in testing was offered as part of routine care. After group and individual counselling, a rapid HIV test was performed and results were given with post-test counselling on the same day. For newly diagnosed HIV-infected women, specimens were sent to external laboratories for CD4 cell count enumeration and results were available at the service within 2 weeks. In the proximal and distal models of care, women eligible for HAART were given a referral letter to each ARV service linked to the antenatal service, where treatment initiation occurred. At all sites neonatal prophylaxis was administered at birth for HIV-infected women in the delivery room.

#### **4.2.2 Study design and data collection**

This retrospective cohort included all women who presented at the four antenatal facilities between 1 January and 31 December, 2005. Antenatal data including demographic information, HIV status and CD4 cell count were extracted from PMTCT registers kept on-site using a standardized data extraction tool (Appendix 3). Field workers fluent in local languages searched paper-based and electronic data sources for patient name variations and supplemented this with other personal identifiers, such as date of birth where needed, to maximise follow up. Missing data, including CD4 cell counts were obtained from the National Health Laboratory Services patient database.

The subset of HIV-infected women eligible for HAART based on a CD4 count  $\leq 200$  cells/ $\mu$ l was identified through patient registers and then traced through antenatal care and HIV care and treatment programme records to determine HAART initiation and obstetric and newborn outcomes. HAART coverage was defined as evidence of initiating HAART during pregnancy, or evidence of being on HAART at delivery. Patients with missing information on obstetric, PMTCT and/or HAART-related variables were traced manually

through the records and data bases of each relevant health facility, including secondary and tertiary referral hospitals as well as every clinic providing HAART in the city.

Data were analysed using STATA 9.0 (STATA Corporation, College Station, USA). Proportions were estimated for each step of the PMTCT cascade and HAART coverage was calculated both for the entire cohort and separately for the integrated, proximal and distal service models. Bivariate associations were calculated using  $\chi^2$  tests for categorical variables and one-way ANOVA models or the Kruskal-Wallis test for continuous data. Multiple logistic regression was used to examine the independent predictors of HAART initiation in pregnancy. The inclusion of the dependent variables was based upon *a priori* knowledge, their significance in univariate analyses and model fit in the regression analysis. Approval for the study was obtained from the University of Cape Town Research Ethics Committee and local government health authorities (Appendix 4).

## 4.3 Results

### 4.3.1 Patient and pregnancy characteristics

A total of 14 987 women presented for antenatal care at the four sites (Table 4.1, overleaf). The mean age was 25 years (standard deviation, 6 years). Overall 88% of women were tested for HIV and 26% were HIV-positive (Figure 4.1, on page 93). Uptake of testing and HIV prevalence varied between service models: the proximal model had the lowest coverage of 79% and the integrated model had the highest seroprevalence of 30% ( $p < 0.001$  for both associations, Table 4.1).

**Table 4.1 Description of sample by service delivery model, 2005**

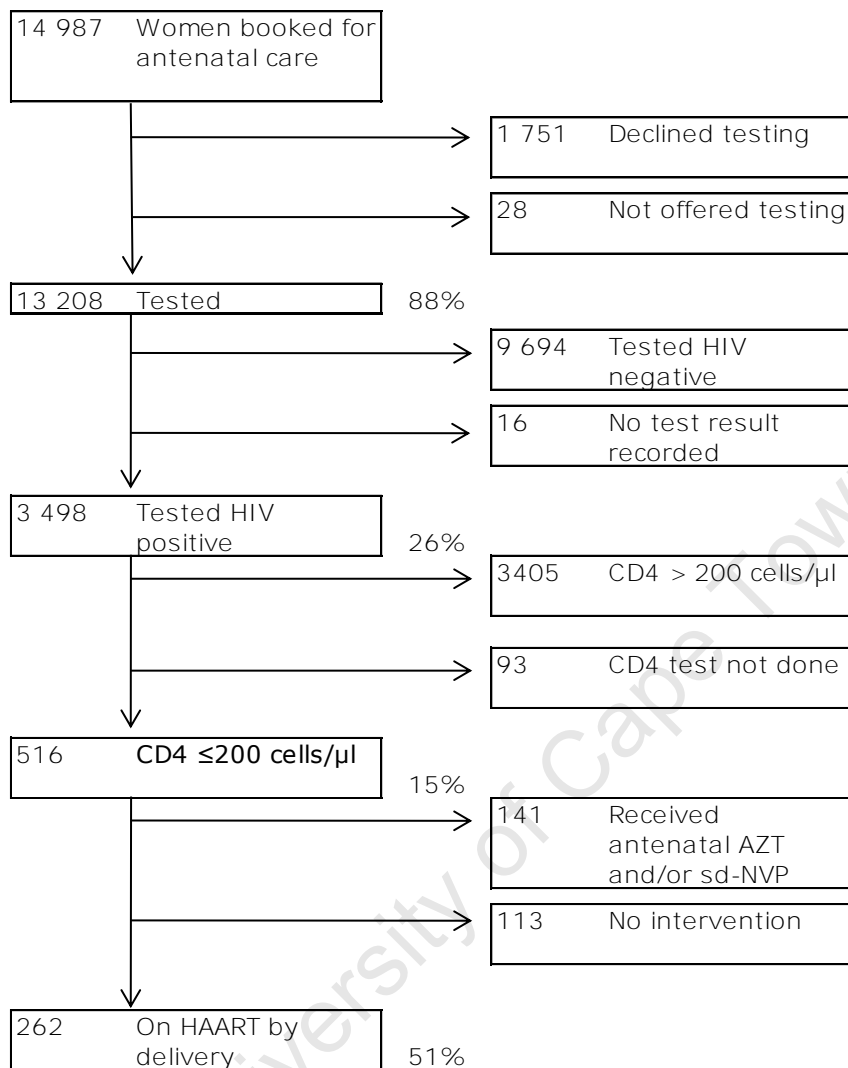
|   | Model 1 (integrated) | Model 2 (proximal) | Model 3 (distal) | P-value* | Total         | Notes       |
|---|----------------------|--------------------|------------------|----------|---------------|-------------|
| All women presenting for antenatal care                   | 4,823                | 4,783              | 5,381            |          | 14,987        |             |
| Mean age in years at 1st presentation (SD)                | 26                   | 26                 | 26               | 0.010    | 26            | 6.10        |
| Tested (% of all women)                                   | 4,727                | 3,784              | 4,697            | <0.001   | 13,208        | 88%         |
| Tested HIV-positive (% of all tested)                     | 1,415                | 1,076              | 1,007            | <0.001   | 3,498         | 26%         |
| Median CD4 count (IQR)                                    | 367 (251-523)        | 385 (248-562)      | 400 (269-554)    | 0.005    | 382 (256-542) |             |
| CD4 ≤200 cells/μl (% of tested HIV-positive)              | 227                  | 159                | 130              | 0.087    | 516           | 15%         |
| <b>HAART eligible women (CD4 ≤200)</b>                    |                      |                    |                  |          |               |             |
| Mean age at 1st presentation (SD)                         | 27                   | 28                 | 27               | 0.406    | 27            | 4.90 (1)    |
| Median gestational age in weeks at 1st presentation (IQR) | 27 (22-31)           | 27 (22-32)         | 23 (20-29)       | 0.017    | 26            | (21-31) (2) |
| Nulliparous   | 68                   | 44                 | 33               | 0.665    | 145           | 36%         |
| Median CD4 count (cells/μl, IQR)                          | 143 (97-171)         | 135 (94-167)       | 139 (106-172)    | 0.527    | 140           | (98-170)    |
| Intervention received                                     |                      |                    |                  |          |               |             |
| Initiated HAART during pregnancy                          | 124                  | 77                 | 61               | 0.291    | 262           | 51% (3)     |
| Received a non-HAART PMTCT regimen                        | 59                   | 44                 | 38               | 0.880    | 141           | 56% (4)     |
| Median gestational age at HAART initiation (IQR)          | 32 (28-35)           | 33 (29-36)         | 31 (26-34)       | 0.113    | 32            | (28-36) (5) |
| Initiated HAART before 32 weeks gestation                 | 54                   | 27                 | 26               | 0.959    | 107           | 48% (6)     |
| Initiated HAART postpartum                                | 22                   | 29                 | 10               | 0.008    | 61            | 24% (7)     |

\* Bivariate comparisons using  $\chi^2$ , ANOVA and Kruskal-Wallis tests

**Notes:**

1. Of 414 women with available data
2. Of 403 women with available data
3. Of 516 women eligible for HAART
4. Of 254 eligible women who did not receive HAART
5. Of 223 women with available data
6. Of women initiating HAART before delivery
7. Of women not initiating HAART before delivery

**Figure 4.1 Cohort description of women accessing antenatal services, 2005**

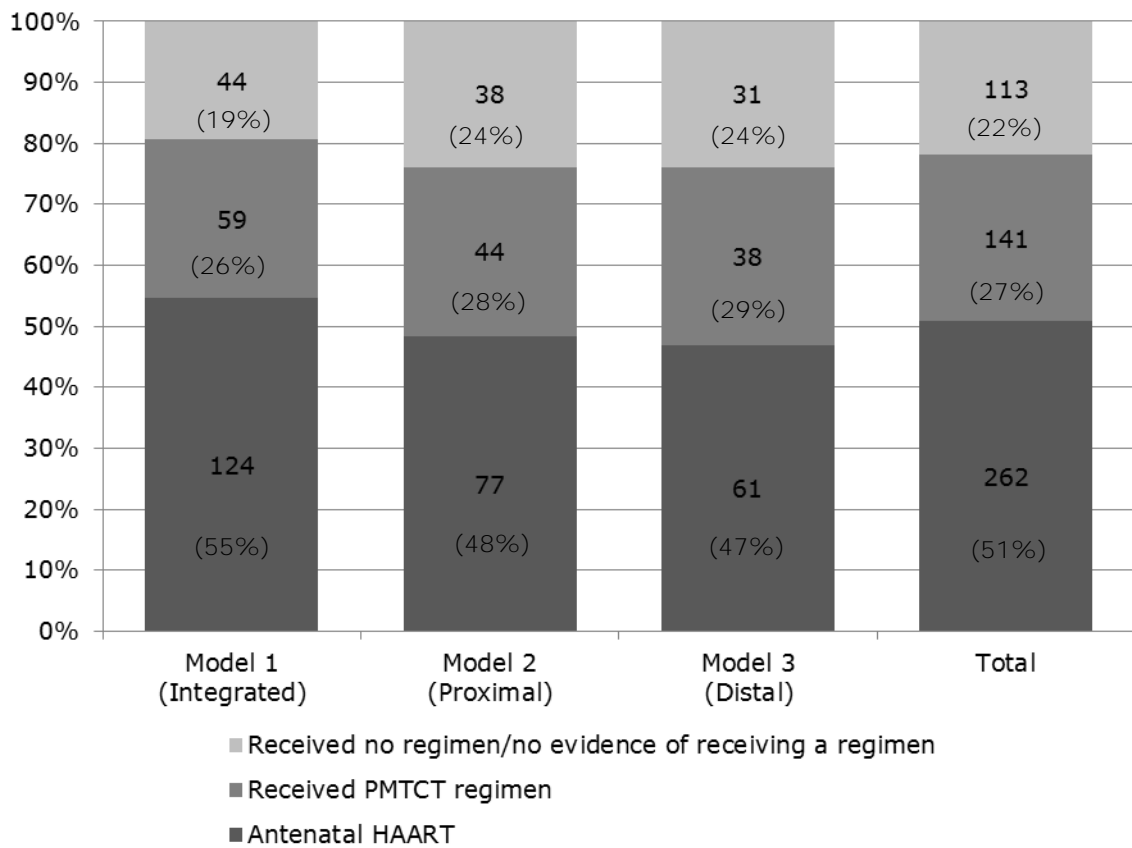


Overall, 97% of women who tested HIV-positive had a CD4 test completed by external laboratories; 15% (n=516) had a CD4 cell count of  $\leq 200$  cells/ $\mu$ l and were eligible for HAART. Twenty-nine percent (n=986) of HIV-infected women had a CD4 cell count  $>200$  cells/ $\mu$ l but  $\leq 350$  cells/ $\mu$ l. The proportion of women eligible for HAART did not vary between the service delivery models ( $p=0.09$ , Table 4.1). The median gestational age at time of first presentation among HAART-eligible women was 26 weeks (Interquartile Range: 21-31 weeks) and varied significantly by service delivery model ( $p=0.02$ , Table 4.1), with women in the distal service model presenting earlier than those in the other two models. Fewer than

25% of HAART-eligible women presented for their first antenatal clinic visit by 20 weeks gestation, 71% by 30 weeks, and 89% presented by 35 weeks.

Of the HAART-eligible women, 391 (76%) had complete delivery information available. Of these women, 70% had normal vaginal deliveries and 30% had caesarean sections. Of the 404 resulting babies born, 6% ended in perinatal loss (stillbirth or early neonatal death). Data on birth weight were recorded for 367 live infants, of whom 20% were under 2500 grams.

**Figure 4.2 HAART coverage by service delivery model, 2005**



#### 4.3.2 HAART initiation

A total of 51% (n=262) of all women with a CD4 cell count of  $\leq 200$  cells/ $\mu$ l had initiated HAART by the time of delivery (Figure 4.2). The proportion of eligible women initiating HAART was 55%, 48% and 47% in the integrated, proximal and distal models, respectively (p=0.29, Table 4.1). The median gestational age at first antenatal clinic attendance was lower

among women who initiated HAART in pregnancy (24 weeks) compared to those who did not (29 weeks,  $p < 0.001$ ). For women who were on treatment by delivery, the median gestational age at initiation was 32 weeks (IQR: 28-36 weeks). Of these women, 48% had more than 8 weeks of HAART; 32% had between 4 and 8 weeks of HAART, and 20% had less than 4 weeks of HAART. The proportion of women who received more than 8 weeks of HAART versus those who received 8 weeks or less of HAART did not vary by service model ( $p = 0.96$ , Table 4.1). Of the 254 women who did not start HAART before delivery, 24% ( $n = 61$ ) went on to initiate HAART in the ensuing 2 years postpartum, half of whom started within 7.5 months after delivery.

In a logistic regression model to predict HAART initiation during pregnancy, there was no association between the model of care and whether HAART was started in pregnancy ( $p = 0.19$ , Table 4.2). However, women who presented for their first antenatal visit in the third trimester of pregnancy were 75% less likely to be on HAART at delivery than those who had presented in the first or second trimester (Adjusted Odds Ratio: 0.25, 95% CI: 0.17-0.39).

**Table 4.2 Multivariate model predicting HAART initiation by delivery, 2005**

| Variable  | Odds Ratio | P-value   | 95% Confidence Interval |
|---|------------|-----------|-------------------------|
| Age (Ref $\leq 27$ years)                         |            |           |                         |
| Age $> 27$ years                                  | 1.09       | 0.68      | (0.72-1.66)             |
| Service Model (Ref: Model 1 - Integrated)*        |            |           |                         |
| Model 2 - Proximal                                | 0.77       | 0.30      | (0.48-1.26)             |
| Model 3 - Distal                                  | 0.62       | 0.07      | (0.37-1.04)             |
| Gestational age at booking (Ref: $<$ Trimester 3) |            |           |                         |
| Trimester 3                                       | 0.25       | $< 0.001$ | (0.17-0.39)             |

\*Wald test for global p-value: 0.19

A further 27% ( $n = 141$ ) of women who were eligible for HAART were recorded as receiving some form of PMTCT prophylaxis, usually zidovudine with single dose nevirapine (Figure 4.2). The remaining 113 women (22%) did not receive any antiretroviral intervention

in pregnancy, according to either their antenatal clinic records or HAART initiation registers across the city. The proportion of patients receiving other forms of ARV-based PMTCT interventions, versus no intervention at all, also did not differ by service model ( $p=0.88$ , Table 4.1). Gestational age at first presentation was a strong predictor of PMTCT coverage: among women who presented in the second trimester 70% initiated HAART and another 23% received ARV prophylaxis, while among women who presented in the third trimester 39% started HAART and another 48% received prophylaxis.

#### 4.4 Discussion

This analysis demonstrates substantial missed opportunities to initiate HAART among pregnant women with advanced HIV disease within public sector antenatal care services. Only 51% of HAART-eligible women initiated treatment before delivery, while another 27% received a short-course PMTCT regimen and more than one-fifth of women received no intervention. Importantly there were no significant differences in these proportions between the integrated service in which antenatal care and HAART were co-located, the proximal service with separately run services on the same premises and the distal model with off-site antenatal HAART provision.

Recently, the WHO revised its ARV treatment guidelines to recommend the initiation of HAART in all adults including pregnant women with CD4 cell counts  $\leq 350$  cells/ $\mu\text{l}$ .<sup>44</sup> Our study showed very high CD4 cell count testing coverage, and based on our data, shifting to a CD4 cell count threshold of  $\leq 350$  cells/ $\mu\text{l}$  would have raised the proportion of eligible HIV-infected women from 15% to 44%, amounting to a threefold increase in women eligible for life-long treatment. While this change in threshold for treatment initiation is likely to yield significant improvements in maternal health outcomes, as well as reduce perinatal transmission, our study points to the challenges of implementing these guidelines and initiating large numbers of women on HAART during pregnancy.

Part of the challenge is likely due to the difficulty in initiating HAART in a midwife-driven antenatal care service and the subsequent logistical demands of coordinating HIV and antenatal care. As doctors are not routinely available in antenatal clinics in this setting and midwives are not certified to prescribe HAART, eligible women must attend separate HIV services or return to the antenatal clinic when a HAART prescriber is available. Furthermore, at the time of this study, it was reported that the duration of treatment adherence preparation in patients eligible for HAART was 4-6 weeks. The possibility of 'fast-tracking' eligible women onto HAART during pregnancy has been suggested but there are few reports of such an approach in practice, and its impact, given that the availability of appropriate providers is static. Particular concerns may exist around how patient preparation before HAART initiation influences long-term outcomes, although there are few data evaluating this possibility. The availability of appropriate clinical personnel to initiate HAART in antenatal care has been raised as an additional concern. One option that has been suggested to address this is nurse-driven HAART initiation which has proven effective and feasible in African settings;<sup>313</sup> in the context of pregnancy, midwives are a potentially valuable human resource for HAART initiation and the possibility of midwife-driven HAART services deserves consideration.<sup>314</sup>

Meanwhile, the challenge of starting HAART in newly diagnosed pregnant women should not be underestimated. Unknown HIV serostatus in pregnancy and labour has been described as an important factor hindering PMTCT scale-up.<sup>16</sup> In this setting where utilization of antenatal care services is high, universal HIV screening was not achieved, with a substantial proportion of women not testing for HIV. Attrition at this point contributes to the pool of infected women of unknown serostatus who will not receive PMTCT

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<sup>1</sup> Subsequent to the publication of this article, nurse administered and managed ART (NIMART) has been rolled out in South Africa, and is discussed in the concluding chapter of this thesis.

programme support in pregnancy, and who are consequently at increased risk of MTCT. The integrated model achieved 98% testing coverage, which was most likely due to individual provider influences at this site, as the opt-in guidelines were consistent across the sites at the time of the study. By modelling the collective data on 100% testing coverage, it is predicted that a further 70 HAART-eligible women would have been missed due to failure at this step in the cascade. In addition, recent evidence suggests that services are failing to identify HAART-eligible HIV-infected women through clinical and immunological assessment.<sup>257,315</sup> Furthermore, the psychosocial impact of HIV infection on pregnancy has been documented in women with both pre- and post-conception HIV diagnosis, and anxiety during pregnancy is commonly associated with disease-related stigma and fear of the risk of vertical transmission.<sup>147,316-318</sup> In addition, among non-pregnant adults psychosocial barriers to HAART uptake and adherence have been reported to include fear of treatment side effects, stigma and a lack of belief in the efficacy of HAART,<sup>319</sup> However, little is known about the psychosocial challenges to initiating HAART during pregnancy, particularly among women who are diagnosed with HIV while seeking antenatal care. It is plausible that the combined psychosocial effects of an HIV diagnosis and HAART initiation during pregnancy may be particularly problematic, but this possibility requires further research.

We found no difference in HAART initiation during pregnancy between the integrated, proximal and distal models of antenatal HAART delivery. *A priori* our hypothesis was that the integrated model would be associated with a significantly greater proportion of women starting HAART during pregnancy through increased access to combined antenatal and HAART services. The fact that the integrated model, which had a higher disease burden and more women eligible for HAART, initiated HAART in more women in absolute terms could be demonstrative of a better model. Other authors have also suggested that the integrated model of antenatal HAART services may be expected to facilitate HAART initiation in pregnancy: for example, antenatal care and HAART integration resulted in an

increase of HAART uptake in pregnant women from 46% to 71% in one urban South African hospital.<sup>320</sup> While our data suggest that in this setting the specific service delivery model may not be a major determinant of HAART initiation in pregnancy, the failure to observe this could be related to the fact that the integrated service was limited to one day a week. Since it was not available to pregnant women during all antenatal service hours, it may not have been optimally “integrated,” and it is likely that the frequency of the service offered may have impacted on coverage. Despite limited capacity, it is impressive that this model performed as well, if not better than models where the referral service was operating every day. Clearly, health systems need to shift from disease specific programmes towards strengthening approaches to integrated maternal and child health and HIV services, to increase the uptake of HAART in pregnancy.

This study focused on HAART initiation during pregnancy; it does not address the issues of long-term follow-up of HIV-infected mothers. It is unclear whether a specific model of antenatal HAART initiation may be associated with better long-term retention of mothers in HIV care services postpartum. Specifically, it is plausible that an integrated model of HAART initiation during antenatal care leads to more women starting HAART during pregnancy, but the transition to routine adult HIV services postpartum is more difficult, compared to an antenatal HAART model where pregnant women are referred immediately to routine HIV care services. The postpartum follow-up of women who initiated HAART during pregnancy appeared problematic in one study<sup>321</sup> but another suggested that initiation during pregnancy is not associated with outcomes that are worse than in non-pregnant women;<sup>322</sup> clearly this possibility requires further investigation.

We found that gestational age at first antenatal visit was a major determinant of HAART initiation during pregnancy, with women making their first antenatal visit during the third trimester 75% less likely to start HAART while pregnant. At the time of the study, the PMTCT protocol recommended not initiating HAART in women beyond 36 weeks

gestation, and this guideline in conjunction with late presentation may have impacted on providers' decisions to initiate treatment close to the time of delivery. However, discussions with local service providers (not presented here), suggested that this guideline was not fully implemented. Furthermore, as duration of HAART is an important factor in achieving viral suppression and in turn preventing vertical transmission of HIV, late presentation is a significant concern. Our study suggests that of those women who received HAART, less than half received more than 8 weeks of treatment before delivery. Data from the European Cohort Study suggest that at least 8 weeks of HAART are required to achieve viral suppression in women with advanced HIV disease <sup>128</sup> and one study in South Africa demonstrated that in women initiating HAART during pregnancy, every additional week of treatment reduced the odds of transmission by 8%. <sup>323</sup> Efforts to encourage women to seek antenatal care earlier in pregnancy are likely to face a host of patient- and health service related barriers. <sup>144,324</sup> Continued progress towards achieving universal HIV testing, particularly in pre-conception care, could ensure that more women are aware of their serostatus prior to conception. Furthermore, moving towards the adoption of provider-initiated counselling and testing, CD4 cell count enumeration and improved systems of expedited HAART initiation should be explored. <sup>16</sup>

These data should be interpreted in light of several limitations. This research was conducted in a high HIV prevalence urban setting within well-established maternal and child health care services. We may anticipate that the proportion of eligible women initiating HAART during pregnancy may be lower in settings with less robust antenatal care systems. These data are from retrospective reviews of clinic records, rather than purposively collected prospective data. However, the system of clinic registries for antenatal care and HAART services that served as the primary data sources is well established and is frequently used for HIV-related research in this setting, <sup>325</sup> and hence unlikely to be an appreciable cause of apparently low uptake of HAART/PMTCT. Also, it is possible that our results do not reflect

context-specific differences between facilities and since we selected only four sites to represent the three service delivery models, inter-clinic variability, rather than inter-model variability may be an explanation for the observed findings. The small sample size may have also contributed to the lack of statistically significant associations, due to lack of power. Furthermore, these data come from 2005 when the local public sector HAART programme, and its links to antenatal care and PMTCT, was still being established. However, the situation of relatively new HIV care and treatment programmes that are exploring the options of how to interface with more established antenatal care structures, particularly in light of recent WHO policy developments, is likely to be closer to the norm across most of sub-Saharan Africa.<sup>123</sup> Thus these results are valuable in highlighting the significant hurdles facing health care services and HIV-infected women starting antenatal HAART.

In summary, this study illustrates that in this setting with clear PMTCT protocols, a high proportion of eligible women did not initiate HAART before delivery. A range of important health service and patient-level challenges may be associated with initiating HAART in pregnant women. Further research into specific models of care is needed to understand the optimal approaches to linking antenatal care with HAART delivery.

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## Chapter 5

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Paper 3: Service delivery approaches for antiretroviral therapy initiation during pregnancy in South Africa.

Stinson, K; Myer, L. Service delivery approaches for antiretroviral therapy initiation during pregnancy in South Africa. (To be submitted in 2012 to PLoS Medicine).

University of Cape Town

## **Background**

Pregnancy is an important time for identifying HIV infection in women to prevent mother-to-child transmission. Antenatal services can also identify women with advanced disease and link them to lifelong antiretroviral treatment (ART). ART services have more often been established outside of antenatal care, however, emerging research supports calls to strengthen service linkages to promote improved maternal and child health outcomes. To investigate the effect of service linkage between antenatal care and ART services, this study evaluated treatment initiation in three different service delivery models in a cohort of women accessing antenatal care in Cape Town during 2008.

## **Results**

Of 14 617 women who presented at the three selected antenatal services in 2008, 94% tested for HIV. HIV prevalence was 29% and 698 (17%) were eligible for ART. Of these women, 11% had initiated ART prenatally, and a further 46% initiated ART before delivery. Overall ART coverage was 52%. A service delivery model in which ART was integrated into the antenatal service performed significantly better than both the proximal and distal models of separate services (62% vs. 49% and 44% ART coverage, respectively, global  $p=0.001$ ), with women presenting at separate services being almost half as likely to be on ART at delivery (Adjusted Odds Ratio: 0.54, 95% Confidence Interval: 0.34-0.85; and AOR: 0.47, 95% CI: 0.28-0.79 respectively). Late antenatal presentation impacted significantly on failed coverage.

## **Conclusions**

Although ART initiation in pregnancy remains a challenge, this research suggests that integrating ART services within antenatal care may help lead to a larger proportion of women starting treatment during pregnancy. More research into novel approaches to initiating more women earlier in pregnancy is required.

## 5.1 Introduction

The effectiveness of antiretroviral (ARV) regimens administered to pregnant women and exposed infants during pregnancy and postpartum to prevent mother-to-child transmission (MTCT) and improve maternal health is well established.<sup>7</sup> Prevention of mother-to-child (PMTCT) programmes have been implemented in most countries in Africa, where the highest proportion of HIV-infected pregnant women live.<sup>11,14</sup> Yet in comparison to well-resourced settings, progress in the scale-up and subsequent coverage of PMTCT programmes has been slow, in spite of the fact that 70% of HIV-infected pregnant women in these settings access antenatal services at least once in pregnancy.<sup>15</sup> Estimates of programme coverage in 2008 reported that 53% of HIV-infected pregnant women and 35% of exposed infants received antiretroviral drugs in 2009.<sup>15,17</sup>

Antiretroviral therapy (ART) to treat maternal infection and prevent vertical transmission has become the most important component of PMTCT programmes to date.<sup>257</sup> Historically, simple regimens for PMTCT have been integrated within antenatal services successfully in resource-constrained settings. Current PMTCT guidelines developed by the WHO recognise the value of initiating women with higher CD4 cell count thresholds earlier in pregnancy on lifelong ART.<sup>36</sup> Yet HIV care and treatment services for adults with advanced stage disease have more often been established as stand-alone services, potentially compromising care for pregnant women who are eligible for ART.<sup>24</sup> There have been calls to integrate antenatal and HIV care and treatment services, given the importance of providing ART to eligible women.<sup>83,115</sup>

Several studies have explored innovative service delivery models to strengthen the continuity of care for these women. In Zambia, Killam *et al.* report that introducing ART once to twice weekly within the antenatal setting doubled the uptake of ART within 60 days of delivery (32% in the intervention group versus 14% in the control group), although the

intervention did not have any effect on the time to initiation or retention in care outcomes.<sup>123</sup> Evidence from a South African study found that weekly provision of providers to identify and facilitate referral of eligible women to participating ART services reduced median time to initiation, with intervention coverage of 75%.<sup>125</sup> Another study in Rwanda, demonstrated that pregnant women who attended facilities offering integrated ART services were almost twice as likely to enrol at the ART service as women who attended stand-alone antenatal and ART services. Yet there was no significant difference between these two service models in terms of ART initiation, which was 83% overall.<sup>124</sup>

While these studies demonstrate the feasibility of integrating ART within ANC services, their results also suggest challenges to rapid uptake of interventions before delivery and suboptimal treatment initiation in pregnancy. In turn, there is a clear need for more operational research to ascertain the optimal models of service delivery for ART in pregnancy. We have documented similar challenges in Cape Town, South Africa in 2005 (as shown in Chapter 4) when ART for pregnant women was becoming available. At that time, we found that 51% of ART-eligible women commenced ART in pregnancy. We also reported that there was no significant difference in uptake between three different service delivery models designed to link women to ART care in pregnancy, each defined by the proximity of the antenatal service to an ART service.<sup>245</sup> The objectives of this study, conducted in 2008, were to ascertain whether initiation of ART in pregnancy had increased over time in this population in the same services studied during 2005, and whether any differences in uptake between the service models could be observed with the maturation of the programme.

## 5.2 Methods

### 5.2.1 Overview

Antenatal and obstetric primary care in the Cape Town metropole is midwife-run, with referral to secondary and tertiary care when indicated.<sup>311,312</sup> We identified retrospectively a cohort of pregnant women who presented during the 2008 calendar year at three antenatal services. PMTCT services were available in this setting from 1999.<sup>218</sup> In 2004, Western Cape PMTCT protocols were redrafted to include referral of pregnant women who were identified as ART-eligible to ART sites.<sup>214</sup> Satellite clinics were set up within the antenatal service or in close proximity to the service to facilitate referral.<sup>219</sup> National guidelines at the time of this study recommended ART initiation in women with CD4 counts  $\leq 200$  cells/ $\mu\text{L}$ .<sup>212</sup> During 2008, the selected sites began to roll-out ART to women with CD4 counts  $\leq 250$  cells/ $\mu\text{L}$  in advance of the release of updated PMTCT guidelines for the Western Cape in June 2009.<sup>326</sup>

### 5.2.2 Setting design

The three sites each implemented a different service model for delivering ART to eligible pregnant women. The first consisted of an 'integrated' approach in which women were able to initiate ART within the antenatal clinic on specific days when community obstetricians with an HIV specialisation were on site (Site 1). The second we denoted a 'proximal' approach in which women were referred (by letter) to a separate ART service located within 100m of the maternity unit (Site 2). The third service model, the 'distal' approach, delivered ART at another primary health care facility within five kilometres of the antenatal service, also using a referral letter (Site 3). Each of these sites was assumed to be the designated site for initiation in ART-naïve pregnant women, as stipulated by the service delivery model provided. At the time of the study, there were 31 other primary health services which were providing ART services within the metropolitan area.

### 5.2.3 *Procedures*

HIV counselling and testing coverage, HIV status and CD4 cell count result were determined from antenatal service registers. A folder review of all HIV-infected women who presented with a CD4 cell count of  $\leq 200$  cells/ $\mu\text{L}$  was conducted to incorporate antenatal and obstetric history. The labour ward registers of each site, as well as those of secondary and tertiary referral sites, were also reviewed. Details pertaining to sociodemographic characteristics, antenatal and obstetric history, and PMTCT or ART coverage were captured (Appendix 5). In instances of missing data, electronic sources for CD4 cell counts and obstetric information were accessed. To ascertain ART initiation and coverage among women with CD4 cell counts  $\leq 200$  cells/ $\mu\text{L}$ , an on-site electronic data base search was conducted in conjunction with a matching paper-based folder review at all 31 ART clinics in the metropolitan area by fieldworkers fluent in local languages. Following this, all remaining ART eligible HIV-infected women with missing ART data were searched for in the electronic Western Cape ART monitoring database.

### 5.2.4 *Measures*

The primary outcome of this study was the proportion of women with a CD4 count  $\leq 200$  cells/ $\mu\text{L}$  who initiated ART during pregnancy, stratified by service delivery model. Antenatal initiation was confirmed by a date which fell between first antenatal presentation and delivery date, or in the event of no available initiation date, evidence from the antenatal folder or labour ward register indicating ART coverage. Among women who were confirmed to have initiated ART after first presentation, but for whom a delivery date was missing, antenatal ART initiation was assumed to have occurred within 90 days of antenatal presentation, and postnatal initiation  $>90$  days after antenatal presentation. This assumption was based on a calculation of the average time between presentation and delivery in the cohort of HIV-infected women with known delivery dates. Among women with CD4 cell

counts  $\leq 200$  cells/ $\mu\text{L}$ , those either documented as not being on ART antenatally, or those who were not found in any of the available data sources, were coded as not having initiated antenatal ART.

ART coverage was defined according to pre-pregnancy and antenatal initiation. Pre-pregnancy coverage was determined by evidence of an ART initiation date prior to antenatal presentation. Postnatal coverage was confirmed by a postpartum ART initiation date which was searched for up to August 2011 in women who were classified as having received no antenatal ART. The ART treatment site was noted where possible for each woman who initiated in pregnancy. Where this information was not available, the ART treatment site was assumed to be the service linked to the specific model of service delivery. Where information on gestational age at presentation or delivery date was not available, an assumption of a 39 week gestation period was made.

### **5.2.5 Analysis**

The data were cleaned and analysed in Stata 12 (STATA Corporation, College Station, USA). In women who appeared in the antenatal register twice, the date recorded for the first HIV test was retained. Proportions for each step of the PMTCT cascade were estimated according to service delivery model. Bivariable associations were tested using statistical methods for categorical and continuous non-parametric data (Pearson's Chi-squared test and Kruskal-Wallis test, respectively). Kaplan-Meier estimates were calculated to determine time to treatment initiation among eligible women with available information, and a log-rank test was performed to assess the significance of differences in time to treatment between sites. Logistic regression modelling was used to test the association between ART initiation and service delivery model (integrated/Site 1 vs proximal/Site 2 vs distal/Site 3), adjusted for potential confounding variables identified through bivariable analysis. Study approval was

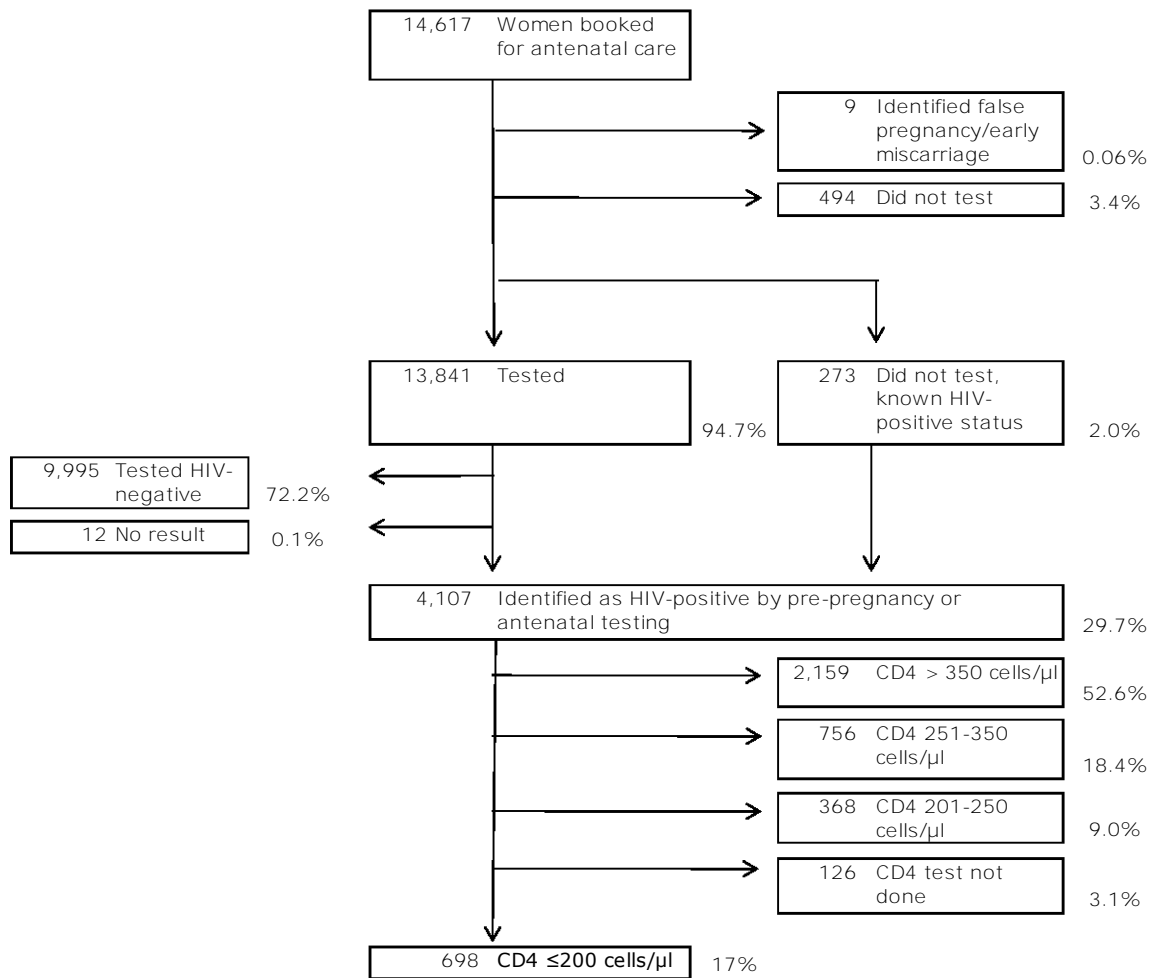
obtained from the University of Cape Town Research Ethics Committee and local government health authorities (Appendix 6).

## 5.3 Results

### 5.3.1 Cohort description

In 2008, 14617 women presented for antenatal care at the three antenatal services. Nine women were identified as having early miscarriage or had a false-positive pregnancy test and were excluded from the analysis. The median age at presentation was 25 years (Interquartile Range [IQR]: 22-30 years), with the median age of women at Site 1 being 2 years higher than women at the other sites. HIV counselling and testing uptake was high, but varied significantly between the sites ( $p < 0.001$ ), with Site 1 achieving near universal coverage (99%) and Site 3 testing the fewest women (89%). Site 3 had the lowest HIV prevalence among those who tested (18%), while Site 1 had the highest, with 32% of women testing HIV-positive. Three per cent of women did not have a CD4 cell count result recorded either in paper or electronic sources. The median CD4 cell count among all HIV-infected women was 373 cells/ $\mu\text{L}$  (IQR: 240-542), and 17% ( $n=698/4107$ ) of all women had a CD4 cell count of  $\leq 200$  cells/ $\mu\text{L}$ , up from 15% reported in 2005.<sup>245</sup> These proportions varied significantly between the three sites ( $p=0.037$ ) with Site 2 contributing the highest proportion of ART-eligible women (39%,  $n=277/698$ ), followed by Site 1 (36%, 252/698) and Site 3 (24%, 169/698). A further 9% of women presented with CD4 cell counts of 201-250 cells/ $\mu\text{L}$ ; 18% of HIV-infected women had a CD4 cell count of 251-350 cells/ $\mu\text{L}$ , and just over half (52%) of women had a CD4 count  $>350$  cells/ $\mu\text{L}$  (Figure 5.1).

**Figure 5.1 PMTCT cascade of women accessing antenatal services, 2008**



**Table 5.1 Descriptive characteristics of the cohort, 2008**

|   | Site 1 (integrated) | Site 2 (proximal) | Site 3 (distal) | P-value* | Total         |
|---|---------------------|-------------------|-----------------|----------|---------------|
| <b>All women presenting for antenatal care</b>  | 4,879               | 4,990             | 4,748           | 32.5     | 14,617        |
| Total excluding women who were not pregnant or identified as experiencing miscarriage | 4,877               | 4,987             | 4,744           | 32.5     | 14,608        |
| Median age in years at 1st presentation (IQR)   | 27 (23-31)          | 25 (21-30)        | 25 (21-30)      | <0.001   | 25 (22-30)    |
| Tested (% of all women)   | 4,864               | 4,725             | 4,252           | 89.6     | 13,841        |
| HIV-prevalence (all)  | 1,609               | 1,458             | 1,040           | 21.9     | 4,107         |
| HIV prevalence (among those who tested)   | 1,599               | 1,458             | 777             | 18.3     | 3,834         |
| Median CD4 cell count (IQR)   | 382 (252-561)       | 372 (231-538)     | 362 (242-532)   | 0.050    | 373 (241-542) |
| Missing CD4 cell count  | 53                  | 30                | 43              | 4.1      | 126           |
| <b>CD4 ≤200 cells/μl (% of tested HIV-positive)</b>                                   | 252                 | 277               | 169             | 16.2     | 698           |
| CD4 201-250 cells/μl (% of tested HIV-positive)                                       | 134                 | 141               | 93              | 8.9      | 368           |
| CD4 251-350 cells/μl (% of tested HIV-positive)                                       | 307                 | 238               | 211             | 20.3     | 756           |
| CD4 >350 cells/μl (% of tested HIV-positive)  | 865                 | 773               | 525             | 50.3     | 2,159         |

**Table 5.2 Descriptive characteristics of women with CD4 counts  $\leq$ 200 cells/ $\mu$ L, 2008**

|   | Site 1 (integrated) | Site 2 (proximal) | Site 3 (distal) | P-value* | Total         |
|---|---------------------|-------------------|-----------------|----------|---------------|
| Median age at 1st presentation (SD)   | 29 (24-32)          | 28 (24-32)        | 28 (24-32)      | 0.3708   | 28 (24-32)    |
| Median gestational age in weeks at 1st presentation (557/698 women with available data, IQR)                          | 26 (21-32)          | 27 (21-32)        | 23 (19-28)      | <0.001   | 26 (21-31)    |
| Nulliparous (522/698 women with available data)   | 63 (12%)            | 73 (14%)          | 40 (8%)         | 0.646    | 176           |
| Median CD4 cell count (cells/ $\mu$ L, IQR)   | 144 (106-172)       | 139 (103-167)     | 145 (99-175)    | 0.263    | 142 (103-171) |
| <b>Pre-ANC presentation ART in women with CD4 cell counts <math>\leq</math>200 cells/<math>\mu</math>L</b>            |                     |                   |                 |          |               |
| Initiated ART before antenatal presentation   | 37 (14.7%)          | 30 (10.8%)        | 14 (8.3%)       | 0.048    | 81 (11.6%)    |
| <b>Remaining women who were eligible for ART initiation in pregnancy</b>  |                     |                   |                 |          |               |
| Initiated Antenatal ART (% of remaining 617 eligible women who had not initiated before antenatal presentation)       | 215 (85.3%)         | 247 (89.2%)       | 155 (91.7%)     |          | 617 (88.4%)   |
| Did not initiate antenatal ART (% of remaining 617 women who had not initiated before antenatal presentation)         | 120 (55.8%)         | 94 (38.1%)        | 70 (45.2%)      | 0.003    | 284 (46.0%)   |
| Unknown   | 77 (35.8%)          | 115 (46.6%)       | 64 (41.3%)      |          | 256 (41.5%)   |
| No documentation of antenatal ART (% of remaining eligible women who were not documented as being on ART by delivery) | 18 (8.4%)           | 38 (15.4%)        | 21 (13.5%)      |          | 77 (12.5%)    |
| Received a PMTCT regimen (% of women who did not receive HAART antenatally or whose intervention status was unknown)  | 95 (44.2%)          | 153 (61.9%)       | 85 (54.8%)      |          | 333 (54.0%)   |
| Initiated ART postpartum  | 40 (18.6%)          | 58 (23.5%)        | 51 (32.9%)      | 0.015    | 149 (24.1%)   |
|   | 46 (21.4%)          | 50 (20.2%)        | 29 (18.7%)      | 0.228    | 125 (20.3%)   |
| <b>ART coverage at delivery (% of all women who were on ART at delivery)</b>  |                     |                   |                 |          |               |
| Initiation in ART-eligible women (n=617)  | 157 (62.3%)         | 124 (44.8%)       | 84 (49.7%)      | 0.001    | 365 (52.3%)   |
| <b>Initiation in ART-eligible women (n=617)</b>   |                     |                   |                 |          |               |
| Median gestational age in weeks at 1st presentation (500/617 women with available data, IQR)                          | 26 (21-31)          | 27 (21-32)        | 23 (19-29)      | <0.001   | 26 (21-31)    |
| Median gestational age at ART initiation (of 164/284 women with available data, IQR)                                  | 31 (28-34)          | 31 (28-34)        | 30 (27-34)      | 0.946    | 31 (28-34)    |

\*Bivariable associations derived using Kruskal-Wallis and Pearson Chi 2 tests

### 5.3.2 *ART initiation among eligible women with CD4 cell counts $\leq 200$ cells/ $\mu\text{L}$*

Of the 658 women with a CD4 cell count  $\leq 200$  cells/ $\mu\text{L}$ , 11% (n=81) were already on ART at presentation. This varied significantly between the sites (p=0.04) with Site 1 representing the highest percentage (14%) and Site 3 representing the lowest percentage (8.3%). When excluding the 81 women with a CD4 cell count  $\leq 200$  cells/ $\mu\text{L}$  who were on ART at presentation, the percentage of eligible women who were initiated on ART during pregnancy was 46% (n=284/617). There was a significant difference in the proportions of women who initiated between the sites (p=0.003): Site 1 initiated 55% of women; Site 2 initiated 38% of eligible women and Site 3 initiated 45% of eligible women, respectively. The remaining 333 (54%) women had no documentation of antenatal ART initiation. Among the women initiating ART during pregnancy, 5% of women presenting at Site 1 initiated at another site, while 14% of women from Site 2 initiated at a different site and 22% of women from Site 3 initiated at another site not designated as the referral site.

### 5.3.3 *Gestational age at first presentation*

The estimated median gestational age at first presentation among all women with a CD4 cell count  $\leq 200$  cells/ $\mu\text{L}$  was 28 weeks (IQR: 24-32 weeks, n=698). After excluding the 81 women who had already initiated treatment and a further 117 women for whom data could not be retrieved, the median gestational age of the remaining 500 women eligible to initiate ART, was 26 weeks (IQR: 21-31 weeks), varying significantly between the sites (p<0.001) with women from Site 3 presenting at 23 weeks and women from Sites 1 and 2 presenting at 26 and 27 weeks respectively. Maternal age was not significantly associated with gestational age at presentation (p=0.601).

There was a significant difference in median gestational age at first presentation between women who were on ART by delivery and those who were not. The median

gestational age at presentation among women who were on ART at delivery was 23 weeks, compared to 29 weeks for women who were not on ART at delivery ( $p < 0.001$ ;

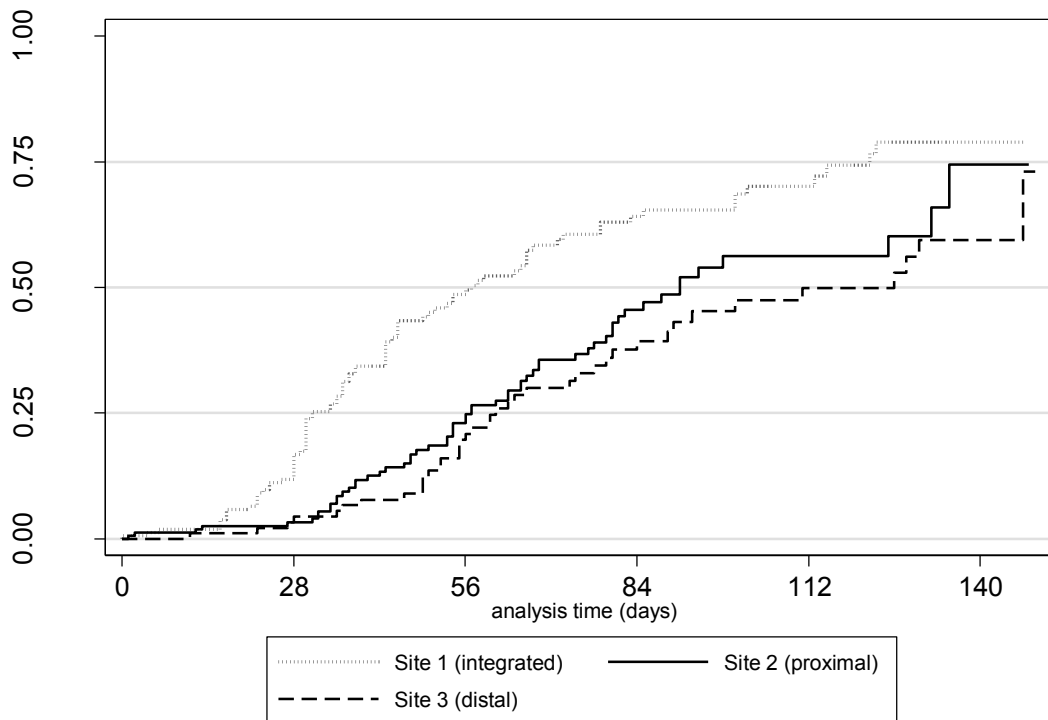
Table 5.2). Among 164 of 284 women who initiated ART in pregnancy and for whom gestational age at antenatal initiation was available, the median gestational age at initiation was 31 weeks (IQR: 28-34), which did not vary significantly between the three sites ( $p = 0.946$ ). When modelling gestational age at initiation as a continuous variable, no significant differences between sites were observed ( $p = 0.967$  for Site 2 and  $p = 0.764$  for Site 3, Site 1 as reference).

#### 5.3.4 *Time to treatment initiation*

Half of women starting ART did so within 49 days of presenting at the antenatal service. The median time to treatment initiation varied significantly between the three sites ( $p < 0.001$ ), with 50% of women at Site 1 initiating within 36 days of presentation, 50% of women initiating within 54 days at Site 2 and within 59 days at Site 3 respectively. Across all the sites, 75% of women had initiated within 9 weeks of presentation. However, the proportions of women initiating by 9 weeks after antenatal presentation varied by site. By 9 weeks after presentation, Site 1 had initiated 85% of women, while Site 2 had initiated 71% and Site 3 had initiated 62% of women. Kaplan-Meier estimates of time to treatment (restricted to 189/284 women with a date of ART initiation and 244/333 censored women who did not start ART but who had a recorded delivery date) showed significant differences in time to ART between sites ( $p < 0.001$ , Figure 5.2). Overall, Site 1 initiated 36% of all eligible women in the cohort who presented up to 31 weeks gestation (104/284), while Site 2 initiated 27% (77/284) and Site 3 initiated 20% (56/284) of these women respectively. After 31 weeks, there was little difference in the proportion of women initiating ART between sites, with

Sites 1 and 2 both initiating 6% of women respectively and Site 3 initiating the remaining 5% of women ( $p=0.435$ ).

**Figure 5.2 Kaplan-Meier failure estimates of time to treatment in pregnancy, 2008**



Note: Among women with  $CD4 \leq 200$  cells/ $\mu$ L ( $n=433/617$ )

When comparing time to treatment across CD4 cell count percentiles (CD4 cell count  $\leq 100$ , 101-169 and  $\geq 170$  cells/ $\mu$ L) there was no significant difference in time to treatment initiation ( $p=0.419$ ). A further 20% of women (125/617) who did not receive ART in pregnancy went on to initiate up to 3 years postpartum. The median time of initiation after delivery was 34 weeks and the time to postpartum initiation was not significantly associated with the antenatal site ( $p=0.149$ ).

### 5.3.5 Coverage of ART among women with CD4 cell counts $\leq 200$ cells/ $\mu\text{L}$

Overall ART coverage (defined as the proportion of women who were on ART by delivery) among women with a CD4 cell count  $\leq 200$  cells/ $\mu\text{L}$ , was 52% (n=365/698), this comprised 284 eligible women initiating ART during pregnancy and 81 women who were already on ART at first presentation. There was significant variation in coverage between the three sites (p=0.001), with 62% coverage at Site 1, 49% coverage at Site 3 and 44% coverage at Site 2, reflecting the trend in initiation between the sites.

### 5.3.6 Characteristics of women who did and did not initiate ART

Table 5.3 shows that significant bivariable associations were found between ART initiation during pregnancy and service delivery model and gestational age at presentation. However, maternal age at presentation, gravidity and parity were not significantly associated with initiating ART (Table 5.3).

**Table 5.3 Characteristics of eligible women who did and did not initiate ART, 2008**

|  | Initiated ART |     | Did not initiate ART |     | p-value |
|--|---------------|-----|----------------------|-----|---------|
|  |               | n   |                      | n   |         |
| Total number of women (n=617)                  |               | 284 |                      | 333 |         |
| Median age at presentation (years)             | 28            | 283 | 27                   | 329 | 0.104   |
| Site 1 (%)                                     | 56%           | 120 | 44%                  | 95  | 0.001   |
| Site 2 (%)                                     | 39%           | 94  | 61%                  | 153 |         |
| Site 3 (%)                                     | 45%           | 70  | 55%                  | 85  |         |
| Median gestational age at presentation (weeks) | 23            | 256 | 29                   | 244 | <0.001  |
| Median gravidity                               | 2             | 235 | 2                    | 228 | 0.752   |
| Median parity                                  | 1             | 235 | 1                    | 227 | 0.315   |

In a logistic regression model predicting antenatal ART initiation (Table 5.4), women who attended Sites 2 and 3 were at most only half as likely to initiate ART in pregnancy when compared to women attending Site 1, with the odds of initiating decreasing with each service delivery model (Adjusted Odds Ratio (AOR): 0.54, p=0.008 for Site 2 and AOR: 0.47, p=0.004 for Site 3, respectively). In addition, increasing gestation at first antenatal presentation was associated with decreased odds of antenatal ART initiation. Women

presenting between 25 and 28 weeks' gestation were less than half as likely to start ART compared to women who presented before 20 weeks' gestation (AOR: 0.42, 95% CI: 0.24-0.73,  $p=0.002$ ). Women who presented between 29 and 32 weeks' gestation were almost 70% less likely to initiate ART than women who presented in the first 20 weeks of pregnancy (AOR: 0.29, 95% CI: 0.16-0.53,  $p<0.001$ , Table 5.4). Women between the ages of 29 and 31 years were more likely to initiate ART (AOR: 1.91, 95% CI: 1.07-3.38,  $p=0.027$ , Table 5.4).

**Table 5.4 Logistic regression showing predictors of ART initiation in eligible women, 2008**

| Variable                        | Adjusted Odds Ratio | p-value | 95% Confidence interval |
|---------------------------------|---------------------|---------|-------------------------|
| Service delivery model          |                     |         |                         |
| Site 1 (Integrated)             | Reference           |         |                         |
| Site 2 (Proximal)               | 0.54                | 0.008   | (0.34-0.85)             |
| Site 3 (Distal)                 | 0.47                | 0.004   | (0.28-0.79)             |
| Maternal age                    |                     |         |                         |
| ≤24 years                       | Reference           |         |                         |
| 25-28 years                     | 1.31                | 0.313   | (0.78-2.20)             |
| 29-31 years                     | 1.91                | 0.027   | (1.07-3.38)             |
| >31 years                       | 1.40                | 0.228   | (0.81-2.40)             |
| Gestational age at presentation |                     |         |                         |
| ≤20 weeks                       | Reference           |         |                         |
| 21-24 weeks                     | 0.81                | 0.509   | (0.44-1.50)             |
| 25-28 weeks                     | 0.42                | 0.002   | (0.24-0.73)             |
| 29-32 weeks                     | 0.29                | <0.001  | (0.16-0.53)             |
| 33-36 weeks                     | 0.07                | <0.001  | (0.03-0.14)             |
| 36-40 weeks                     | 0.05                | <0.001  | (0.01-0.20)             |

## 5.4 Discussion

We evaluated treatment initiation and coverage for HIV-infected pregnant women eligible to initiate ART in three public sector antenatal care services in Cape Town during 2008.

Although overall ART initiation was sub-optimal, these findings suggest that an integrated model of care may facilitate higher ART uptake more rapidly than other models with a

greater degree of separation between antenatal and ART services. Also, women who present to services at late gestational age are dramatically less likely to initiate ART before delivery.

Our evaluation of different approaches to delivering ART in pregnancy demonstrates that an integrated approach in this context may lead to the highest percentage of women initiating antenatal ART, as reported in another African setting.<sup>123</sup> Site 1 demonstrated a 55% uptake of ART among pregnant women, and 62% overall treatment coverage through an integrated service model, which was significantly better than the other two models both in bivariable and multivariable analysis. The 'proximal' approach to initiating ART by referring women to treatment services within the same complex both had the largest proportion of treatment eligible women and the poorest coverage outcome of 44%.

These findings also show that in spite of service linkages or integration, late antenatal presentation is a persistent barrier to timely treatment initiation and optimal ART coverage. Our results indicate that women in this setting present for care in pregnancy well into the second trimester, decreasing the opportunity for rapid ART initiation. The median gestational age at first presentation among ART-eligible women in the 2008 cohort described here was 26 weeks, which did not deviate from our 2005 findings.<sup>245</sup> Furthermore, women who initiated ART in pregnancy presented at services up to six weeks earlier (23 weeks' gestation) than those who did not initiate, underscoring the contribution of late antenatal presentation to failed ART coverage. Women who presented after 26 weeks' gestation were significantly less likely to be on ART at delivery. This evidence is consistent with two other studies of ART initiation in pregnancy in addition to our 2005 results, where late presentation compromised ART uptake.<sup>126,127</sup> In an observational study in Botswana which reported 37% uptake of ART in pregnancy, it was found that women who presented for antenatal care at 20 weeks gestation or more, were less likely to initiate ART.<sup>126</sup> Another study from South Africa reported that late presentation and subsequent late diagnosis was a significant challenge to timely ART initiation in an integrated service in pregnancy.<sup>127</sup>

Pregnancy provides a limited period for ART initiation, and with successful uptake, the risk of vertical transmission in utero and the peripartum is decreased with every week of antenatal ART.<sup>128</sup> Hence it is imperative to initiate women as soon as possible after they have been identified for treatment. Our results suggest that the integrated service initiated a higher proportion of women more rapidly after first presentation than other models, however, the median gestational age at ART initiation (31 weeks) did not vary significantly between the three sites. This finding is similar to that found by Killam *et al.*, who reported that while an integrated approach increased the percentage of women initiating antenatal, it has little influence on time to ART initiation in Zambia.<sup>123</sup> This may again underscore the impact of late presentation which compromises time to treatment, regardless of service delivery model.

The superiority of the integrated service delivery model was further confirmed by the fact that 95% of ART-eligible women at this site initiated treatment on site, with the balance seeking treatment initiation elsewhere. This proportion was lower at the other sites (86% at Site 2 and 78% at Site 3), suggesting that with the increasing distance between antenatal and ART services, so the choice of referral services may become less important to women and possibly factors such as convenience or desire for privacy may come into play. For example, a qualitative study from Malawi has suggested that pregnant women have a preference for integrated ART services over access to ART in general primary level services where they would be required to mix with HIV-infected men and non-pregnant women, as well as those with other communicable diseases such as tuberculosis.<sup>327</sup>

Since initiating women at CD4 cell counts  $\leq 250$  cells/ $\mu\text{L}$  was not uniformly carried out, our outcome reflects national guideline recommendations in 2008. Overall treatment coverage in women with a CD4 cell count of  $\leq 200$  cells/ $\mu\text{L}$  was 52%, reflecting a poor increase in coverage of 1%, when compared with 2005 coverage results reported previously.<sup>245</sup> It seems implausible that this sub-optimal coverage can be attributed to a substantial increase in the proportion of ART-eligible pregnant women presenting at

services: according to our data, this increase was 2% between 2005 and 2008. In our study, few HIV-infected pregnant women presented at antenatal services having already initiated ART (11%). It is possible that ART-eligible women are either not being identified or retained in care at other primary health care services prior to pregnancy, thus supporting the contention that antenatal services provide a crucial gateway to HIV treatment and care.<sup>24</sup> Low ART initiation and coverage among pregnant women in this study may be interpreted in light of several factors. First, the psychological wellbeing of newly diagnosed HIV-infected women is a neglected area of service provision in this setting.<sup>328</sup> While little is known about the psychosocial needs of women who are diagnosed HIV-positive in pregnancy and who urgently require lifelong ART both for their own health and for the prophylactic benefit to their unborn children, we have previously described in qualitative research conducted in this setting that women struggle to accept diagnosis and a lifelong commitment to treatment within the context of pregnancy.<sup>329</sup> Second, it is possible that a healthy physiological status during pregnancy has the potential to mask advanced stage disease, resulting in women refusing treatment. Furthermore, the impact of haemodilution in pregnancy has been known to lead to decreased CD4 cell count, leading to healthier women starting ART at the same cut-off as their non-pregnant counterparts.<sup>330,331</sup> In a recent study of adults accessing HIV testing and treatment services in Johannesburg, 20% refused ART initiation on the grounds of 'feeling healthy'.<sup>199</sup> This suggests that supportive efforts may be required to mitigate the risk of treatment refusal.

Finally, the integrated service approach led to the highest proportion of women initiated on ART. However, uptake at this service was still sub-optimal. These findings call into question the definition of integration, and whether ART services provided by outreach doctors based in the antenatal facility once per week are sufficient. Such services illustrate a 'functional separation' of patient care through the limited provision of specific services on

certain days of the week, and task-oriented work which is delivered by different levels of health care provider.<sup>332</sup>

We found that 20% of eligible women who did not start antenatal ART, initiated treatment within 3 years of being identified for initiation in pregnancy. The median initiation time of three months among postpartum women could suggest that women are being identified through well-baby services when presenting for immunization and PCR testing. The high postpartum uptake of ART in this cohort may further support anecdotal evidence that service providers, upon identifying women for ART in advanced pregnancy may prefer to initiate treatment postpartum out of concern for loss to follow up and poor postpartum retention in care, which has been previously associated with women who are fast tracked onto ART during pregnancy in this setting.<sup>333</sup> It is also plausible that many women are only identified in a subsequent pregnancy for ART, and this possibly required further investigation.

Our results raise concern around the potential increased burden on antenatal services to initiate treatment in a greater proportion of women as required by the updated national PMTCT guidelines, which require initiation at CD4 cell count thresholds  $\leq 350$  cells/ $\mu\text{L}$ .<sup>279</sup> Given the proportion of women presenting with a CD4 cell count  $\leq 350$  cells/ $\mu\text{L}$ , antenatal services would have needed to ensure coverage in 48% of HIV-infected women should these guidelines have applied in 2008.

The interpretation of these data comes with several limitations.<sup>334</sup> The greatest limitation of this study is that it is difficult, if not impossible, to attribute causality directly to the different service delivery models alone. Unobserved (and unobservable) heterogeneity between the models may play a role too. Given our results, this should be a focus of further research. This research was conducted in an urban setting with a high prevalence of antenatal HIV (16.1% provincial prevalence in 2008),<sup>335</sup> and may only be applicable to similar contexts with mature primary level antenatal services which demonstrate high access and uptake.

Furthermore, these data are from retrospective clinical records and electronic registries and hence lack the accuracy and completeness of purposefully collected prospective data. There were no significant differences between the proportions of missing data on variables of interest from each service delivery model.

We estimated gestational age at presentation and treatment initiation in women who started antenatal ART assuming delivery at 39 weeks in all women, as information on estimated due date and gestational age at birth was limited. Hence we may have overestimated the gestational age at ART initiation in women who delivered preterm, resulting in women initiating ART closer to delivery than deemed optimal in the PMTCT guidelines, though it is unlikely that such misclassification could have occurred differentially by site. Despite this, our data calibrate well with data from another study in this setting which suggest that women presented at 26 weeks gestation and received a median duration of 7.6 weeks antenatal therapy.

With the efficacy of drug regimens for PMTCT well-established, PMTCT programme impact is substantially dependent on sufficient infrastructure and the implementation of appropriate and effective service delivery models. Evidence of weak linkage between HIV prevention and treatment services within the maternal health programmes fuels the complexity behind defining optimised approaches to care for pregnant women with advanced stage disease.<sup>34</sup> Furthermore, it has been shown that the best PMTCT outcomes are in women who conceive on ART, suggesting that more needs to be done outside of antenatal services to identify women of reproductive age for treatment and to retain them in care.<sup>127,128</sup> Despite this, specialised management of ART in pregnancy is important in order to prevent potential adverse pregnancy outcomes, including teratogenicity associated with the use of Efavirenz in the first trimester of pregnancy,<sup>336</sup> preterm birth and/or low birth weight;<sup>337</sup> infant resistance to ART,<sup>338</sup> and hepatotoxicity associated with the use of Nevirapine in women with high CD4 cell counts.<sup>339,340</sup> While there is evidence that both

supports and disputes the frequency of occurrence of adverse events, there is still a need for a continuum of care which extends both pre- and postnatally in HIV-infected women of reproductive age.<sup>341</sup> Given the separate administration of services, and in some cases, distinct funding streams and the capacity of services to deliver specialised training and expertise across programmes, this may prove challenging to implement.<sup>24</sup> Continued efforts are required to ensure that new approaches to increasing early pregnancy presentation and timely ART initiation in pregnancy are evaluated for the benefit of HIV-infected mothers and their children.

University of Cape Town

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## Chapter 6

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Paper 4: Barriers to initiating antiretroviral therapy during pregnancy: a qualitative study of women attending services in Cape Town, South Africa

Stinson, K., Myer, L. (2012) Barriers to initiating antiretroviral therapy during pregnancy: a qualitative study of women attending services in Cape Town, South Africa. *African Journal of AIDS Research*, (in press)

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## **Abstract**

Despite the rapid expansion of antiretroviral treatment (ART) programmes, uptake of ART in pregnancy remains suboptimal. Little is known about the barriers to initiating lifelong ART in pregnancy and the challenges to postpartum retention in care, particularly in sub-Saharan African contexts with a high burden of disease. In this qualitative study, 28 HIV-positive pregnant or postpartum women who had either initiated ART or who were eligible for ART and 21 service providers were interviewed to explore the barriers associated with initiating ART in pregnancy in Cape Town, South Africa. Prevention of vertical transmission was often the primary motivation for starting treatment. Key challenges included late first presentation; denial of diagnosis; fear of disclosure and treatment side-effects. Women expressed difficulties in accepting a lifelong commitment to treatment for maternal health. Pregnant women who require ART face a triple burden of transition into pregnancy, HIV diagnosis and the urgent requirement to start lifelong ART before delivery. Focused interventions are needed to address the psychosocial barriers of ART uptake and linkages to care for pregnant HIV-positive women.

University of Cape Town

## 6.1 Introduction

Prevention of mother-to-child transmission of HIV (PMTCT) programmes have long been recognised as a gateway to HIV treatment services with pregnancy serving as a crucial period to identify and treat HIV-positive women, and to deliver comprehensive care to their families.<sup>24,27</sup> The WHO advocates a two-tiered approach to PMTCT programmes in order to optimize both infant and maternal health in low- and middle-income settings.<sup>44</sup> Lifelong antiretroviral therapy (ART) is recommended for women who require treatment for their own health, while short course antiretroviral (ARV) prophylaxis is recommended during pregnancy, labour and breastfeeding for infected women who do not require treatment for their own health.<sup>21</sup> The effectiveness of PMTCT programmes, which aim to reduce the burden of paediatric HIV and provide treatment and care for HIV-infected women and their families, is contingent on comprehensive coverage of HIV-infected women in pregnancy and postpartum. This may be achieved through the early identification of HIV-infected women in pregnancy, the timely uptake of appropriate ARV interventions before and during delivery, continued postpartum follow up of the infant until cessation of breastfeeding and retention in care for women on lifelong ART.<sup>60</sup>

Considerable progress has been made toward the scaling-up of PMTCT programmes in sub-Saharan Africa.<sup>14</sup> Yet in this region only 53% of all pregnant women eligible for antiretroviral prophylaxis received treatment in 2009, raising concern over sub-optimal coverage in pregnancy.<sup>15,17</sup> Barriers to PMTCT programme uptake include fear of an HIV-positive diagnosis and subsequent death; denial, fear of disclosure and stigma, and poor emotional support and insufficient counselling.<sup>158,342,343</sup> Socioeconomic factors, including younger age and lower educational status, as well as the lack of partner support have been linked to poor testing uptake and postpartum loss to follow-up.<sup>204,344,345</sup> Research into the social aspects of HIV has provided insight into the experience of HIV testing and diagnosis

in pregnancy and further informed the models of counselling and treatment preparation used in PMTCT programmes.<sup>179</sup> Yet, service-related barriers stemming from health system weaknesses are still prevalent, amounting to the limited reach of antenatal HIV counselling and testing and delays in the return of test results in some settings.<sup>23</sup> Continuity of care is frequently compromised by the lack of linkage between maternal and child health and HIV programmes, leading to poor uptake of ART in pregnancy.<sup>24,346</sup> Poor integration of antenatal services with ART services is further compounded by the dearth of infrastructure for laboratory testing and programme monitoring.<sup>34</sup>

Much of the literature on PMTCT effectiveness pertains to programme uptake in general and few distinctions are drawn between women who require different regimens according to the WHO two-tiered approach in different settings. Little is known about the experience of pregnant women who are eligible for ART and the challenges they experience regarding initiating lifelong treatment, particularly in developing country contexts where the burden of HIV is greatest. One study from Uganda has cited stigma, non-disclosure, as well as poor access to services with limited human resources capacity as barriers to ART access in pregnancy.<sup>198</sup> Yet it is these women with advanced disease who are at greatest risk of vertical transmission and mortality, and who stand to benefit the most from rapid initiation of ART during pregnancy.<sup>119,322,347</sup>

Pregnancy provides a limited period to optimize treatment initiation, and the risk of vertical transmission in utero and the peripartum decreases with every week of antenatal ART.<sup>128</sup> In South Africa, which employs the two-tiered approach to PMTCT programmes, guidelines at the time of this study recommended that women with a CD4 count of  $\leq 200$  cells/ $\mu$ L be initiated on ART. While it is imperative for ART-eligible women to be identified early in pregnancy in order to provide sufficient time for treatment initiation and to optimize treatment efficacy, attrition seems particularly pronounced among women eligible for ART in this setting.<sup>125,245</sup> The purpose of this qualitative study is to explore the barriers to initiating

lifelong ART during pregnancy in order provide a clearer understanding of the experience of South African women with advanced stage disease.

## 6.2 Methods

### 6.2.1 *Study setting*

This study was conducted between August 2007 and March 2008 in four Cape Town public sector primary health care facilities as well as two referral hospitals which offered antenatal and delivery care and/or ART services for pregnant and postpartum women. A sample of 28 HIV-positive ART-eligible or ART-initiated pregnant or postpartum women, and 21 health care providers was purposively derived using a snowballing technique. The primary author worked through clinical staff and support group facilitators to identify participants representative of the target group. Participants were considered to be suitable for inclusion if they were pregnant or < 6 months postpartum, and if they had either initiated ART in their current or most recent pregnancy; or if they were deemed ART-eligible in pregnancy, but had not initiated treatment. Service providers were sampled from different antenatal and HIV care services attended by the pregnant and postpartum women. Participants were sampled to saturation, and fieldwork was concluded once no new data arose from the interviews.

Approval for the study was granted by the Human Research Ethics Committee of the University of Cape Town and local government (Appendix 2). The study instrument comprised a structured questionnaire with a combination of open and closed questions (Appendices 7 and 8). Socio-demographic information relating to pregnancy was also requested. Written informed consent was obtained for all participants, and each interview lasted approximately 1 hour. One participant and two providers declined to be interviewed for reasons of privacy. Participant interviews were conducted in the participant's mother tongue (isiXhosa) and provider interviews in English by one field assistant and the primary

author respectively, both of whom were trained in qualitative techniques. Role plays and a pilot of the instrument were undertaken prior to fieldwork. All interviews were digitally recorded, transcribed verbatim in the mother tongue and translated into English with the assistance of a linguist who worked with a mother tongue speaker to ensure congruence in thematic interpretation.

A thematic content approach was used in analysis. Data from the interviews were reviewed and categorised and salient themes were identified from early commencement of the fieldwork. A coding scheme was developed from the key themes by the two authors. Transcripts were loaded into a qualitative analysis software package (Atlas ti 5.2, Scientific Software Developments, Berlin) for text management and coding. Pertinent themes concerning barriers to initiating ART in pregnancy were identified and categorised. Verbatim quotations were selected if deemed to support the thematic interpretation and represent the balance and depth of feeling among the participants. Trends in the data were reviewed and consensus was reached between the two authors on the reporting of the themes in the results.

### 6.3 Results

Among the 28 women who were interviewed, 17 were pregnant and 11 had delivered in the past 6 months. All postpartum women were on ART, while 4 of the 17 pregnant women had not yet initiated ART. The mean maternal age was 27 years, and 10 women lived with a spouse or partner, 15 women lived with close or extended family and three women lived alone. All but 5 women were unemployed. A range of clinicians was interviewed, including 9 doctors specialising in obstetrics, HIV care or paediatrics, 3 nurses specialising in PMTCT care, 3 service managers and 1 HIV counsellor. Different referral patterns were observed between antenatal and ART services. Two institutions offered an integrated antenatal and ART service with ART provided at the facility for pregnant women on particular days of the

week, while other antenatal and ART services were more remote, either housed in a separate building on the premises or at a different facility. In all cases, counselling and testing protocols comprised an opt-in approach with group counselling, followed by individual counselling and testing, with post-test counselling at the first visit. Midwives at the antenatal service supplied women with referral letters for treatment initiation at the nearest ART service, where they were to be seen by doctors with a specialisation in HIV care. All but one antenatal service had an NGO-based lay counsellor presence on site for women enrolling on the PMTCT programmes. These lay counsellors assisted women with referral to ART services and hosted support groups which covered a range of topics pertinent to antenatal and postpartum care for HIV-positive women.

### **6.3.1**     *First presentation in late pregnancy*

Presentation in advanced pregnancy was highlighted by providers as an obstacle to timely enrolment of newly diagnosed HIV-positive women on the PMTCT programme, as well as referral for, and initiation of, ART. When asked about the optimal time to present for antenatal care, all women agreed it was better to present early in pregnancy. Of the 8 women who could recall their first visit, timing of the visit ranged between 2 and 8 months, with the most common gestational age for first visit being cited to be around 4 months. The motivation for coming to services was to check the health of the foetus and to ensure registration at the labour ward. Some women suggested a few socio-economic and cultural factors which influenced the timing of the first pregnancy visit. Barriers to early presentation included unaffordable transport fares and the fear of job loss due to time off work and subsequent disclosure of the pregnancy. Hence a personal cost of pregnancy care was evident: one respondent mentioned that she was not paid for the hours she took off to access antenatal care. Another described how her life had become “really difficult” because she had lost her job as a result of her pregnancy leading to time off work, and the father of

her child had “run away.” Another woman suggested that ensuring an adequate daily food supply took precedence over seeking early pregnancy care.

Furthermore, providers and women alike described that women perceived the need to have evidence of the pregnancy externally visible – to be ‘showing’ – before they went to have their pregnancy confirmed at a clinic. One woman explained:

I think it is because maybe [women] don’t really feel pregnant. They want to see that they are really pregnant or not ... If it is your first time in pregnancy, you don’t really think you are pregnant.  
(Participant [P] 26, pregnant woman, 31 years)

Providers felt that women were also more likely to present late in cases of an unplanned pregnancy due to denial. One provider mentioned that delays were caused by fragmented reproductive health services which offered pregnancy diagnosis and termination of pregnancy at primary health care services but not antenatal services themselves. Women might go to one facility for a pregnancy test, but take weeks to act on it by booking an appointment for antenatal care at a separate service.

### **6.3.2 Denial of HIV diagnosis**

Another barrier to swift initiation of ART in pregnancy was the women’s capacity to accept their HIV diagnosis and need to start lifelong treatment at the time of accessing antenatal care. Many women interviewed had not tested before presenting in pregnancy, and they recalled shock and disbelief when being diagnosed HIV-positive. One woman explained:

I wasn’t aware enough about AIDS, I never thought it was a serious disease ... I knew there is AIDS, but I never thought deeply about it ... I never thought that I might be [infected] ... There was no need to [test] - I was not sick - there were no symptoms. I never thought that I could march into the clinic saying, “I’m here for testing.” (P6, pregnant woman, 34 years)

Providers agreed that the most challenging aspect of HIV testing in pregnancy was that women felt well when coming for a consultation, which exacerbated the shock and

difficulty in acceptance of diagnosis. These factors provided little motivation for initiating ART. Women concurred, suggesting that the difficulty associated with acceptance of being HIV-infected arose from the fact that frequently there were no visible signs or symptoms of disease. One woman described that:

You see I will believe if could see signs. Here on the body, or if something could itch on the body, or if I could vomit or have diarrhoea - but I never had any of these things. (P 27, postpartum woman, 25 years)

Providers also believed that women newly diagnosed with HIV struggled to accept an HIV-positive diagnosis in the context of antenatal care. They suggested that the impact of an HIV-positive test result, in combination with pregnancy and news of advanced stage disease, which required swift work up to life long therapy, was too much for some women to manage. Providers speculated that this burden was compounded by unplanned pregnancy in some cases, although this was not volunteered by any women in the interviews. One service provider suggested that:

With a woman who is diagnosed in pregnancy on account of an attendance at antenatal clinic – it is as though she hasn't really thought, "I think I might have HIV and I think I had better go and get tested because maybe I'll need ART." It hasn't happened like that. She's pregnant and she's gone to an antenatal clinic, and suddenly someone tells her she's HIV-positive. She might be very well ... and suddenly she's told that she needs ART. So the commitment, the buy-in and the person's belief in the need for ART is much less. (Provider [Pr] 19, HIV specialist)

Denial of illness was an important recurrent theme for providers and women alike. One woman reported that after testing HIV-positive at the antenatal service, she retested elsewhere because she did not believe the result. Providers felt that women who could not accept their status seemed less likely to present at services for ART initiation in pregnancy. Providers empathized with their participants, saying that there were too many issues a woman had to deal with at once. A service provider explained:

It's denial, because if they are in denial, they don't accept that they are sick or that they must take this kind of test while pregnant. Secondly, when the counsellors counsel them - they tell them, "If your CD4 cell count is less than 200 (cells/ $\mu$ l), then you'll have to start ART" - and that it is for life, and then they say, "For life?" They cannot take treatment for life. So they would rather not start ART if they have to take it for life. So they don't come back. (Pr 21, midwife)

### 6.3.3 *Disclosure of HIV status*

The time needed to accept and disclose their HIV diagnosis in order to commence treatment represented a barrier to ART initiation in pregnancy for many women. Most respondents preferred to wait between a week and a month to disclose their HIV status to a partner, relative or close friend. Some mentioned that they waited until they had no option but to disclose in order to start treatment, while others would return for antenatal follow-up and report that they had not found someone to disclose to, or that they were not ready to disclose. A service provider noted:

Disclosure is a huge problem, the only problem usually that keeps them from not accessing ARVs. Because when they come, the counsellors tell them, "Please bring a treatment partner." Usually the treatment buddy is a partner and then we lose them ... They don't come back ... They don't start because of a treatment buddy problem. (Pr 15, HIV specialist)

Internalized stigma was central to the fear of disclosure. Women anticipated that the confidant would be "disgusted" and unsupportive, or spread information about their status. While most women disclosed their status to a partner, many women chose to disclose first to a female relative or friend. Fear of disclosure due to the threat of abandonment was a recurrent theme for women in partnerships. Despite this assumption, many women subsequently disclosed to their male partners and described that their partners had been accepting and emotionally supportive. A woman noted:

I asked him what was going to happen and he told me that nothing was going to happen, that he was not going to get rid of me because it had been discovered that I was HIV-infected. "I will love you if

you have it. That means that I have it, as we are still continuing even now.” (P 22, pregnant woman, 24 years)

For two women, however, partner disclosure resulted in negative consequences ranging from derision and disbelief to abandonment. One woman described:

The father of the child ran away and changed his phone number. No one came to see me at the hospital, the person who came to see me was his brother-in-law. His family cursed me, saying that I brought AIDS to their brother. (P 12, postpartum woman, 30 years)

#### **6.3.4 Fear of initiating lifelong ART**

All women interviewed were eligible for lifelong ART in pregnancy, and most were started on PMTCT regimens while waiting to initiate ART as stipulated by treatment guidelines. For some of the women who were on ART, treatment initiation was not perceived to be difficult; they “accepted” that they had to start treatment, and felt “comfortable,” or “happy” in the knowledge that they were going to be “protecting” their babies. Other women suggested it was difficult to initiate ART because it required a life-long commitment. Particular reservation was expressed by those who were asymptomatic. One woman mentioned that women who were eligible for short course treatment could envisage treatment as a means to an end in pregnancy, whereas lifelong ART post-delivery was harder to justify in the absence of physical evidence of disease. Most women felt that they had no choice but to start lifelong treatment because they were pregnant and they needed to protect their children. One woman explained:

It was difficult. I got home to the house with them and I had to start them. I had never taken any [pills] before that day, it had been my way. I am not a person who takes things hard, but then I realized ... yhuu!! I am very scared about taking pills for my whole life! What would I be doing to myself if I didn't take them? I had to take them because I am thinking about that person I am carrying - so then I just started them. Now I just take them. (P 2, postpartum women, 29 years)

Providers concurred that women found it challenging to accept that they needed to initiate lifelong treatment in pregnancy. One provider described:

She accepted the fact that she was HIV- positive ... but for her to take ART, especially when she was told that you have to take [it] for the rest of your life, she said if it was just for the baby, she would have taken it and then just left it afterwards. (Pr 9, midwife)

The fear associated with ART side-effects was raised as another factor which delayed or prevented treatment initiation. Fear was associated with imagined negative consequences of treatment, often derived from community perceptions rather than based on fact. A woman commented that she would have refused to start ART if she had not been pregnant, despite her CD4 cell count being low, due to her concern over side-effects. Her main motive for initiating treatment was “to protect my child.” Other women described that they were afraid that ART would affect their unborn child or lead to miscarriage. Providers suspected that participants who refused treatment might be seeking traditional or religious alternatives. They felt that the fear of side-effects was sufficient for some participants to delay treatment initiation. One provider noted:

We find out that sometimes the participant doesn't even come [to the ART service]. They stay with their referral letters at home ... By the time they come through it's already almost too late. “Why didn't you come early?” – “I was afraid of taking the medication, it might affect me and my baby,” they say. Then once you explain everything to them and the risk they've taken by not coming through, they're willing to try afterwards. It's fear. Most of the participants don't want to start the medication because they fear side-effects, which people who have taken the medication have exaggerated. (Pr 20, nurse trained in HIV care)

### **6.3.5     *ART beyond pregnancy and retention in care***

Even though women were motivated to start treatment to benefit their children, by the time of the interviews most women who had initiated ART believed that treatment would be advantageous to both themselves and their offspring. Women who were taking ART postpartum were positive about continuing their treatment, citing fears of potential illness

and death if they were to stop. One woman mentioned that by taking ART postpartum, she was 'protecting' herself. Another pregnant woman associated continuing ART with the benefit of remaining healthy in order to care for her children:

It is my problem; my life. I have to be healthy to raise my children. I'm concerned about my children. If I'm healthy, my children are healthy. (P 6, pregnant woman, 34 years)

Providers were more sceptical about postpartum retention in care. They expressed a concern that a mother's care of her infant continued to take precedence over her own health and this, combined with poor disclosure and the absence of signs and symptoms of disease, was a likely cause of losses in postpartum retention in care among women newly initiated on ART.

I found that some people default after they start - they default a month later. I don't think it is service related. Part of it is that they don't need the medication for the baby anymore. They start the medication because they want to protect the child, and then they test the child; they still feel well because they were well to begin with, so they feel that they can actually stop this medication ... I still feel that they're not ready to start - to continue for the rest of their lives with medication when they're really feeling well. (Pr 16, HIV specialist)

#### 6.4 Discussion

This study highlights several barriers which may prevent or delay initiation of ART in eligible pregnant women. First, our research suggests that multiple factors influence a pregnant woman's decision when to present for antenatal care, this often being after the first trimester once there is physical evidence supporting a pregnancy. Despite strong utilization of institutional antenatal and obstetric care, late first presentation in pregnancy has been documented in other South African settings<sup>139</sup> and other developing countries<sup>144</sup> and has been cited as a challenge to PMTCT programme success.<sup>127,348</sup> Women in this setting perceive antenatal services as a means of ensuring registration for the labour ward, hence accessing services closer to the time of birth makes sense to them. Late presentation has also been shown to impact significantly on the timely initiation of ART in pregnancy.<sup>323</sup>

Our results suggest that women who screened for HIV in pregnancy frequently felt clinically well and found it hard to accept an HIV diagnosis in the absence of signs and symptoms of disease. Providers concurred by reporting that women did not expect an HIV-positive diagnosis when testing in pregnancy. A woman's rationale for HIV testing in pregnancy may be different to that of a non-pregnant individual voluntarily testing in mainstream HIV services, in that the decision to test is commonly made in context of the potential benefits accrued to the child.<sup>23</sup> Patient perceptions of wellness, despite advanced stage disease have been documented elsewhere, where ART initiation has been refused, even after up to 2 months of counselling, due to reasons of "feeling healthy."<sup>199</sup>

It is well documented that women undergo severe emotional stress when confronted with an HIV-positive test result.<sup>179</sup> Furthermore, pregnancy is a life event accompanied by hormonal changes, and as with HIV diagnosis, places women at risk of depression.<sup>180</sup> Evidence from sub-Saharan Africa suggests that HIV-positive women suffer greater levels of psychological distress than non-infected women during pregnancy<sup>181</sup> and it is possible that women who diagnose HIV-positive in pregnancy may be more at risk of depressive and somatic illness than women of known HIV-status who become pregnant.<sup>182</sup> One South African study suggested a high background prevalence of depressive disorders associated with unplanned pregnancy and poor socio-economic circumstances in rural women enrolling for PMTCT services, regardless of HIV status.<sup>183</sup> Thus it is likely that a woman diagnosed HIV-positive in pregnancy is faced with a process of complex and pressing decisions when she may already be vulnerable to, or experiencing psychological distress. Denial of the need for treatment has been shown to be associated with pregnancy, lower educational level and greater age, as well as advanced stage disease and poor ART adherence.<sup>349</sup> Shock emanating from a positive diagnosis frequently arises from feelings of betrayal of a partner.<sup>350</sup>

In light of this evidence, we argue that women who are eligible for ART face a triple burden; of transition into pregnancy, HIV diagnosis and the urgent requirement to start

lifelong ART before delivery. In turn, it is plausible that this combination of life events, which requires complex psychosocial reorganization and adjustment, may be too overwhelming to contemplate, subsequently leading to a lack of acceptance, denial and loss to follow up either in pregnancy or postpartum. Denial, a recognized coping mechanism for HIV diagnosis in pregnancy,<sup>351</sup> was also seen to prevent or delay ART initiation in pregnancy in this study. It would seem according to the women and providers that both denial of HIV status and fear of committing to lifelong ART in the context of asymptomatic disease could be areas of focus for future interventions.

At the time of this study, disclosure was a widely used psychosocial criterion for ART initiation,<sup>352</sup> with some treatment services requiring the participation of treatment supporters prior to initiation. Disclosure, however, is particularly challenging in the context of pregnancy.<sup>147,316</sup> Concern about disclosure of HIV status is linked to perceived stigma associated with infection. Although disclosure is advocated by both the WHO and CDC as a means to decrease anxiety, garner social support and to decrease risk of transmission through uptake of preventive interventions and behavioural change,<sup>165</sup> evidence suggests that fear of abandonment, discrimination and rejection by partners or family members are common barriers to disclosure of HIV status in pregnancy. Fear of partner rejection was of particular concern to women who were economically dependent on their partners.<sup>147</sup> A recent study of women from Tshwane, South Africa, portrays women as balancing the risk of abandonment with the desire for support and to raise transmission risk awareness within their intimate relationships. Few women experienced adversity as a result of disclosure, as has been documented elsewhere.<sup>147,166</sup> While our study did not examine relationship dynamics with intimate partners, nor explore the impact of unplanned or unwanted pregnancy, evidence has shown that the decision to disclose in this setting is often based upon the nature of a couple's relationship, and the interplay of dependency and economic factors.<sup>317</sup> As illustrated in our results, while disclosure elicited a positive reaction for most women, a minority of

women experienced loss of support and emotional abuse as a consequence. The promotion of partner testing in antenatal care and linked family-based ART services could address social barriers to disclosure and treatment for both pregnant women and their partners.<sup>24,204,353</sup>

Our findings suggest that women may need time to accept and disclose their HIV status. Given that many women are predisposed to presenting late in pregnancy, delays in accepting and disclosing diagnosis may further decrease the window for initiating ART before delivery. This points to the need for focused interventions to support HIV-infected pregnant women that ensure successful referral and rapid ART initiation. Such interventions require a structured approach to address the issues faced by pregnant women, including those highlighted here, to strengthen the uptake of ART. For instance, integration of antenatal care with ART services can facilitate women's access to both antenatal and ART services during pregnancy.<sup>125</sup> Although not fully explored in this study, service integration has shown to increase initiation of ART in pregnancy,<sup>123</sup> however, late presentation can still comprise integrated services by allowing insufficient time for treatment uptake and suboptimal treatment duration in pregnant women with advanced disease.<sup>127</sup>

Knowing someone who is on ART has been associated with higher uptake of testing and treatment adherence in pregnancy,<sup>131</sup> and there is preliminary evidence pointing to the role of peer-driven support groups for HIV-infected pregnant women facilitating PMTCT uptake.<sup>354</sup> Other research has shown the benefits of family and group-based psychosocial support in assisting HIV-infected pregnant women with adjustment and coping.<sup>354,355</sup> These models have the potential to complement stretched public health services which frequently lack the resources to offer psychosocial care, however, more research is required to identify the optimal design and eventual impact of different types of interventions.

Of note in these findings is the pervasive sentiment among women that any antiretroviral intervention started in pregnancy (whether short-course PMTCT or lifelong ART) was motivated primarily by the need to protect the unborn child. This is supported by

providers' concerns that women who initiated ART in pregnancy often perceived treatment to be episodic and pregnancy-bound. While all the postpartum women interviewed did not believe that they would default, providers suggested that women who felt clinically well had the greatest potential to be lost to care postpartum because there was no longer an incentive to continue with treatment. This assumption may provide insight into existing quantitative data from this setting, which suggest that women who initiate ART in pregnancy may be at elevated risk of loss to follow-up postpartum.<sup>333,334</sup>

A limitation of this study is that only women who were either on ART or waiting to initiate ART were interviewed. Hence the views of those who either refused treatment initiation or who were lost to follow up are unknown and the experiences of this sub-population may be different to those of our respondents. Yet the inclusion of providers may serve to provide a more holistic view of the challenges faced by all women who access the services regardless of treatment status.

It is possible that women who are identified as ART-eligible and who start treatment before pregnancy may be more likely retained in care (compared to women who initiate ART only during pregnancy) because the rationale for treatment is not associated with child outcomes. The most favourable paediatric outcomes are observed in women who conceive once established on ART.<sup>4,323</sup> In this case, identifying women of reproductive age, and linking them to ART services before they become pregnant and providing strengthened preconception screening and care, could dramatically reduce the challenges associated with late antenatal presentation.<sup>356</sup>

## 6.5 Conclusion

This study suggests that HIV-infected women face considerable challenges when initiating ART in pregnancy. Major barriers exist for many women concerning coping with a new pregnancy, coming to terms with an HIV diagnosis, and acknowledging the need for lifelong

therapy. Although much progress has been made to close the gaps in PMTCT programmes across sub-Saharan Africa, services can be further strengthened through interventions that address key psychosocial challenges to ART initiation in pregnancy.

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## Chapter 7

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### Paper 5: HIV-infected women's experiences of pregnancy and motherhood in Cape Town, South Africa

Stinson, K., Myer, L. (2012) HIV-infected women's experiences of pregnancy and motherhood in Cape Town, South Africa. *Vulnerable Children and Youth Studies*, (in press)

University of Cape Town

## Abstract

Antenatal services provide a valuable opportunity for the uptake of prevention of mother-to child transmission (PMTCT) of HIV interventions and antiretroviral treatment (ART) for maternal health. While knowledge of HIV status during pregnancy is beneficial to both the mother and child, PMTCT programmes may focus more on prevention and the physical aspects of health than the psychosocial impact of HIV on pregnancy and motherhood. The objective of this **study was to examine South African women's perceptions of HIV infection in pregnancy and how they related to motherhood in the context of HIV infection.** In-depth interviews were conducted with 17 HIV-positive pregnant and 11 ≤6 month postpartum women to elicit perspectives on HIV-positive pregnancy and motherhood. For most women who tested in pregnancy, the primary rationale for testing stemmed from a concern for their children and anxiety around the risk of vertical transmission was highly prevalent. Women did not perceive any superficial differences between themselves and non-infected pregnant women and they compared HIV to any other chronic condition. However, they voiced anxiety about being infected and were preoccupied with keeping their children safe, both in pregnancy and postpartum. They described a diminished sense of pride about motherhood, and an additional burden of guilt associated with carrying a vulnerable child, which made pregnancy different for them in comparison to uninfected women. Feeding posed a particularly difficult issue because by choosing formula feeding, women were protecting their children, yet this seemed to diminish their status as a mother, while at the same time publicising messages about being infected with HIV. While women identified externally with the social value of motherhood, the burden of HIV infection was seen as a destabilising threat to their identity as mothers.

## 7.1 Introduction

Across sub-Saharan Africa, antenatal services provide a valuable opportunity for the uptake of prevention of mother-to child transmission (PMTCT) of HIV interventions and antiretroviral treatment (ART) for maternal health.<sup>24</sup> While knowledge of HIV status during pregnancy is beneficial to both the mother and child, PMTCT programmes may focus more on the clinical benefits of interventions than the psychosocial aspects of HIV diagnosis and disease management in pregnancy.<sup>318</sup> Women who test HIV-positive during pregnancy may not only face emotional adjustment and the simultaneous requirement for treatment initiation, they also may experience challenges concerning disclosure, the perceived threat of stigma and fear of future disease impact for themselves and their children.<sup>179,351,357,358</sup>

Evidence suggests that the psychosocial burden associated with HIV-positive motherhood necessitates much work by these women to maintain and protect their maternal identities and to preserve maternal and child health.<sup>196,197</sup>

PMTCT programmes comprise a comprehensive strategy that promotes both maternal and infant health through the prevention of vertical transmission and the treatment of maternal HIV, starting with maternal testing and diagnosis.<sup>105</sup> Yet, acceptance of HIV testing in pregnancy and the uptake of PMTCT interventions may be motivated more by the need to protect the unborn child than the perceived benefit to the mother of knowing her status.<sup>23,359</sup> It has been documented that many women in sub-Saharan Africa, including women in South Africa, present at late gestational age for antenatal care<sup>136-140</sup> and there may be little time to consider the effect that a lifelong chronic illness may have on motherhood.

In most parts of Africa, motherhood is highly valued. Childbearing in South African society is considered the norm among married and co-habiting couples.<sup>184-186</sup> Motherhood is laden with social meaning: reproduction is viewed both publically and privately as confirmation of a woman's social identity.<sup>187,188</sup> Yet the attainment of this role is dependent

on social connection and acceptance that are shaped by greater political processes.<sup>189</sup> Women are exposed to paradoxical social messages: while pregnancy is socially desirable and is seen to elevate a woman's status, HIV infection is a stigmatizing condition that may raise a punitive social response.<sup>190,191</sup> In the context of maternal identity, HIV infection is commonly perceived as deviance from the norm.<sup>190,191</sup> Previous research has suggested that while faced with this paradox, HIV-infected pregnant women, either whose HIV-positive status is known prior to pregnancy, or who are diagnosed in pregnancy, may experience a conflict between social constructs of motherhood and the stigma associated with HIV infection, leading to internalized negative attitudes towards motherhood.<sup>192</sup> While HIV-infected women experience and internalize stigma, motherhood still remains a priority, and decision-making processes around pregnancy care and the avoidance of vertical transmission entail counterbalancing the social risks of HIV infection with the benefits of motherhood.<sup>194</sup>

Despite the public health significance of pregnancy and HIV, little research into their intersection with motherhood exists. Few studies have evaluated women's perceptions of HIV-positive motherhood, and much of this evidence describes the experience of women in Western countries, where the burden of HIV and the social context of pregnancy differ from sub-Saharan Africa.<sup>190,316,318,357</sup> While the values assigned to motherhood may be universal, in Western societies HIV infection is linked to minorities and is associated with behaviours outside of social norms. In contrast, resource-poor contexts experience a higher burden of HIV through heterosexual transmission, fuelled by multiple factors including poverty and gender power differentials.<sup>360</sup> Hence the burden of HIV may impact on women's perceptions of HIV-positive motherhood differently in this setting, compared to the perceptions held by their counterparts in resource-rich countries. We investigated the experience of pregnancy and HIV infection within the broader context of motherhood in South African women.

## 7.2 Methods

The objective of this study was to examine South African women's perceptions of HIV infection in pregnancy and how they related to motherhood in the context of HIV infection. In-depth interviews were conducted to elicit perspectives on their reaction and coping with HIV-positive pregnancy and motherhood.

**Table 7.1 Characteristics of women interviewed, 2007-08**

| Characteristics           | n           | Interquartile range/% |
|---------------------------|-------------|-----------------------|
| Pregnant                  | 17          | 61%                   |
| Postpartum                | 11          | 39%                   |
| Median age (IQR)          | 26<br>years | (23.5-31.5 years)     |
| Parity                    |             |                       |
| No children               | 6           | 22%                   |
| 1 child                   | 12          | 43%                   |
| 2 children                | 6           | 22%                   |
| 3 children                | 2           | 7%                    |
| 4 children                | 2           | 7%                    |
| Lives with                |             |                       |
| Husband/partner/boyfriend | 10          | 36%                   |
| Parents/other relatives   | 13          | 46%                   |
| Alone                     | 5           | 18%                   |
| Work                      |             |                       |
| Employed                  | 6           | 22%                   |
| Unemployed                | 18          | 64%                   |
| Unknown                   | 4           | 14%                   |

Twenty-eight women who were either pregnant (n=17) or six month's postpartum (n=11), were purposively sampled between August 2007 and March 2008 from four public sector primary health clinics and two referral hospitals in Cape Town, which offered either antenatal and delivery care or antiretroviral services. Four women tested before pregnancy, and one pregnant woman tested before she knew she was pregnant. Four of these women tested due to clinical manifestations of opportunistic infections, and one tested due to suspicion of disease. At the time of the study, PMTCT guidelines offered antiretroviral treatment (ART) to women with CD4 cell counts  $\leq 200$  cells/ $\mu$ L and all but four women

were on ART. Ten women lived with a spouse or partner and the median age of the women was 26 years (Inter Quartile range: 23.5-31.5 years, Table 7.1).

In this setting, women characteristically present for antenatal care in the second trimester, and most antenatal and delivery services are provided by midwives at primary care clinics. Prior to the interview, written informed consent was obtained from participants and to protect privacy and confidentiality, no names were used or recorded during the interviews.

Interviews were conducted in the participant's mother tongue (isiXhosa) and recorded; transcribed verbatim and translated into English for analysis (Appendix 7). A thematic approach to narrative analysis was applied. This approach seeks to reveal aspects about trends existing in a wider social context through the recounting of individual personal experience<sup>361</sup>. Women's stories relating to their experiences of testing for HIV both among those who tested prior to pregnancy and those who tested during pregnancy, as well as their perceptions of motherhood while pregnant or postpartum were conceptually grouped. Common themes were compared and interpreted in light of current evidence from PMTCT research and theories of motherhood.

## 7.3 Results

### 7.3.1 *Experience of HIV testing in pregnancy and perception of HIV infection*

In the interview, the 23 women who tested in pregnancy were asked to describe the circumstances around their HIV test. Most women tested because they were pregnant and they wanted to know their HIV status for the sake of their children. They recalled that they had not considered the possibility of HIV infection prior to pregnancy because they did not have any disease symptoms and believed that they were not at risk.

For these women, an HIV-positive test result came as a substantial shock. Some women suggested that had they experienced physical manifestations of illness, for example, a

rash or diarrhoea, it would have been easier for them to believe that they were infected. There was general acknowledgement of the association between HIV, morbidity and death, and while some women mentioned that they had no choice but to accept their status, others mentioned that acceptance was linked to less anxiety, making treatment initiation easier. A respondent reflected that, “After it was explained to me that I mustn’t think I am going to die, I just put the thought away; I relaxed and it doesn’t bother me anymore.” Among the five women who had tested prior to pregnancy, diagnosis had also come as a shock, with one woman suggesting that she had not acknowledged her diagnosis or ‘followed it up’ until she was pregnant. With pregnancy, she realised that she had to accept her HIV-positive status in order to protect her unborn child. One woman said she tried not to think about HIV when she became pregnant and another said that she felt it would have been better if it were her alone, and not her unborn child who was exposed to HIV:

It would be much easier if it was me alone ... like trying to fight it, to protect the child, it is much more difficult.

Among both those who tested prior to and during pregnancy, a significant number of women drew parallels between HIV and other manageable chronic diseases. HIV infection was perceived to be “common” and “the same as other diseases.” One woman remarked:

It is like other sicknesses and even if you have got it, you can live, and a person who hasn’t got it could still die before you from an accident. You should not tell yourself that you will die because you have it.

### **7.3.2 Perception of being pregnant and HIV-infected**

Women were asked to discuss whether they perceived themselves to be different from HIV-negative pregnant women. Some women drew superficial comparisons, noting that all pregnant women “looked the same,” and that “no person can see if you have the virus.” Other women acknowledged that taking ART highlighted a difference associated with managing HIV:

It can't be the same, possibly it could be nice, I don't know ... There is this thing at the back of my mind that I am HIV-infected. Now you see [without HIV], I would be living cleanly, just living without worrying that maybe I should be taking the pills, I should be going to the clinic - those worries would not be there.

Preoccupation with health status and a personal concern around wellness postpartum were also prevalent. Respondents felt that HIV-infected women were not able to make “mistakes,” and that they had to take “special care” regarding their health, particularly because they were “made sick by something small.” Yet uninfected women could afford to be more lenient with their lifestyle choices during pregnancy. A respondent noted that she perceived HIV-infected women as “giving birth and then dying.” Even among women who viewed HIV as a manageable chronic disease, fear of advanced disease and death resulting in orphanhood was an additional emotional burden which set them aside from uninfected women in pregnancy. A woman stated.

If you are pregnant and you don't have the virus it is nice for you, but if you are pregnant and HIV-infected, you think about the child. What will happen to the child? You also think again about the possibility of getting sick and maybe dying after the delivery, if maybe it was really difficult, you see, your child has to grow up having been left alone.

Women also expressed anxiety about the wellbeing of their unborn children. In spite of the availability of effective prophylaxis and treatment, they were preoccupied with the fear of transmission. A woman remarked, “You see, you cannot be 100 per cent sure that your child will not come out with the germ if you have it.” She described that not only did an HIV-infected woman have to ensure that she took ART “to protect herself and the baby,” but she feared an adverse event during labour could increase transmission risk. Other women discussed that they were “always worried” about their unborn children. HIV-infected women had to “protect” their children “under any condition” and it remained a ubiquitous concern:

You can still get sick - you the parent. Then the main thing that sits on your conscience is that the child should not get infected. It just must not get infected, and it must grow well. And me too, I must not get sick so that I can look after the child.

While most women suggested that they were hesitant to initiate lifelong treatment, they saw ART as a source of hope to prevent transmission. The prospect of bearing an HIV-free child provided the impetus for many to initiate lifelong therapy in pregnancy, although some women were also motivated to initiate treatment to preserve their own lives to ensure that they would be able to look after their children.

I didn't want to start on ART, the reason being that I was afraid. Then it was imperative that I start them because my CD4 count was low, and the main advice I got was that I should accept myself and take the pills ... It is fine when they are taken by some other person, but when it was going to be me – and that I was going to have to be on treatment for my whole life! But there was no doubt that I must prepare myself that if they [CD4 cell count] didn't increase, then I would be putting my child in danger and my own life in danger.

A postpartum woman mentioned that the fear of having an HIV-infected child was the most challenging aspect of her pregnancy. She felt relieved when her infant tested HIV-negative, and expressed that, “At least I feel I can have a child ... in this situation it would be hard if I live and the child dies.” One pregnant woman expressed anxiety around child care and safety:

You have to be careful with your hands. Everything you touch you must make sure there is no cut ... Like if you were doing something and you cut yourself, [you must] immediately find something to clean it and cover it - don't do anything else. So you can't say you know you have a cut and you are bleeding when the baby is busy crying. You rush to the baby and although your blood is running, you must make sure that you cover that before you touch anything and the baby.

### **7.3.3**      *Perceptions of HIV-infection and motherhood*

Most women did not think that their feelings around motherhood had or would be changed because of HIV infection. Several women suggested that motherhood was not different for

them when compared to HIV-negative mothers. One woman stated, “I will feel like other mothers ...I will always be the same mother.” However, while it was believed that uninfected women could be “proud” of their pregnancies and motherhood, infected women felt “more guilty to bring a new life.” One woman described:

You don't feel proud like a normal person you just feel like 30 per cent proud. You feel less than a person who is not HIV-infected.

Women's perceptions of HIV-related stigma in pregnancy and postpartum were mixed. Some believed that people “gossiped” about women who were pregnant and infected. Many women, however, felt that their diagnosis was private and not externally visible. One woman mentioned that it was easier for women to cope with prevailing social attitudes of HIV by coming to terms with the diagnosis, and through this, “You don't hear what other people say, especially if it is negative.” A few women believed that other people felt “disappointed” or “ashamed” of women who were HIV-infected and pregnant and that HIV-infected women should not have children.

The complexity of balancing motherhood with HIV infection manifested prominently during the postpartum period, primarily around feeding choice. Women were most likely assumed to be HIV-infected if they were seen to be formula feeding, yet there was a mixed reaction to the perceived stigma associated with this choice. Some women felt that fetching formula at the clinic identified women as HIV-infected, while others defended this assumption by saying that there were many reasons for women choosing not to breast feed, for example, needing to go to work or having another health condition which prevented breastfeeding. One woman suggested

It's obvious that many people already know now. I don't know how, because for a long time children who cannot breast feed have been given formula from the clinic. But now most people just know that if you are holding [the formula], it is obvious you are [HIV-]positive. I don't mind because the person who looks down on you perhaps does not know her status, and then when she does know, it will be too late for her.

Feeding choice was clearly an important aspect of motherhood which made most of the respondents feel differently about their identity, with one woman describing it as making her feel that motherhood was 'incomplete.' One woman described that mothers who breast fed could feel 'proud' and another mentioned that she was sad that she would never experience breastfeeding because she chose to formula feed. Although they wished to breast feed, all but one mother reported that they would or did formula feed. Feeding choice was predicated on the desire to ensure that the exposed child remained uninfected:

I will bottle feed because I am not going to do anything else apart from protect my child. I am not going to have time for [paying attention to] people [who may judge me]...I will be happy because I have told myself there is no other way in which I can protect my child. I would never forgive myself if I breast fed because I didn't want people to see that I am HIV[-positive], so let them just talk and finish.

#### 7.4 Discussion

The results of this study show that many women in this setting are motivated to test for HIV in pregnancy primarily for the benefit of their children. Most women of unknown HIV status prior to pregnancy had not expected a positive HIV result, because they felt physically well. Just as the primary rationale for testing in pregnancy stemmed from a concern for their children, fears around vertical transmission were foremost. Women who had been diagnosed prior to pregnancy shared the same concerns for the wellbeing of their children in spite of knowing their HIV status prior to pregnancy. While women did not perceive any superficial differences between themselves and uninfected pregnant women and they compared HIV to any other chronic condition, they voiced anxiety about being infected and were preoccupied with keeping their children safe, both in pregnancy and postpartum. Linked to this was an attenuated sense of pride about motherhood, and an additional burden of guilt associated with carrying a vulnerable child, which made pregnancy different in comparison to uninfected women. Feeding posed a particularly difficult issue: by choosing formula feeding,

women were protecting their children, yet this seemed to diminish their status as a mother, while at the same time publicising messages about being HIV-infected.

These data suggest that while respondents did not feel superficially different from uninfected pregnant women and mothers, women believed that uninfected women did not experience the pervasive underlying anxiety they associated with being HIV-infected and the guilt of an HIV-positive pregnancy. Previous approaches have suggested that social representations of HIV-infected women present them as threatening and 'bad,' even when associated with the positive construct of motherhood.<sup>362</sup> Representations of HIV-positive motherhood further extend to the social stereotype of the deviant or 'bad' mother, a societal scapegoat who is identified as one who is unable to or fails to protect her child from harm, juxtaposed against the 'good' mother who is revered as nurturing and self-sacrificing.<sup>193</sup> HIV infection and motherhood place a woman in a 'double-bind' such that while social expectations dictate reproduction, so society condemns HIV-positive motherhood.<sup>190,191</sup> Teetering on the brink of failure while trying to maintain the identity of a 'good' mother, HIV-infected pregnant women report elevated levels of emotional distress: they envision a future threatened by loss through vertical transmission and maternal or child illness and death.<sup>318,357,358</sup> Through their narratives, respondents hinted at these characteristics of the 'good' mother, who was free of the burdens associated with living with HIV, and who was able to take pride in motherhood. Hence while they identified externally with the social value of motherhood, these women acknowledged that life as a mother without HIV would have been less burdensome.

Our study shows that the preoccupation with preventing vertical transmission was a prevailing mental and physical task. Discourse on experiences of HIV-positive motherhood has described a typology of 'work' that HIV-infected mothers engage in to preserve their identities as 'good' mothers as well as to protect their children.<sup>195</sup> One previous analysis suggested that women conduct surveillance and safety 'work' to protect their children from

transmission and stigma; they engage in information and accounting ‘work’ to make decisions on care and to weigh up benefits and risks associated with illness-related activity. Among other types of ‘work’, they manage hope and worry ‘work’ when contemplating the impact of HIV on their children.<sup>196,197</sup> The emotional aspects of this ‘work’ have also been described as ‘defensive mothering’, suggesting the mental effort required to protect against discrimination.<sup>363</sup>

In our study, women suggested that they were driven to protect their children “under any conditions”. In applying the above discourse, ‘work’ to achieve this was undertaken, including surveillance and safety ‘work’ in postpartum care. Similar findings have been described in a study of women in another African setting, where fear of contagion went so far as to alter the daily patterns of infant care.<sup>364</sup> As found elsewhere, participants in this study also engaged in hope and worry work concerning infant testing outcomes<sup>365</sup> and ART was associated with the hope of reduced transmission risk and prolonged life in the absence of advanced disease.<sup>366</sup>

Choices regarding infant feeding highlighted in the narratives are particularly suggestive of the predicament faced by HIV-infected women and the ‘work’ they faced in terms of accounting for benefit and risk and the preservation of positive maternal identity. While breastfeeding was aligned with the social representation of the ‘good’ mother, it was also seen as a risk for transmission, and women were forced to balance replacement feeding interventions to prevent HIV with personal desires and social expectations to breast feed. Replacement feeding, while presented as a choice, was more a requirement that sought to transform the identity of the ‘bad’ mother to ‘good’ mother, by protecting against vertical transmission.<sup>191,196</sup> In South Africa where breastfeeding is the cultural norm, the women in this study felt set apart from others not so much because they were HIV-infected, but because they were HIV-infected mothers who could not breast feed.

Among these women, the duality of the 'good' and 'bad' mother was maintained privately in much of pregnancy, yet it became public postpartum when these women confronted their choices about infant feeding. With the introduction of new South African infant feeding guidelines which advocate the support of exclusive breastfeeding for the first six months of life and extended postpartum maternal and infant prophylaxis regimens.<sup>280</sup> It is possible that the negotiation of this choice will be easier in future. However, while these interventions are evidence-based, little is known of their effectiveness in operational settings, particularly those with high seroprevalence and sub-optimal ART coverage.

While mothers may work to maintain their maternal identity within the context of the psychosocial burden of HIV, their illness in conjunction with situational factors has the potential to influence the long-term physical and mental health, as well as the social and behavioural outcomes of their children.<sup>367</sup> The physical health of an HIV-positive mother is known to influence child mortality, with children of mothers who have died of AIDS having a 3 to 4 fold increased mortality risk, regardless of HIV status.<sup>19,20</sup> Compromised maternal physical health has also been associated with poorer development of self-concept and higher depression risk in children.<sup>368</sup> Furthermore, studies from the United States have reported a negative relationship between increased maternal stress, poorer parenting skills in HIV-positive mothers and child problem behaviours.<sup>369</sup> Formative evaluations of interventions which address the psychosocial stressors of HIV-positive motherhood and enhance parenting skills and social support are promising.<sup>370</sup> These interventions need to be integrated into postpartum PMTCT care in order to address the psychosocial needs of mothers and enhance early childhood development.

Our hypothesis was that while perceptions of motherhood are universal, the contrasting epidemiology of HIV in South Africa may have resulted in different perceptions of HIV-positive motherhood among the women interviewed in this setting when compared to women in developed contexts. However, this was not the case, and similar resounding

themes of deviance and the psychosocial burden of HIV-positive motherhood were expressed. Our findings further suggest that like women from other settings,<sup>196,197</sup> these women also performed much 'work' to protect and maintain their maternal identities in the context of HIV infection. Hence despite these women describing HIV as a manageable disease, more is required to address their psychosocial needs in motherhood.

Our study has several limitations. First, snowball techniques led to the identification of women who were attending services, most of whom had accepted treatment initiation and who were part of the PMTCT programme. Hence their perceptions regarding HIV-positive motherhood may have been different from those women who were lost to services either through their own volition or for reasons of poor access. Our sample was small and from an urban setting with established PMTCT services, hence these results may not be generalizable to less resourced settings. Furthermore, during our data collection and analysis, we did not distinguish between pregnant and postpartum women, and hence we may have overlooked potential differences or changes in attitudes towards HIV-positive motherhood between these women. We also did not examine the impact of parity on perceptions of motherhood. More research is needed into the impact of timing of diagnosis, parity and the changes over time in the experience of HIV-positive motherhood.

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## Chapter 8 — Conclusions

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This thesis sought to detail the coverage of the PMTCT programme in Cape Town, both in terms of prophylaxis to women who required interventions for prevention, and more specifically, to examine ART initiation in pregnant women who required treatment for their own health. This thesis also investigated the barriers to ART initiation and women's perspectives on the lived experience of HIV in pregnancy and HIV-positive motherhood. Three research projects were undertaken, each of which has covered questions posed at the start of this thesis. These questions explored the proportion of women who were identified by services as requiring PMTCT interventions, and the coverage of these interventions; the uptake of ART among eligible pregnant women; and whether there was a difference in this uptake between different models of service delivery. The research questions also focused on the barriers to ART initiation, as perceived by HIV-infected women and health care providers, and investigated women's perceptions of HIV-positive pregnancy.

Prior to this research, little was known of the operational effectiveness of PMTCT programmes in Cape Town, and PMTCT coverage estimates were for the most part limited to reported routine service data. In particular, qualitative research into the challenges to ART initiation and women's perceptions of HIV diagnosis and initiating ART in pregnancy were unknown in this setting. The conclusions here present a synthesis of these findings, and put forward the reasons for suboptimal programme coverage in this setting.

Recommendations for improvement are also provided.

## 8.1 Summary of findings

The first research project, set out in Chapter 3, investigated PMTCT programme coverage at three delivery sites in Cape Town during 2007-2008, using cord blood surveillance. This manuscript provided evidence for suboptimal programme performance in terms of coverage, demonstrating that just over half of the women identified as cord blood HIV-positive received the standard of care (dual therapy or ART), and about three quarters of women testing cord blood HIV-positive received some form of ARV. Furthermore, cord blood ARV coverage in mothers was significantly lower than the coverage documented in routine data. Two reasons for suboptimal coverage were gleaned from this study. First, one in five women did not test for HIV in pregnancy, 12% of whom had an undocumented HIV-positive status. As a consequence of not being identified as HIV-infected by the services, they did not receive an intervention, which was confirmed by no evidence of ARV coverage in the cord blood surveillance. This finding represents a missed opportunity for prevention. Second, this study demonstrated that there was a difference between clinical record coverage and adherence to ARV regimens according to cord blood surveillance. This occurred even when the analyses were restricted to patients who were definitively known to be HIV-infected. This finding suggests that treatment adherence may be another barrier to coverage and hence, may impact on programme effectiveness. Through the use of cord blood surveillance, missed opportunities in prevention that would have not have been identified with the use of service data alone, were exposed. Similar findings have been reported in other settings.<sup>371</sup>

Chapters 4 and 5 examined ART initiation in eligible women in selected Cape Town clinics in 2005 and 2008 respectively, within the context of different service delivery models. Poor coverage was documented in both evaluations, raising concern about the effectiveness of PMTCT programmes for women with advanced stage disease. While the 2005 data did not show any significant differences between the degrees of service linkage in terms of the

proportion of women who were on treatment by delivery, the 2008 analysis showed that integrating ART within the antenatal service setting was significantly more effective than service delivery models demonstrating separate services. It is possible that improvement in the integrated model over time reflects early challenges around the co-ordination of ART for pregnant women in 2005, where there may have been limited availability of personnel and resources to support this approach, as well as subsequent improvements in service delivery through the maturation of the programme. These findings support global PMTCT strategy which underscores the importance of promoting linkages between services over verticalised models.

In both evaluations, late antenatal presentation was a significant factor influencing ART initiation. As evidenced elsewhere, women who presented at earlier gestational age were more likely to have initiated ART by delivery. Furthermore, the results suggested that women needed time to initiate ART, and many women went on to initiate postpartum. While not directly investigated in these two analyses, it is possible that psychosocial barriers which were examined in Chapter 6, may have played a role in either treatment refusal or delays in initiation.

The findings in Chapter 6 confirmed that late antenatal presentation compromises ART initiation in eligible women, giving limited time for treatment start before delivery. These findings which were supported by HIV-infected women and service providers alike, suggested that in combination with late presentation, women require time to accept HIV diagnosis - this acceptance possibly being compounded by a pre-existing need for psychological adjustment to pregnancy itself. Shock and denial are common reactions to HIV diagnosis and the findings in this chapter suggested that women who are found to be eligible for ART in pregnancy face a triple burden of pregnancy, HIV diagnosis and the urgent requirement for treatment start, a combination which may be too overwhelming to contemplate.

This chapter also documented further reasons for delayed initiation or treatment refusal including the lack of symptoms and signs of disease. This phenomenon has been reported in non-pregnant populations elsewhere.<sup>199</sup> Fear of partner disclosure was another treatment disabler to ART initiation in this study.

The results in Chapters 5 and 6 both suggest that women's primary motivation for testing for HIV in pregnancy centres around prevention of vertical transmission. This has implications for women who require lifelong ART because the motivation for continued therapy after delivery may subside. As described in Chapter 6, the preoccupation with preventing vertical transmission was translated into psychological 'work' for such women, a phenomenon documented in resource-rich settings. Furthermore, the findings in Chapter 6 suggested that HIV-infected women experience the paradox of both "good" and "deviant" mothering identities, which contribute to an attenuated sense of maternal pride and an additional emotional burden of living with HIV. Adherence to PMTCT interventions were challenged particularly in the postpartum period when women were confronted with infant feeding choices.

## 8.2 Limitations

Study-specific limitations are discussed in each chapter, and these include the potential impact of missing data associated with the use of routine service data. As noted, sensitivity analyses showed no significant differences between records with missing data and those which were complete, suggesting that missing data were missing at random. Furthermore, there are several cross-cutting limitations to this thesis which require mention. First, this evaluation specifically focuses on Cape Town services and hence these findings may not be wholly generalizable to other settings. As detailed in the literature review in Chapter 2, Cape Town runs the flagship PMTCT programme in South Africa, and a mix of political will and

available funding resources led to service expansion which was unique in the early years of the programme in South Africa.

As a result, the challenges to coverage faced in this setting may be different from those in other parts of South Africa or the continent. For example, Chapters 4 and 5 which cover ART initiation in pregnancy, show high CD4 cell count testing and return of results, which has been reported as problematic in other South African settings, for example KwaZulu-Natal.<sup>372</sup> However, the results from Chapters 6 and 7 which cover the barriers to ART initiation and women's experience of HIV-positive motherhood, share similarities with findings in other settings, for example, women's motivation for ART initiation, their fear of stigma and their perceptions of HIV-positive mothering.

Second, these data are a reflection of the PMTCT programme as it was implemented between 2005 and 2008, hence the findings presented in this thesis may be construed as out of date. PMTCT programmes undergo rapid change as new evidence from trials and observational research becomes available. While protocols are frequently updated, there is a recognised implementation lag in these protocols. Despite this, Cape Town has always been at the forefront of implementing the most up-to-date interventions. As illustrated in the local PMTCT guidelines which were being implemented at the time of data collection for Chapters 3, 4 and 5, these services were ahead of the rest of the country in the implementation of dual and triple therapy for pregnant women, which came into effect nationally in 2008.

A weakness of this thesis is that it does not evaluate the guidelines implemented in 2010. As already described in Chapter 2, the latest guidelines incorporate a strong focus on earlier ART initiation at higher CD4 cell thresholds and emphasise postpartum interventions to prevent breastfeeding transmission. Despite this limitation, the findings from this research may well still be applicable regardless of updated guidelines. For example, the missed opportunities for prevention linked to suboptimal adherence in dual regimens found

in Chapter 3 is a challenge independent of guideline change, and requires further investigation and intervention. Late antenatal presentation which resulted in a higher risk of failed ART initiation in Chapters 4 and 5 remains a pertinent finding, particularly in light of the promotion of earlier treatment start for ART-eligible pregnant women, as well as those requiring dual therapy from 14 weeks gestation. Since more women will be requiring ART at higher CD4 cell count thresholds, a greater volume of women requiring these interventions may only serve to exacerbate these existing weaknesses, suggesting the need for further evaluation and intervention to ensure optimal programme coverage.

While from the outset, the aim and scope of this thesis was never to examine postpartum services, the papers presented here provide valuable insights into ART initiation in this setting which have not been previously documented. Future areas of operations research would include evaluations of postpartum maternal adherence to ART and retention in care, infant feeding practices and adherence to infant prophylaxis and child outcomes.

### 8.3 Recommendations

The findings in this thesis have provided insight into the reasons influencing sub-optimal PMTCT programme coverage in Cape Town antenatal services. Based on this evidence, the following recommendations are put forward to improve service coverage. First, on a service level, more women need to be identified for PMTCT interventions in pregnancy, in order to increase the reach of the programme. Working towards universal testing is an area where operational effectiveness could be improved. Modelling exercises have shown that failure to achieve near universal testing has a greater impact on vertical transmission than attrition further along the PMTCT cascade.<sup>129</sup> While repeat testing is advocated in current PMTCT guidelines, little is known of the extent of the implementation of repeat testing, or its effectiveness. Approaches such as cord blood surveillance could be used to assist in the interpretation of programme data to improve programme effectiveness.

Second, integration of maternal and child health with ART services is critical in improving service coverage for women who require ART in pregnancy.<sup>132</sup> Novel approaches to strengthening the linkages between antenatal and ART services need to be tested at the district, regional and national levels to gain insights as to how integration may lead to enhanced programme outcomes.<sup>373</sup> However, there are several limitations to integration. On a service level in many instances these approaches will be incorporated into facilities in which fragmentation is already inherent. At district and regional levels, the vertical structure of programmes becomes even more apparent through their administration and funding streams.

There is also a lack of a common conceptual framework for service linkage and integration, it being understood and implemented in multiple ways within health services.<sup>374</sup> Even services which claim to be integrated are subject to degrees of ‘functional separation,’ illustrated by the limited provision of specific services on certain days of the week, or the separation of services by consulting room or different service locations.<sup>332</sup> This has also resulted in negative patient perceptions of ‘segregated’ services for HIV-infected and uninfected pregnant women.<sup>375</sup>

Furthermore, health services are predominantly task-oriented, and these tasks are frequently divided between different service providers, according to specialization and for the benefit of streamlined patient flow.<sup>332</sup> These features were found to be operating in the integrated service delivery model for ART initiation in pregnancy in Chapters 4 and 5. While the integrated model supported in-service ART initiation at the antenatal site, this was not available every day of the week. Furthermore, it was delivered by specialised doctors who had no other involvement in pregnancy care. On both a programme and service level, challenges such as these should be closely examined.

It is also believed that integration may jeopardise existing service operations. This has been documented in reproductive health services where integrated care was found to place

excessive strain on resources and health care providers.<sup>376,377</sup> Overloaded services in turn may lead to increased patient waiting times and poor quality of care.<sup>367,368</sup> Therefore, feasible approaches which allow the development of service linkages are required.

Task shifting has been identified as a valuable means of broadening the reach of HIV treatment and care services, and may potentially smooth over structural challenges inherent in vertical services that are driven by task-oriented and specialist practices. Emerging research has suggested lay health worker and expert patient programme assistance in PMTCT services has increased referral and programme uptake, and provided important educational and psychosocial benefit to HIV-positive pregnant women.<sup>354,378,379</sup> Decentralised delivery models which utilize nurse-initiated management of ART (NIMART) are part of the current South African accelerated AIDS plan and have been shown in a pragmatic trial to be feasible in this setting.<sup>380,381</sup> NIMART may assist the strengthening of integrated approaches to antenatal ART initiation and training midwives in NIMART could provide a natural extension to the existing doctor-based initiation model in antenatal services, described in Chapters 4 and 5. In Cape Town, NIMART is currently being rolled out through a joint partnership between local and provincial health authorities. However, to date primary health care clinics, rather than dedicated antenatal services (midwife obstetric units), have been the target of this strategy, and the feasibility of training midwives in NIMART at these services has yet to be tabled for discussion.<sup>382</sup>

Third, continued mobilisation of efforts to implement improved PMTCT interventions which have been shown to be effective in resource-rich settings need to be embraced at policy level. For example, universal ART provision for all HIV-infected women for the duration of pregnancy through breastfeeding cessation is a recent approach which has been tabled for resource-constrained settings.<sup>13,36</sup> Through universal ART in pregnancy, the absence of the requirement to distinguish between eligible and non-eligible women for

ART may lead to more streamlined services, a model resulting in higher treatment coverage and improved effectiveness.

This ‘test and treat’ approach to initiating all pregnant HIV-infected women on ART, through pregnancy and breastfeeding, is outlined as Option B in the current WHO PMTCT guidelines,<sup>36</sup> and has been proposed for high burden countries with resource challenges, particularly where CD4 cell count testing technologies are lacking.<sup>13,383</sup> Furthermore, “Option B-Plus” is an innovative approach to universal ART which was developed in Malawi in 2011. Due to the lack of availability of service infrastructure to perform CD4 cell count testing, Malawi places all pregnant HIV-infected women on lifelong ART, as per the ‘test and treat’ model proposed by Granich *et al.*<sup>283,384</sup> Option B-Plus promises to improve PMTCT coverage in Malawi; eliminate the need for treatment tapering during breastfeeding cessation, and minimize the associated risks of viral rebound, and will contribute to reductions in heterosexual transmission.<sup>385,386</sup> By relaying the simple message that lifelong ART is beneficial for the mother, Option B-Plus also addresses the underlying challenge of motivation for treatment initiation that is predominantly associated with direct benefits during pregnancy.

The benefits of the Option B ‘test and treat’ approach, however, need to be weighed up against the risks of drug resistance, foetal exposure to multiple drugs, the long term impact of treatment interruption and the cost.<sup>34</sup> While some of these limitations also apply to Option B-Plus, resource allocation to, and management of, this approach may be the most challenging aspect of this strategy. The application of the ‘test and treat’ approach may have different implications in resource-constrained settings where there is a higher HIV disease burden, more widespread prevalence of opportunistic infection and a more advanced immunological stage at which they occur.<sup>387</sup> Furthermore, poorer nutrition and the availability of sufficiently resourced maternal and health services which are integrated with HIV treatment and care services may compromise the feasibility of implementation.<sup>120</sup>

Nonetheless, this novel approach needs to be explored at both a policy and programme level in South Africa, as it would increase programme coverage and accelerate progress towards the virtual elimination of paediatric HIV.

Fourth, HIV-infected women need to be identified timeously for ART. While this may be underscored at programme level, more needs to be achieved in terms of improvements at the service level for women attending antenatal or HIV care services. Viral load is the strongest predictor of vertical transmission<sup>40,388</sup> and ART can reduce viral load to undetectable levels, hence the timing of ART initiation in pregnancy is an influential factor in effective care.<sup>389</sup> Early findings from the European Collaborative Study suggested that the median time to achievement of undetectable viral load among pregnant women of West African origin was 4.4 weeks for women on NVP-based ART and 6 weeks for protease inhibitor-based ART. Median time to undetectable viral load in non-African women was longer; being 7.1 weeks for women on NVP-based regimens and 9.8 weeks for women on PI-based regimens.<sup>128</sup> Findings from a recent study in Zambia suggest that women with less than 4.4 weeks of ART prior to pregnancy had more than a five-fold increased odds of HIV transmission. Regression analyses showed that the additional prophylactic benefit of more than 13 weeks of ART was limited.<sup>390</sup>

Even if a threshold effect at around 13 weeks of ART is apparent, this threshold pertains to vertical transmission risk alone and the consideration of the benefits of prolonged ART for maternal health still remain a priority. There is a strong argument for identifying women for treatment prior to pregnancy. While fertility is decreased in women with advanced stage disease, studies have shown that ART initiation is associated with increased fertility intentions in HIV-infected women<sup>391</sup> and the incidence of pregnancy increases in women who are on ART.<sup>392</sup> The most successful paediatric outcomes are observed in women who conceive once established on ART.<sup>4,323</sup> Hence, by providing comprehensive preconception screening and care; identifying infection in women of

reproductive age, and linking them to ART services before they become pregnant, the challenges associated with late antenatal presentation could be mitigated.<sup>356</sup> This is possible given the new evidence supporting highly effective regimen combinations which have the potential to be safely utilized by women both during and outside of pregnancy, thus sustaining the continuum of care.<sup>336</sup>

Recent guidelines have been proposed by the Southern African HIV Clinicians Society for conception care in HIV-infected couples. These guidelines underscore the need for holistic approaches to the support of decision-making around treatment and conception and have the potential to further promote linkages between HIV treatment services and maternal and health care.<sup>393</sup> Identifying and linking ART-eligible women of reproductive age to ART services and providing them with adequate knowledge and psychological support in this way would afford them the opportunity to make informed decisions about conception and pregnancy. This would reduce the risk of dealing with the triple burden of simultaneous HIV diagnosis, pregnancy and the need for lifelong treatment.

Furthermore preconception ART initiation would decrease the urgency attached to initiation in pregnancy and reshape the motivation for initiating lifelong treatment. It is likely that women who initiate ART prior to conception would be more ready to acknowledge the direct treatment benefits to mothers themselves, before perceiving ART as a means of prevention of vertical transmission. This could ameliorate the high losses in postpartum retention in care reported in this setting.<sup>333</sup>

Fifth, women need more psychosocial support. It has been suggested that HIV-infected women look to health care providers not only for clinical advice, but for comfort and counselling during pregnancy. However, the management of their mental health is frequently neglected.<sup>328</sup> Evidence from evaluations of peer support group interventions have shown improved adherence in pregnant women.<sup>394</sup> Again, through task shifting, the psychosocial aspects of HIV-infected women in pregnancy have been successfully managed

through support group initiatives run by trained peer counsellors who provide information regarding HIV in pregnancy, disclosure, ART and PMTCT regimens and safe infant feeding. In some cases, support groups are run by women who are HIV-infected mothers themselves and these encounters are enriched through shared personal experience.<sup>354</sup>

A support group intervention study in this setting for HIV-infected pregnant women showed promising findings, including increased disclosure rates, and improved adaptive and coping behaviour during pregnancy and the peripartum. Long term benefit, however, was reduced, pointing to the need for the development of more sustained approaches to psychosocial interventions over time.<sup>395</sup> Support services such as these are commonly the result of partnerships between non-governmental organizations and the Department of Health. More work towards formalising psychosocial support services for pregnant, HIV-positive women on a programme level as well as their evaluation in order to inform best practice, needs to be done. Furthermore, the promotion of family-based approaches which not only provide treatment and care for mothers, but extend services to their partners and children, need to be implemented to improve PMTCT outcomes.<sup>204,396</sup>

Sixth, ongoing improvements in monitoring and evaluation of PMTCT programmes are required in order to measure progress accurately. While surveillance systems such as the annual antenatal survey provide useful data on the burden of disease in pregnant women, this methodology could be expanded to provide data on treatment needs in this population. Furthermore, early infant diagnosis surveys promise to provide data on perinatal transmission,<sup>252</sup> yet more operational research is required to ascertain the impact of the 2010 PMTCT guidelines on late postpartum transmission in light of changes to infant feeding strategy. Strengthened data collection systems which combine relevant indicator data need to be developed, and appropriate staff training needs to be given in the collection and interpretation of routine data to ensure completeness and accuracy. Recognition of the value of good quality data needs to be instilled at all levels of service provision. This can be

achieved through regular feedback of data which could be used for immediate programme improvement. Routine data reporting could be supplemented with findings from periodic cord blood surveillance to shed light on aspects of the PMTCT cascade not covered by routine data.

Improvement in PMTCT programme coverage cannot be achieved without national level leadership and accountability. The role of the National Department of Health in ensuring that the latest PMTCT evidence is operationalised through iterative policy change and careful spending is crucial in achieving virtual elimination of paediatric HIV.

#### 8.4 Conclusions

This thesis demonstrates that, as documented in other low-and middle-income African settings, PMTCT service coverage in Cape Town is sub-optimal, and that there are missed opportunities for identifying HIV-infected women for PMTCT interventions to prevent peripartum transmission. In particular, this thesis shows low uptake of ART in pregnant women with advanced stage disease, among whom the greatest gains in prevention could be made.

Political will and the availability of adequate resources, combined with a low burden of HIV and a rapid response to the management of maternal infection, gave rise to very low rates of MTCT and the virtual elimination of paediatric HIV in developed countries. There is no denying that the challenges faced by health services to implementing PMTCT programmes in resource-constrained settings are different and more complex, leading to many factors which compromise progress towards an HIV-free generation. Yet it has been demonstrated that treatment and prevention interventions for pregnant women and their children are feasible in developing countries, leading to lives saved and improved health outcomes. While it was initially believed that this would not be possible, much ground has been gained in the past decade since the first programmes which incorporated prophylaxis

and ART for pregnant women were implemented. There is no room for complacency and continued improvements at policy, programme and service level are required to ensure that the health outcomes of HIV-infected mothers and their children remain a priority.

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## Appendices

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Appendix 1 – Chapter 3 (Surveillance form)

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Appendix 2 – Chapter 3 (Ethics)

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Appendix 3 – Chapter 4 (Data extraction form)

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Appendix 4 – Chapter 4 (Ethics)

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Appendix 5 – Chapter 5 (Data extraction form)

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Appendix 6 – Chapter 5 (Ethics)

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Appendix 7 – Chapters 6 and 7 (Patient interview guide  
and informed consent)

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Appendix 8 – Chapters 6 and 7 (Provider interview guide  
and informed consent)

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## Appendices

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## Appendix 1 – Chapter 3 (Surveillance form)

PE3 - SURVEILLANCE FORM

Study number

|       |  |   |      |  |
|-------|--|---|------|--|
|       |  | - |      |  |
| MONTH |  |   | YEAR |  |

**PART A** Complete form with a blue or black pen

1. Date of delivery   -

2. Mother's age (years)

3. Gravidity\*  \*Total number of pregnancies including this one and any past stillbirths/miscarriages/abortions

4. Where did mother have her first prenatal visit?  No ANC visits  This facility  Other \_\_\_\_\_

5. Total number of ANC visits

6. Date of last ANC visit:   -

7. HIV test before this pregnancy?  Yes, when?   -    No  Unknown

If No or Unknown skip to question 9

8. Previous result?  Positive  Negative  Indeterminate  Not applicable

**DURING THIS PREGNANCY:**

9. Was mother pretest counseled for HIV?  Yes, when?   -    No  Unknown

10. Was HIV test performed?  Yes, when?   -    No  Unknown

11. If test performed, HIV test result:  Positive  Negative  Indeterminate  Unknown

12. Maternal NVP dispensed?  Yes  No  Unknown

13. AZT dispensed?  Yes, month started:   -    No  Unknown

14. HAART therapy dispensed?  Yes, month started:   -    No  Unknown

Staff name \_\_\_\_\_ Signature \_\_\_\_\_

**PART B**

15. Mode of delivery:  Vaginal  Caesarean

16. Hours after delivery the mother was discharged:  17. Hours after delivery the baby was discharged:

18. Not yet discharged (tick in the box)

19. Did the baby receive ARV prophylaxis?  No 20. Reason:

Mother was not tested  Baby died or was stillborn  
 Mother tested HIV-negative  Baby was transferred  
 Mother was transferred  Baby NVP given in ANC  
 Other \_\_\_\_\_

Yes 21. Number of hours after delivery:

22. Which ARVs?  NVP only  AZT only  AZT + NVP  
 Other \_\_\_\_\_

23. Was mother discharged with replacement feeding?  Yes  No  Unknown

24. Birth weight of baby (in grams)

25. In case of twins, birth weight of baby 2 (in grams)

Staff name \_\_\_\_\_ Signature \_\_\_\_\_

PE3 - SURVEILLANCE FORM - v 2.0 23 OCT 07

PE4 - LABORATORY TEST

Study number

[Empty box for study number]

Laboratory facility: \_\_\_\_\_

**PART A** *To be filled in by midwives and nurses from maternity ward*

|   |  |
|---|--|
| <input type="checkbox"/> Sample collected. Date and time:<br>Date <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/><br><small>DAY MONTH YEAR</small><br>Time <input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/><br><small>H H M M</small><br><i>Write date and time sample collected on the blood tube</i> | <input type="checkbox"/> It was not possible to collect a sample. Tick the primary reason:<br><input type="radio"/> Macerated stillbirth (MSB) <input type="radio"/> Born before arrival at clinic<br><input type="radio"/> Fresh stillbirth (FSB) <input type="radio"/> Mother transferred<br><input type="radio"/> Cord snapped / broke <input type="radio"/> Forgot to take sample<br><input type="radio"/> Sample spilled / broke <input type="radio"/> Other reason, specify: _____<br><input type="radio"/> Placenta / cord unhealthy / too thin |
|---|--|

\_\_\_\_\_  
 Staff name \_\_\_\_\_ Signature \_\_\_\_\_ Date \_\_\_\_\_

**PART B** *To be filled in by laboratory*      Date sample tested   -   -    
DAY MONTH YEAR

- Determine HIV test result. *Perform this test on all samples.*  
 Positive  
 Negative  
 Not done. Reason:  Blood clotted  Insufficient sample  Sample spilled / broke  Other reason, specify: \_\_\_\_\_
- Dried Blood Spot sample. *Prepare when Determine test is positive.*  
 Prepared  
 Not prepared. Reason: \_\_\_\_\_
- QC Specimen Prepared  
 Prepared  
 Not prepared  
 Not applicable
- Specimen selected for 10% QC  
 Yes  
 No  
 Not applicable

Laboratory staff name \_\_\_\_\_ Signature \_\_\_\_\_ Date \_\_\_\_\_

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## Appendix 2 – Chapter 3 (Ethics)

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UNIVERSITY OF CAPE TOWN

Health Sciences Faculty  
Research Ethics Committee  
Room E52-24 Grootte Schuur Hospital Old Main Building  
Observatory 7925  
Telephone (021) 406 6338 • Facsimile (021) 406 6411  
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09 February 2007

REC REF: 038/2007

Dr D Coetzee  
IIDMM  
Public Health and Family Medicine  
Falmouth Building, Level 1

Dear Dr Coetzee

**PROJECT TITLE: PMTCT EFFECTIVENESS IN AFRICA: RESEARCH AND LINKAGES TO CARE PART: CORD BLOOD SURVEILLANCE PROTOCOL VERSION 1.0**

Thank you for submitting your study to the Research Ethics Committee for review.

I have pleasure in informing you that the Ethics Committee has formally approved the above mentioned study.

This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

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

Please quote the REC. REF in all your correspondence.

Yours sincerely

*Osley Henley*  
PROF. M. BLOCKMAN  
CHAIRPERSON, HSF HUMAN ETHICS

cc: jrd

|  |                          |                          |                          |                          |                          |                    |                          |       |                          |                          |                          |         |                          |         |                          |          |                          |            |                          |  |
|--|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------|--------------------------|-------|--------------------------|--------------------------|--------------------------|---------|--------------------------|---------|--------------------------|----------|--------------------------|------------|--------------------------|--|
| field worker   | <input type="checkbox"/> | Quality control          | <input type="checkbox"/> | Date                     | d                        | d                  | m                        | m     | form no.                 | <input type="checkbox"/> | <input type="checkbox"/> | HIV neg | <input type="checkbox"/> | CD4s200 | <input type="checkbox"/> | CD4s-200 | <input type="checkbox"/> | not tested | <input type="checkbox"/> |  |
| <b>Antenatal Care facility (MOU/CHC)</b>                                   |                          |                          |                          |                          |                          |                    |                          |       |                          |                          |                          |         |                          |         |                          |          |                          |            |                          |  |
| Vanguard CHC   | <input type="checkbox"/> | Gugulethu MOU            | <input type="checkbox"/> | Khayelitsha (Site B) MOU | <input type="checkbox"/> | False Bay Hospital | <input type="checkbox"/> |       |                          |                          |                          |         |                          |         |                          |          |                          |            |                          |  |
| <b>SHADED AREAS FOR DATA EXTRACTION ONLY. NOT FOR CAPTURE IN DATA BASE</b> |                          |                          |                          |                          |                          |                    |                          |       |                          |                          |                          |         |                          |         |                          |          |                          |            |                          |  |
| <b>Patient identifiers</b>   |                          |                          |                          |                          |                          |                    |                          |       |                          |                          |                          |         |                          |         |                          |          |                          |            |                          |  |
| Folder number  | <input type="text"/>     |                          |                          |                          |                          |                    |                          |       |                          |                          |                          |         |                          |         |                          |          |                          |            |                          |  |
| First name(s)  | <input type="text"/>     |                          |                          |                          |                          |                    |                          |       |                          | Surname                  | <input type="text"/>     |         |                          |         |                          |          |                          |            |                          |  |
| <b>MOU Register</b>  |                          |                          |                          |                          |                          |                    |                          |       |                          | <b>MOU Folder</b>        |                          |         |                          |         |                          |          |                          |            |                          |  |
| Age  | <input type="text"/>     |                          | <input type="text"/>     |                          |                          |                    |                          |       |                          |                          |                          |         |                          |         |                          |          |                          |            |                          |  |
| Date of first booking  | d                        | d                        | m                        | m                        | y                        | y                  | y                        | y     |                          |                          |                          |         |                          |         |                          |          |                          |            |                          |  |
| Accept VCT at booking Y/N  | <input type="checkbox"/> | <input type="checkbox"/> |                          |                          |                          |                    |                          |       |                          |                          |                          |         |                          |         |                          |          |                          |            |                          |  |
| If Yes, tested Y/N   | <input type="checkbox"/> | <input type="checkbox"/> |                          |                          |                          |                    |                          |       |                          |                          |                          |         |                          |         |                          |          |                          |            |                          |  |
| Test result MTCT positive Y/N  | <input type="checkbox"/> | <input type="checkbox"/> |                          |                          |                          |                    |                          |       |                          |                          |                          |         |                          |         |                          |          |                          |            |                          |  |
| CD4 count  | <input type="text"/>     |                          |                          |                          |                          |                    |                          |       |                          |                          |                          |         |                          |         |                          |          |                          |            |                          |  |
| <b>NHSL Database</b>   |                          |                          |                          |                          |                          |                    |                          |       |                          |                          |                          |         |                          |         |                          |          |                          |            |                          |  |
| Date of laboratory Test  | d                        | d                        | m                        | m                        | y                        | y                  | y                        | y     |                          |                          |                          |         |                          |         |                          |          |                          |            |                          |  |
| Confirm CD4 match  | <input type="checkbox"/> | <input type="checkbox"/> |                          |                          |                          |                    |                          |       |                          |                          |                          |         |                          |         |                          |          |                          |            |                          |  |
| <b>ARV Care Facility</b>   |                          |                          |                          |                          |                          |                    |                          |       |                          |                          |                          |         |                          |         |                          |          |                          |            |                          |  |
| Langa Clinic   | <input type="checkbox"/> | Hannan Crusaid           | <input type="checkbox"/> | Khayelitsha Site B (MSF) | <input type="checkbox"/> | Masiphumelele      | <input type="checkbox"/> | Other | <input type="checkbox"/> |                          |                          |         |                          |         |                          |          |                          |            |                          |  |
| Referral completed Y/N   | <input type="checkbox"/> | <input type="checkbox"/> |                          |                          |                          |                    |                          |       |                          |                          |                          |         |                          |         |                          |          |                          |            |                          |  |
| If yes, date referral completed  | d                        | d                        | m                        | m                        | y                        | y                  | y                        | y     |                          |                          |                          |         |                          |         |                          |          |                          |            |                          |  |
| Date ART initiated   | d                        | d                        | m                        | m                        | y                        | y                  | y                        | y     |                          |                          |                          |         |                          |         |                          |          |                          |            |                          |  |
| Weeks gestation ART initiated  | <input type="text"/>     |                          |                          |                          |                          |                    |                          |       |                          |                          |                          |         |                          |         |                          |          |                          |            |                          |  |

| Obstetric Care and Neonatal Service |   |                      |  |   |                          |                          |                          |             |  |  |  |
|-------------------------------------|---|----------------------|--|---|--------------------------|--------------------------|--------------------------|-------------|--|--|--|
| <b>Delivery Site</b>                |   |                      |  |   |                          |                          |                          |             |  |  |  |
| Vanguard CHC                        | <input type="checkbox"/>  | Gugulethu MOU        | <input type="checkbox"/>                   | Khayelitsha (Site B) MOU                              | <input type="checkbox"/> | False Bay Hospital       | <input type="checkbox"/> |             |  |  |  |
| Somerset Hospital                   | <input type="checkbox"/>  | Groote Schuur        | <input type="checkbox"/>                   | Mowbray   | <input type="checkbox"/> | Lost to follow up        | <input type="checkbox"/> |             |  |  |  |
| <b>Labour Ward Register</b>         |   |                      |  |   |                          |                          |                          |             |  |  |  |
| Date admitted                       | <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> |                      |  |   |                          |                          |                          |             |  |  |  |
| On HAART                            | <input type="checkbox"/> Y <input type="checkbox"/> N   | OR                   | ARVs given during labour                   | <input type="checkbox"/> Y <input type="checkbox"/> N |                          |                          |                          |             |  |  |  |
| Delivery outcomes                   | 1   | C/s                  | NVD  | Live  | Stillborn                | Neonatal death           |                          |             |  |  |  |
|                                     | 2   | single               | twins                                      | triplets  |                          |                          |                          |             |  |  |  |
|                                     | 3   | Birthweight (grams)  |  | <input type="text"/>                                  | <input type="text"/>     | <input type="text"/>     | <input type="text"/>     |             |  |  |  |
|                                     | 4   | Other comments _____ |  |   |                          |                          |                          |             |  |  |  |
| OUTCOMES AT SIX MONTHS - MOTHER     |   |                      |  |   |                          |                          |                          |             |  |  |  |
| <b>ARV Care Facility</b>            |   |                      |  |   |                          |                          |                          |             |  |  |  |
| Referral completed Y/N              | <input type="checkbox"/> Y <input type="checkbox"/> N   |                      | LOST TO FOLLOW UP <input type="checkbox"/> |   |                          |                          |                          |             |  |  |  |
| If yes, date referral completed     | <input type="text"/>  |                      |  |   |                          |                          |                          |             |  |  |  |
| Langa Clinic                        | <input type="checkbox"/>  | Masiphumelele        | <input type="checkbox"/>                   | Hannan Crusaid  | <input type="checkbox"/> | Khayelitsha Site B (MSF) | <input type="checkbox"/> | Other _____ |  |  |  |
| CD4                                 | <input type="text"/>  | <input type="text"/> | <input type="text"/>                       |   |                          |                          |                          |             |  |  |  |
| Viral load                          | <input type="text"/>  | <input type="text"/> | <input type="text"/>                       |   |                          |                          |                          |             |  |  |  |
| Date ART given                      | <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> |                      |  |   |                          |                          |                          |             |  |  |  |
| OUTCOMES AT SIX MONTHS - BABY       |   |                      |  |   |                          |                          |                          |             |  |  |  |
| <b>Baby Clinic</b>                  |   |                      |  |   |                          |                          |                          |             |  |  |  |
| PCR                                 | <input type="text"/>  | <input type="text"/> | <input type="text"/>                       |   |                          |                          |                          |             |  |  |  |
| Viral load                          | <input type="text"/>  | <input type="text"/> | <input type="text"/>                       |   |                          |                          |                          |             |  |  |  |

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## Appendix 4 – Chapter 4 (Ethics)

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UNIVERSITY OF CAPE TOWN



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14 February 2007

REC REF: 054/2007

Ms KL Stinson  
IDEU  
Public Health & Family Medicine

Dear Ms Stinson

**PROJECT TITLE: AN EVALUATION OF DIFFERENT APPROACHES TO THE INITIATION OF ANTIRETROVIRAL THERAPY AMONG HIV-INFECTED WOMEN DURING PREGNANCY IN CAPE TOWN**

Thank you for submitting your study to the Research Ethics Committee for review.

This protocol is approved using an expedited review procedure (45 CFR46.110). It is a minimal risk programme evaluation (category 7) of existing services for HIV-infected women during pregnancy. Although there is a small risk of breach of confidentiality in the retrospective component of the study, the study includes measures to counter threats to potential breaches. Researchers will obtain informed consent from participants and health services providers.


This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

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

**Please quote the REC. REF in all your correspondence.**

Yours sincerely

  
A/PROF. M. BLOCKMAN  
CHAIRPERSON, HSE HUMAN ETHICS

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## Appendix 5 – Chapter 5 (Data extraction form)

|   |  |   |  |   |  |   |   |           |                |     |     |  |  |  |  |
|---|--|---|--|---|--|---|---|-----------|----------------|-----|-----|--|--|--|--|
| PMTCT HAART eligible <input type="checkbox"/> Y <input type="checkbox"/> N  | Extraction   | ANC folder found <input type="checkbox"/> Y <input type="checkbox"/> N<br>ARV folder found <input type="checkbox"/> Y <input type="checkbox"/> N<br>Baby register <input type="checkbox"/> Y <input type="checkbox"/> N | QC <input type="checkbox"/>  | Capture   | ANC <input type="checkbox"/><br>HAART <input type="checkbox"/><br>Baby <input type="checkbox"/>      | QC <input type="checkbox"/>   |   |           |                |     |     |  |  |  |  |
| ANC Site <input type="text"/>   | FW code <input type="text"/>   | Form number <input type="text"/>  | Date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 0 9   | Neg <input type="checkbox"/><br>HIV Pos <input type="checkbox"/><br>Not tested <input type="checkbox"/><br>Missing <input type="checkbox"/> |  |   | CD4 <input type="text"/>  |           |                |     |     |  |  |  |  |
| On HAART <input type="checkbox"/> Y <input type="checkbox"/> N <input type="checkbox"/> ?   | Date started <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> | <b>PMTCT register</b>   |  |   |  |   |   |           |                |     |     |  |  |  |  |
| Booking date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 0 8  | Folder number <input type="text"/>   | Name(s) <input type="text"/>  | Surname <input type="text"/>   | Age <input type="text"/>  |  |   |   |           |                |     |     |  |  |  |  |
| Known HIV <input type="checkbox"/> Y <input type="checkbox"/> N <input type="checkbox"/> n/a  | Accept VCT <input type="checkbox"/> Y <input type="checkbox"/> N   | Tested <input type="checkbox"/> Y <input type="checkbox"/> N  | Screening <input type="checkbox"/> Pos <input type="checkbox"/> Neg  | Confirm <input type="checkbox"/> Pos <input type="checkbox"/> Neg   | ELISA <input type="checkbox"/> Pos <input type="checkbox"/> Neg                                      | MTCT positive <input type="checkbox"/> Y <input type="checkbox"/> N | CD 4 <input type="text"/>   |           |                |     |     |  |  |  |  |
| Notes <input type="text"/>  |  |   |  |   |  |   |   |           |                |     |     |  |  |  |  |
| On HAART <input type="checkbox"/> Y <input type="checkbox"/> N  | <b>Antenatal patient folder - ANC card/CRADLE</b>  |   |  |   |  |   |   |           |                |     |     |  |  |  |  |
| DOB <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>           | Gravidy <input type="text"/>   | Parity <input type="text"/>   | Mis/SB/NND/other <input type="text"/>  | TB <input type="checkbox"/>   | Medication <input type="text"/>  |   | Relationship <input type="checkbox"/> Single <input type="checkbox"/> Married <input type="checkbox"/> Stable |           |                |     |     |  |  |  |  |
| SF measurement <input type="text"/> cm  | VDRL/RPR test (syphilis) <input type="text"/>  | Hb <input type="text"/> g/dl  | ART <input type="checkbox"/> Y <input type="checkbox"/> Refused <input type="checkbox"/> N   |   | Notes <input type="text"/>   |   |   |           |                |     |     |  |  |  |  |
| LNMP <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>          | EDD <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>          | Future contraception  |  |   | User <input type="checkbox"/> Quitter <input type="checkbox"/> None <input type="checkbox"/>         |   |   |           |                |     |     |  |  |  |  |
| Infant feeding <input type="checkbox"/> Breast <input type="checkbox"/> Formula   | Gestation <input type="text"/> weeks   | Problem list  |  |   | Tobacco <input type="checkbox"/> Alcohol <input type="checkbox"/> Drugs/Sub <input type="checkbox"/> |   |   |           |                |     |     |  |  |  |  |
| Date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>          | 1 <input type="text"/><br>2 <input type="text"/><br>3 <input type="text"/><br>4 <input type="text"/><br>5 <input type="text"/>             |   |  | Notes <input type="text"/>  |  |   |   |           |                |     |     |  |  |  |  |
| <b>Antenatal patient folder - HIV counselling and testing record</b>  |  |   |  |   |  |   |   |           |                |     |     |  |  |  |  |
| Has tested before <input type="checkbox"/> Y <input type="checkbox"/> N   | Known status <input type="checkbox"/> Pos <input type="checkbox"/> Neg   | Knew status prior to pregnancy <input type="checkbox"/> Y <input type="checkbox"/> N  | Tested (current) <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> |   | Notes <input type="text"/>   |   |   |           |                |     |     |  |  |  |  |
| <b>Antenatal patient folder/other - PMTCT prophylaxis/HAART</b>   |  |   |  | <b>PMTCT labour ward register</b>   |  |   |   |           |                |     |     |  |  |  |  |
| AZT dispensed <input type="checkbox"/> Y <input type="checkbox"/> N <input type="checkbox"/> ?  | Date started <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> | Adequate AZT (>2 wks) <input type="checkbox"/> Y <input type="checkbox"/> N <input type="checkbox"/> ?  |  | In labour <input type="checkbox"/> Y <input type="checkbox"/> N   |  | Child NVP <input type="checkbox"/> Y <input type="checkbox"/> N     |   |           |                |     |     |  |  |  |  |
| On HAART <input type="checkbox"/> Y <input type="checkbox"/> N <input type="checkbox"/> ?   | Date started <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> | On HAART <input type="checkbox"/> Y <input type="checkbox"/> N <input type="checkbox"/> ?   |  | NVP AZT <input type="checkbox"/> Y <input type="checkbox"/> N   |  | Child AZT <input type="checkbox"/> Y <input type="checkbox"/> N     |   |           |                |     |     |  |  |  |  |
| <b>Antenatal patient folder/CRADLE - Delivery outcomes</b>  |  |   |  |   |  |   |   |           |                |     |     |  |  |  |  |
| Delivery Date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> | Facility <input type="text"/>  | Feeding at discharge <input type="checkbox"/> BF <input type="checkbox"/> FF  | Singleton <input type="checkbox"/>   | Twins <input type="checkbox"/>  | Triplets <input type="checkbox"/>  | Baby  | Weight (g)  | Sex (M/F) | PAWC folder nr |     |     |  |  |  |  |
|   |  |   |  |   |  | NVD   | C/S   | Live      | SB             | NND | BBA |  |  |  |  |
|   |  |   |  |   |  | 1   |   |           |                |     |     |  |  |  |  |
|   |  |   |  |   |  | 2   |   |           |                |     |     |  |  |  |  |
|   |  |   |  |   |  | 3   |   |           |                |     |     |  |  |  |  |

|  |                                |                           |                                 |                          |                         |                          |
|--|--------------------------------|---------------------------|---------------------------------|--------------------------|-------------------------|--------------------------|
| <b>ARV Clinic data base / ARV patient folder</b> |                                | Folder number             |                                 | ARV Clinic               |                         |                          |
| Medical Assessment - TREATMENT REFERRAL          |                                | <input type="text"/>      |                                 | <input type="text"/>     |                         |                          |
| Screen date                                      | WHO stage                      | CD4                       | HAART started                   | ANC                      |                         |                          |
| <input type="text"/>                             | <input type="text"/>           | <input type="text"/>      | <input type="text"/>            | <input type="text"/>     | <input type="text"/>    |                          |
| Pregnant   | Trimester                      | Current TB Tx             | TB symptoms                     | TB excluded              |                         |                          |
| <input type="text"/>                             | <input type="text"/>           | <input type="text"/>      | <input type="text"/>            | <input type="text"/>     | <input type="text"/>    |                          |
| <b>Counselling Assessment</b>                    |                                |                           |                                 |                          |                         |                          |
| Support group                                    | Group education                | Counselling sessions      | If Yes, Relationship            |                          |                         |                          |
| <input type="text"/>                             | <input type="text"/>           | <input type="text"/>      | <input type="text"/>            |                          |                         |                          |
| <b>Background information</b>                    |                                |                           |                                 |                          |                         |                          |
| Year Dx  | Has partner                    | Partner informed          | Partner tested                  | Partner result           |                         |                          |
| <input type="text"/>                             | <input type="text"/>           | <input type="text"/>      | <input type="text"/>            | <input type="text"/>     |                         |                          |
| No of Children                                   | No of children tested for HIV  | No of children HIV+       | No of pregnancies received PMCT |                          |                         |                          |
| <input type="text"/>                             | <input type="text"/>           | <input type="text"/>      | <input type="text"/>            |                          |                         |                          |
| <b>Clinical summary - TREATMENT INITIATION</b>   |                                |                           |                                 |                          |                         |                          |
| HAART started                                    | HAART naive?                   | Stage at first HAART      | Weight (kg)                     | CD4                      | Viral load              |                          |
| <input type="text"/>                             | <input type="text"/>           | <input type="text"/>      | <input type="text"/>            | <input type="text"/>     | <input type="text"/>    |                          |
| Regimen ARV 1 _____                              |                                |                           |                                 |                          |                         |                          |
| ARV 2 _____                                      |                                |                           |                                 |                          |                         |                          |
| ARV 3 _____                                      |                                |                           |                                 |                          |                         |                          |
| <b>Most recent visit</b>                         |                                |                           |                                 |                          |                         |                          |
| visit date                                       | Most recent clinical/test data |                           |                                 |                          |                         |                          |
| <input type="text"/>                             | Stage                          | Weight (kg)               | CD4                             | Viral load               |                         |                          |
| <input type="text"/>                             | <input type="text"/>           | <input type="text"/>      | <input type="text"/>            | <input type="text"/>     |                         |                          |
| Months on regimen <input type="text"/>           |                                |                           |                                 |                          |                         |                          |
| Notes <input type="text"/>                       |                                |                           |                                 |                          |                         |                          |
| <b>Baby clinic register or NHLS data extract</b> |                                |                           |                                 |                          |                         |                          |
| PCR found  |                                | PCR source                | Clinic name                     | PCR 6 weeks              | Feeding 6 weeks         | Weight 6 weeks           |
| <input type="text"/>                             |                                | <input type="text"/>      | <input type="text"/>            | Pos <input type="text"/> | BF <input type="text"/> | <input type="text"/> gms |
|  |                                | NHLS <input type="text"/> |                                 | Neg <input type="text"/> | FF <input type="text"/> |                          |

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## Appendix 6 – Chapter 5 (Ethics)

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UNIVERSITY OF CAPE TOWN

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09 June 2009

REC REF: 054/2007

Ms K Stinson  
IDEU  
Public Health & Family Medicine

Dear Ms Stinson

**PROJECT TITLE: AN EVALUATION OF DIFFERENT APPROACHES TO THE INITIATION OF ANTIRETROVIRAL THERAPY AMONG HIV-INFECTED WOMEN DURING PREGNANCY IN CAPE TOWN.**

Thank you for your letter to the Research Ethics Committee dated 5<sup>th</sup> June 2009.

It is a pleasure to inform you that the Ethics Committee has **approved** the amendment as described in your letter dated 5 June 2009.

The amendment entails a repeat data collection exercise of research conducted during 2007 and 2008. We note that only the quantitative aspect of the study will be repeated.

We further note that Dr David Coetzee will be included as an investigator on the replication study.

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

**Please quote the REC, REF in all your correspondence.**

Yours sincerely

**PROFESSOR M BLOCKMAN**  
**CHAIRPERSON, HSF HUMAN ETHICS**

S Thomas

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## Appendix 7 – Chapters 6 and 7 (Patient interview guide and informed consent)

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**An evaluation of different approaches to the initiation of antiretroviral therapy during pregnancy among HIV-infected women in Cape Town**

**INFORMED CONSENT FOR PARTICIPATION IN IN-DEPTH INTERVIEWS – CLINIC ATTENDEES – ENGLISH (ALSO AVAILABLE IN ISIXHOSA)**

We are from the School of Public Health and Family Medicine at the University of Cape Town. We are collecting information about health services for pregnant women, specifically the different experiences pregnant women have regarding antenatal care and antiretroviral services. We are interested in finding out what potential factors make it difficult for these women to attend these clinics, and their perceptions regarding the services, as well as how they believe the services could be improved.

This research is part of a study involving the evaluation of different approaches to the initiation of antiretroviral therapy among HIV-infected women during pregnancy in Cape Town. The research is being paid for by the Doris Duke Charitable Foundation. Your participation in this study is voluntary. Whether or not you decide to participate in this study will not affect your right to, or experience of treatment and care at this or any other clinic now or in the future.

**IF YOU DECIDE TO PARTICIPATE:**

- This will involve you answering and discussing questions put to you by the interviewer, for about 30 minutes.
- All of the information that you provide will be kept completely private and confidential and will only be viewed and used by the researchers on this project. Health care providers and other attendees at this clinic will not see this information.
- We will record the information using a digital audio- recorder so that we have an accurate record of what you have said, but we will never record your name or anything that could be used to identify you.
- You have the right to decide not to participate in the study, to refuse to answer any specific questions, or to end the interview at any time without penalty.
- The information you provide may help us to improve health services for pregnant women living with HIV in the Cape Town area.

Your participation in this study will not involve any risks to you.

If there is anything that is unclear or if you need further information, please ask us and we will provide it. Do you have any questions?



INTERVIEW #

Pregnant

Post

An evaluation of different approaches to the initiation of antiretroviral therapy during pregnancy among HIV-infected women in Cape Town

SOCIO-DEMOGRAPHIC INFORMATION FOR PATIENTS - PREGNANT/POSTPARTUM

Interview Date  Interviewer initials

Interview Site

Antenatal service used

PATIENT INFORMATION

Age  years

Patient recall of CD4 count

Number of children alive

Number of previous pregnancies

Details of previous pregnancies/births  Delivery site

Any complications

FOLDER INFORMATION

Folder number

Date of HIV test

CD4 count

ART initiated

If pregnant

If postpartum

Date of first booking

Delivery date of last child

Gestational age  weeks

ART REFERRAL

Referral made

ART service used

Date of referral

If pregnant

Gestational age  weeks

QUALITY OF CARE-RELATED QUESTIONS

How long did it take you to get to the clinic from your house today?  
What mode of transport do you use to get to the clinic today?  
How much does it cost you to get this clinic?

**An evaluation of different approaches to the initiation of antiretroviral therapy during pregnancy among HIV-infected women in Cape Town**

**INTERVIEW GUIDE – pregnant women**

**1 GENERAL INFORMATION ABOUT PARTICIPANT**

- 1.1 Could you tell me about yourself? How are you feeling today?
- 1.2 Where do you live at present?
  - 1.2.1 Can you tell me about where you live, and a little about your family life?
  - 1.2.1 Have you always lived here? If not, what made you move to the area?
  - 1.2.3 Tell me who do you live with, how are you related to them, to whom are you dependent?
  - 1.2.4 How many children do you have? (How old is the youngest one?)
- 1.3 How far away is the clinic from where you are living?
  - 1.3.1 How did you get to the clinic today?
  - 1.3.2 Can you tell me what brought you to the clinic today?
  - 1.3.3 Who did you come to see at the clinic today?
  - 1.3.4 When you arrived, what did you have to do in order to see that person, and how long did it take? (Find out if respondent waited a long time or not, pick up any negative responses)
  - 1.3.5 What would you be doing if you were not here today?

**2 KNOWLEDGE AND PERCEPTIONS OF HIV**

- 2.1 I would like to ask you about your understandings and feelings around HIV.
  - 2.1.1 How would you describe or explain HIV? What does it mean to you to be HIV+?
- 2.2 How did you find out that you were HIV+, can you recall when and where you first tested for HIV?  
(Find out exactly when – independent of pregnancy/before or during latest pregnancy/at antenatal service first booking?)
  - 2.2.1 Can you describe your reasons for deciding to test?
  - 2.2.2 If tested in pregnancy: Would you say that the fact that you were pregnant changed your view on HIV testing?
  - 2.2.3 (If yes, how did being pregnant change your view? What were your reasons for testing?)
  - 2.2.4 (If no, why do you think you would not have tested?)
  - 2.2.5 If tested in pregnancy: Would you have tested for HIV if you were not pregnant and had not come to the antenatal clinic?

**3 EXPERIENCE OF VCT AND HIV TEST**

- 3.1 Did you receive pre-test counselling/VCT?  
If yes, what was the counselling like – what did the counselor say to you?
- 3.1.1 What sort of things did the counselor mention to you about being pregnant and getting a positive result before you tested?
- 3.1.2 Did the counselor mention any important things associated with pregnancy and HIV?)
- 3.1.3 Who gave you your test, and who gave you your result?
- 3.1.4 How did you get your result? Was it in private, or were there other people who were present?
- 3.1.5 How did the health care provider who gave you your result respond to your test result?

**4 UNDERSTANDING AROUND HIV DIAGNOSIS**

- 4.1 Tell me about how it felt when you got your HIV test result.
- 4.1.1 If tested in pregnancy: When you got your HIV result, how did it make you feel about being pregnant?
- 4.1.2 If tested outside of pregnancy: When you got your HIV result, how did you feel?
- 4.1.3 When you are diagnosed with HIV, you are told your CD4 count.)
- 4.2 What do you understand by the CD4 count?
- 4.2.1 What was it?
- 4.2.2 Did the health care provider give you your CD4 count?

**5 EXPERIENCE OF POST-TEST COUNSELING**

- 5.1 When you got your result, what information were you given about managing HIV and pregnancy together?
- 5.2 What did they say about treatment and management of HIV, especially during early pregnancy?
- 5.3 Do you think it is different being pregnant with HIV, than to just being pregnant?
- 5.4 What sort of questions did you have for the health care provider after you got your result?
- 5.4.1 Did you feel comfortable asking the health care provider your questions?
- 5.4.2 Were the questions you had answered to your satisfaction?

**6 PERCEPTIONS ABOUT BEING PREGNANT AND HIV+**

- 6.1 I would like to ask you about your response to being pregnant as well as being HIV+.

- 6.2 How do pregnant women cope with being HIV+?
- 6.3 What is difficult for you about being pregnant and HIV+?
- 6.4 What are the issues you have to consider as an HIV+ woman when you are pregnant?
- 6.5 Do you see your needs as a pregnant woman with HIV as different from the needs of other (negative) women who are accessing antenatal care? (If yes, how?)
- 6.6 What do most people think about HIV+ women being pregnant and having children?
- 6.7 What are the reasons a pregnant woman may decide to test for HIV?
- 6.8 Do you think that all pregnant women should be tested for HIV? (If yes, why? If no, why not?)
- 6.9 How do you think women would benefit or not benefit from testing for HIV when they are pregnant?

## 7 DISCLOSURE AND FAMILY-BASED CARE

- 7.1 Pregnant women may find it difficult to talk to their partners/the father of the child about their status. How do you think women feel about disclosing their status in a relationship?
- 7.2 Have you disclosed to any person about your status?
- 7.3 What would make it easier to tell the father?)
  - 7.3.1 If disclosed to partner/father: how has your partner/the father of your child responded to your HIV status?
  - 7.3.2 If not disclosed to partner/father: what are the reasons for not telling your partner/the father of your baby?
- 7.4 What sort of role do you think a father plays regarding your health and the health of your baby?
  - 7.4.1 Do you think your partner would be prepared to be involved in ARV treatment programmes with you?
  - 7.4.2 If no, why not?
  - 7.4.3 If yes, why – explain

## 8 PMTCT

- 8.1 Do you know of anything a woman can do to prevent her unborn baby from getting HIV?
- 8.2 What words do you use to describe it (prompt PMTCT, if necessary)

- 8.2.1 How does PMTCT work?
- 8.2.2 Who told you about PMTCT, and what things did they say about it?
- 8.3 Who do you think PMTCT benefits more – your child or yourself?
  - 8.3.1 What are these benefits?
- 9 REFERRAL AND ART**
- 9.1 Tell me about your experience of starting on ART.
  - 9.1.1 How many weeks pregnant were you when you started ART?
- 9.2 If woman has made the referral: What was it like to make the referral? Tell me the story of how you went from the antenatal clinic to starting on ART.
  - 9.2.1 What made the referral hard, or what made it easy?  
(Probe transport issues, time, location of clinic, quality of care at the clinic, attitude of staff)
- 9.3 What was it like to start ART while being pregnant?
- 9.4 What sort of side effects did you have to worry about or not have to worry about during your pregnancy, while being on ART?
- 9.5 In your view, what do other people think about pregnant women who take ARVs?
- 9.6 When you think of other people who are on ART and are not pregnant, how do you think being on ART differs for you?
- 10 RETENTION IN CARE**
- 10.1 When you have had your baby, how do you think it will be to care for yourself and your child's needs?
  - 10.1.1 How will you manage feeding your child?  
(Explore ideas/knowledge about breast feeding, formula feeding, mixed feeding etc)
- 10.2 Would you feel differently about motherhood if you were not HIV+?  
(If yes, how)
  - 10.2.1 How do you think other HIV+ mothers in your situation feel?
- 10.3 Tell me what it is like for you to take treatment regularly – at the moment what are the most challenging aspects of being on ART for you? (Explore amount of time off work, clinic opening hours and days, waiting times, financial burden of managing HIV – transport costs, wages lost etc).
- 10.4 Do you think that being a mother will affect your treatment plan?

(Explore ability to get to clinic, pill-taking regimens, potential for feeling train with a new child). Explore idea of ART being perceived as a “chronic” therapy.

- 10.5 What do you think would happen if you stopped taking ART?
- 10.6 What leads some mothers to not continue with their treatment plan?
- 11 QUALITY OF CARE ISSUES – ANTENATAL CARE**
- 11.1 I want to ask you about your experience of antenatal services during your pregnancy.
- 11.2 For what reasons do pregnant women book for antenatal care?  
(Check if early or late booker)
- 11.3 Why did you book for antenatal care when you did?
- 11.4 Where do you plan to give birth? What do you think will happen if you have complications?
- 11.5 What do you imagine your birth experience to be? Do you think anyone you have dealt with in the antenatal services has treated you differently because you are HIV+? (Why, or how?)
- 11.6 What do women need in order to make their birth experiences better?  
Explore improvements regarding facility, staff support, pain management
- 12 QUALITY OF CARE ISSUES – HIV TEST, ART REFERRAL AND TREATMENT SERVICE**
- 12.1 I want to ask you about your experiences relating to your HIV care. How would you describe your treatment by the staff involved in your HIV test at the antenatal clinic?
  - 12.1.1 What sort of help and care did they give you?
  - 12.1.2 Do you feel they had any attitudes towards you and your pregnancy which they made clear? (Did they comment on the fact that you were HIV+ and a mother? What did they say?)
- 12.2 Where do you think the best places are to get ARVs?
  - 12.2.1 Do you think that women have issues with privacy when they go to get their ARVs?
  - 12.2.2 What could be done to make sure a pregnant woman gets onto ART quickly?
  - 12.2.3 How long did it take you to start ART?
  - 12.2.4 Did anyone tell you why it is important for you to start ART quickly when you are pregnant?
- 12.3 If you could change for the better the way in which the health service provides ARVs, what would you do?

12.3.1 In what ways do you think a health service could improve the way they offer mothers and children access to ART and other health care needs?

Do you have any other comments or suggestions you would like to add?

Thank you for your time

**An evaluation of different approaches to the initiation of antiretroviral therapy during pregnancy among HIV-infected women in Cape Town**

**INTERVIEW GUIDE – postpartum women**

**1 GENERAL INFORMATION ABOUT PARTICIPANT**

- 1.1 Could you tell me about yourself? How are you feeling today?
- 1.2 Where do you live at present?
  - 1.2.1 Can you tell me about where you live, and a little about your family life?
  - 1.2.2 Have you always lived here? If not, what made you move to the area?
  - 1.2.3 Tell me who do you live with, how are you related to them, to whom are you dependent?
  - 1.2.4 How many children do you have? (How old is the youngest one?)
- 1.3 How far away is the clinic from where you are living?
  - 1.3.1 How did you get to the clinic today?
  - 1.3.2 Can you tell me what brought you to the clinic today?
  - 1.3.3 Who did you come to see at the clinic today?
  - 1.3.4 When you arrived, what did you have to do in order to see that person, and how long did it take? (Find out if respondent waited a long time or not, pick up any negative responses)
  - 1.3.5 What would you be doing if you were not here today?

**2 KNOWLEDGE AND PERCEPTIONS OF HIV**

- 2.1 I would like to ask you about your understandings and feelings around HIV.
  - 2.1.1 How would you describe or explain HIV? What does it mean to you to be HIV+?
- 2.2 How did you find out that you were HIV+, can you recall when and where you first tested for HIV? (Find out exactly when – independent of pregnancy/before or during latest pregnancy/at antenatal service first booking?)
  - 2.2.1 Can you describe your reasons for deciding to test?
  - 2.2.2 If tested in pregnancy: Would you say that the fact that you were pregnant changed your view on HIV testing?
  - 2.2.3 (If yes, how did being pregnant change your view? What were your reasons for testing?)
  - 2.2.4 (If no, why do you think you would not have tested?)
  - 2.2.5 If tested in pregnancy: Would you have tested for HIV if you were not pregnant and had not come to the antenatal clinic?

**3 EXPERIENCE OF VCT AND HIV TEST**

- 3.1 Did you receive pre-test counselling/VCT?

- 3.1.1 If yes, what was the counselling like – what did the counselor say to you about being pregnant and finding out you are HIV-positive?
- 3.1.2 Did the counselor mention any important things associated with pregnancy and HIV?
- 3.1.3 Who gave you your test, and who gave you your result?
- 3.1.4 How did you get your result? Was it in private, or were there other people who were present?
- 3.1.5 How did the health care provider who gave you your result respond to your test result?

#### 4 UNDERSTANDING AROUND HIV DIAGNOSIS

- 4.1 Tell me about how it felt when you got your HIV test result.
  - 4.1.1 If tested in pregnancy: When you got your HIV result, how did it make you feel about being pregnant?
  - 4.1.2 If tested outside of pregnancy: When you got your HIV result, how did you feel?
  - 4.1.3 When you are diagnosed with HIV, you are told your CD4 count.
- 4.2 What do you understand by the CD4 count?
  - 4.2.1 What was yours?
  - 4.2.2 Did the health care provider give you your CD4 count?

#### 5 EXPERIENCE OF POST-TEST COUNSELING

- 5.1 When you got your result, what information were you given about managing HIV and pregnancy together?
- 5.2 What did they say about treatment and management of HIV, especially during early pregnancy?
- 5.3 Do you think it is different being pregnant with HIV, than to just being pregnant?
- 5.4 What sort of questions did you have for the health care provider after you got your result?
  - 5.4.1 Did you feel comfortable asking the health care provider your questions?
  - 5.4.2 Were the questions you had answered to your satisfaction?

#### 6 PERCEPTIONS ABOUT BEING PREGNANT AND HIV+

- 6.1 I would like to ask you about your response to being pregnant as well as being HIV+.
- 6.2 How do pregnant women cope with being HIV+?
- 6.3 What was difficult for you about being pregnant and HIV+?

- 6.4 What were the issues you had to consider as an HIV+ woman when you were pregnant?
- 6.5 Did you see your needs as a pregnant woman with HIV as different from the needs of other (negative) women who were accessing antenatal care? (If yes, how?)
- 6.6 What do most people think about HIV+ women being pregnant and having children?
- 6.7 What are the reasons a pregnant woman may decide to test for HIV?
- 6.8 Do you think that all pregnant women should be tested for HIV? (If yes, why? If no, why not?)
- 6.9 How do you think women would benefit or not benefit from testing for HIV when they are pregnant?
- 7 **DISCLOSURE AND FAMILY-BASED CARE**
- 7.1 Pregnant women may find it difficult to talk to their partners/the father of the child about their status. How do you think women feel about disclosing their status in a relationship?
- 7.2 Have you disclosed/were you able to disclose/how easy was it to disclose your status to the father of your child? (What would make it easier to tell the father?)
- 7.3 If yes, how has your partner/the father of your baby responded to your HIV status?
  - 7.3.1 If no, what are the reasons for not telling your partner/the father of your baby?
- 7.4 What sort of role do you think a father plays regarding your health and the health of your baby?
  - 7.4.1 Do you think your partner would be prepared to be involved in ARV treatment programmes with you?
  - 7.4.2 (If no, why not?)
  - 7.4.3 (If yes, why – explain)
- 8 **PMTCT**
- 8.1 Do you know of anything a woman can do to prevent her unborn baby from getting HIV?
- 8.2 What words do you use to describe it (prompt PMTCT, if necessary)
  - 8.2.1 How does PMTCT work?

- 8.2.2 Who told you about PMTCT, and what things did they say about it? (for example, how does it work?)
- 8.3 Who do you think PMTCT benefits more – your child or yourself?
  - 8.3.1 What are these benefits?
- 9 REFERRAL AND ART**
- 9.1 Tell me about your experience of starting on ART.
  - 9.1.1 How many weeks of treatment did you get before you gave birth?
- 9.2 What was it like to make the referral? Tell me the story of how you went from the antenatal clinic to starting on ART.
  - 9.2.1 What made the referral hard, or what made it easy?  
(Probe transport issues, time, location of clinic, quality of care at the clinic, attitude of staff)
- 9.3 What was it like to start ART while being pregnant?
- 9.4 What sort of side effects did you have to worry about or not have to worry about during your pregnancy, while being on ART?
- 9.5 Stigma – in your view, what do other people think about pregnant women who take ARVs?
- 9.6 When you think of other people who are on ART and are not pregnant, how do you think being on ART differs for you?
- 10 POSTPARTUM ISSUES AND RETENTION IN CARE**
- 10.1 Now that you have had your baby, how have you found managing your child's own health needs?
  - 10.1.1 How have you managed feeding your child? (Explore whether breast feeding, formula feeding, mixed feeding etc)
- 10.2 Would you feel differently about motherhood if you were not HIV+?  
(If yes, how)
  - 10.2.1 How do you think other HIV+ mothers in your situation feel?
- 10.3 Tell me what it is like for you to take treatment regularly – at the moment what are the most challenging aspects of being on ART for you?  
(Explore amount of time off work, clinic opening hours and days, waiting times, financial burden of managing HIV – transport costs, wages lost etc).
- 10.4 How does being a mother of a new baby affect your treatment plan?

(Explore ability to get to clinic, pill-taking regimens, feeling strain of new child)

(Explore idea of ART being perceived as a “chronic” therapy)

10.5 What do you think would happen if you stopped taking ART?

10.6 What leads some mothers to not continue with their treatment plan?

10.7 What could lead you to not take your treatment?

#### **11 QUALITY OF CARE ISSUES – ANTENATAL CARE**

11.1 I want to ask you about your experience of antenatal services during your pregnancy.

11.2 For what reasons do pregnant women book for antenatal care?  
(Check if early or late booker)

11.3 Why did you book for antenatal care when you did?

11.4 Where did you give birth? Was it at an MOU, or a secondary hospital or other?

11.5 Can you tell me about your birth experience?

11.5.1 What was good, what was bad, particularly in terms of the quality of service you received?

11.5.2 How did you find the staff treated you?

11.5.3 Do you think the labour ward staff, or any staff who helped you in labour, treated you differently because you were HIV+?

11.6 What do women need in order to make their birth experiences better?  
(Explore improvements regarding facility, staff support, pain management)

#### **12 QUALITY OF CARE ISSUES – HIV TEST, ART REFERRAL AND TREATMENT SERVICE**

12.1 I want to ask you about your experiences relating to your HIV care. How would you describe your treatment by the staff involved in your HIV test at the antenatal clinic?

12.1.1 What sort of help and care did they give you?

12.1.2 Do you feel they had any attitudes towards you and your pregnancy which they made clear? (Did they comment on the fact that you were HIV+ and a mother? What did they say?)

12.2 Where do you think the best places are to get ARVs?

- 12.2.1 Do you think that women have issues with privacy when they go to get their ARVs?
- 12.2.2 What could be done to make sure a pregnant woman gets onto ART quickly?
- 12.2.3 How long did it take you to start ART?
- 12.2.4 Did anyone tell you why it was important for you to start ART quickly when you were pregnant?
- 12.3 If you could change for the better the way in which the health service provides ARVs, what would you do?
  - 12.3.1 In what ways do you think a health service could improve the way they offer mothers and children access to ART and other health care needs?
- 12.4 How many clinics do you have to attend between yourself and your baby?
  - 12.4.1 How does managing your baby's clinic visits, as well as your own visits, impact on your every day life?

Do you have any other comments or suggestions you would like to add?

Thank you for your time.

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## Appendix 8 – Chapters 6 and 7 (Provider interview guide and informed consent)

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**An evaluation of different approaches to the initiation of antiretroviral therapy during pregnancy among HIV-infected women in Cape Town**  
**Health Care provider – Informed consent**

I am from the School of Public Health and Family Medicine at the University of Cape Town. I am collecting information about health services for pregnant women, specifically the different experiences pregnant women have regarding antenatal care and antiretroviral services. This research is part of a study involving the evaluation of different approaches to the initiation of antiretroviral therapy among HIV-infected women during pregnancy in Cape Town. The project, which is a joint initiative between UCT and PGWC, is being paid for by the Doris Duke Charitable Foundation.

Your participation in this study is voluntary. Whether or not you decide to participate in this study will not affect your position at this or any other clinic now or in the future.

**If you decide to participate:**

- This will involve you answering and discussing questions put to you by the interviewer, for about 45 minutes.
- All of the information that you provide will be kept completely private and confidential and will only be viewed and used by the researchers on this project. Other health care providers at this clinic will not see this information.
- I will record the information using a digital audio- recorder so that I have an accurate record of what you have said, but I will never record your name or anything that could be used to identify you.
- You have the right to decide not to participate in the study, to refuse to answer any specific questions, or to end the interview at any time without penalty.
- The information you provide may help us to improve health services for pregnant women living with HIV in the Cape Town area.

Your participation in this study will not involve any risks to you.

If there is anything that is unclear or if you need further information, please ask me and I will provide it.

**Participant volunteer declaration**

I have understood that the purpose of the study is to investigate health services for pregnant HIV-infected women, and to understand specifically their experiences of receiving antenatal care and antiretroviral therapy in order to inform health care improvement.

I have read the above information, or it has been read to me. I have had the opportunity to ask questions about it, and any questions that I have asked, have been answered to my satisfaction. I consent voluntarily to participate as a subject in this study and understand that I have the right to withdraw from the study at any time without in any way affecting my position at this or any other clinic now or in the future.

Please indicate your consent with your signature, or a tick if you would prefer.

---

Signature of participant volunteer [tick optional] Date

---

Signature of Investigator

Date

Thank you.



Contact details:

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Infectious Disease Epidemiology Unit

School of Public Health and Family Medicine

University of Cape Town

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**1. Service delivery approaches to ART initiation for pregnant women**

AIM:

- To get provider to describe service delivery approaches specific to their clinic setting along the lines of the PMTCT cascade
- To elaborate upon approaches in terms of patient care and utilization of staff resources

1. Can you tell me about the kind of work you do here?

Probe:

- In terms of pregnant clients, about how many do you see per day/ week?

If antenatal service provider:

- explore numbers of new bookings, follow ups, gestational age
- explore experience of late bookers and reasons women give for booking late.

- If ARV service provider:

- explore number of pregnant women seen as new referrals per week
- Average gestational age of pregnant women who refer
- What proportion of pregnant women arrive quite late in pregnancy?  
(Do you see a lot of women who arrive post 30 weeks?)
- Proportion of women seen as post partum referrals
- How do pregnant women get to you? (source clinics, process of referral)

- Where do most of your pregnant women come from? (ie catchment area vs actual area of residence, explore transportation issues, or other perceived reasons for clinic choice)

2. Can you describe for me how the service process works for a pregnant woman who comes to this facility?

(If antenatal: What are the steps she goes through from the first booking?)

(If ARV service: What happens when she arrives as a referral?)

(If secondary/ tertiary: explore conditions of referral for such care)

Present and explain the cascade, bearing in mind where the service provider slots in and the description given above.

3. I would like to hear about your experiences and opinions of service delivery in terms of the steps of the PMTCT cascade.
- Probe: (probe for good and bad aspects of each)
- Booking for pregnancy – waiting times, treatment by staff, accuracy and usefulness of booking register and folder information
  - VCT – the role of the counselor, privacy, confidentiality, position of testing room, women tested in batches/individually, getting the result.
  - Information systems – processing of test results (CD4 counts etc), waiting times, the recording of patient information and its availability across services (folder, patient cards, data bases)
  - Referral process – who is responsible for the referral, the use (effectiveness) of referral letters, feedback regarding successful or unsuccessful referral, communication between services and individual providers.
  - The role of NGOs in the VCT, referral and support process
  - ARV work up – issues specific to pregnant women (in conjunction with those who present late – explore how this is handled by both antenatal and HIV service providers).
  - Post natal care and follow up, infant testing and follow up and retention in care

Issues influencing ability and comfort in service provision

4. As a service provider what influences your ability and comfort in providing a service to pregnant women?
- Probe:
- What kinds of obstacles make it difficult to manage a pregnant woman who has come for referral, or a woman who refers post partum?
  - How well do you think your time as a professional is used in the job that you are doing?
  - How much time is spent on work unrelated to immediate needs of patients?
  - What sort of operational changes could be made to make your job “easier”?

Role players in treatment and care: explore the role of the midwife, the HIV counselor, patient advocate the HIV doctor, the HIV nurse, the obstetrician, staff involved in post partum care, pharmacists

5. What are your ideas on the roles of different service providers in the treatment and care of pregnant women with HIV?

Probe:

- What is the nature of the multi-disciplinary team?
- What are the benefits and pitfalls of having a multi-level/disciplinary team?
- Is there communication between providers?
- Could/should anything be done to integrate these roles better?
- What effect do you think this has on referrals?

Client perspectives

6. From a client's perspective, what constraints and barriers do you think she faces in terms of accessing and using these health services, *particularly in terms of the referral process?*

Probe:

- Failure to establish connection between antenatal and ARV facilities
- Waiting times, clinic hours
- Socio-economic
- Personal/domestic/social problems – disclosure, child care, stigma, residential area

## 2. Current models of care for HIV+ pregnant women

Explore understandings around PMTCT

7. What do you think a pregnant woman with HIV needs?

8. What do you understand to be the underlying purpose of a PMTCT programme?

Probe

- Provider's perception of the primary endpoint (maternal or child health or both)

9. What is your opinion of the different ARV regimens for pregnant women with HIV?

- Try to elicit ideas about mono therapy vs triple therapy, what are the obstacles; in reality, who gets what (women with low cd4 counts on AZT only etc)?
10. How do you think PMTCT services relate to ART services at present?
- Probe
- Are there close connections between these services?
  - How do you think these services should relate to each other, ideally?
  - What steps or interventions are needed to support this?
11. What other interventions do you think would help HIV-positive pregnant women?
- Probe
- The role of the caesarian in the management of HIV-positive patients – in light of non-advanced vs advanced disease
  - Better access to secondary/tertiary care
  - What steps are followed by health care workers in this facility to provide emotional support, inform about follow up care, and educate women about PMTCT?

Explore experience around referral for ART and fast - tracking

12. I'd like to know what is currently done about women who present for the first time in pregnancy, with advanced-stage disease? How do they fit into the PMTCT model?
- Probe
- How are HIV-infected pregnant women who require ART *initiation* managed in this facility?
  - What is the average length of the work up and how does this impact on women who refer late in pregnancy?
  - Are there any special steps in place to 'fast track' pregnant women onto ART?
  - How does this work?
  - How could fast tracking be improved? (Minimising time to treatment)
  - Are there any short comings in this service that you are aware of?
  - Do you think the length of work up has any bearing on retention in care for pregnant women, or are there other factors which may influence retention in care?
13. Given the above, what do you think the focus of care for ART-eligible pregnant woman should be?

14. What are the procedures for the management of HIV-infected women already on ART who *become* pregnant? (ie after initiating ART earlier)
- How does this work?
  -

**For ART Service Providers: ART delivery**

15. I'd like you to tell me about your experiences as a provider in delivering ART to pregnant women who are ART-eligible.
- Probe
- In your experience, what do you think makes ART delivery easy/feasible?
  - In your opinion, what are the hurdles to effective ART delivery?
  - What do you think is the best way to provide ART to pregnant women who are eligible?

**For antenatal service providers: Secondary/tertiary care**

16. How are pregnancy complications managed in HIV-infected women?
- Probe:
- Could you describe any experiences you have had regarding referral of women to secondary or tertiary level obstetric care.
  - Are there any special steps in place to ensure adequate obstetric care?
17. Where are the gaps/pitfalls in the management of women who present at secondary/tertiary level hospitals, and how do you think things could be improved in terms of case management of these women? (Access to meds, access to patient history, role of folders, access to caesarian sections, better management of complications etc)

**3. Post-partum issues and retention in care**

**Post-partum issues**

18. What are the challenges facing specifically postpartum HIV-positive mothers?
- Probe:
- What kinds of barriers prevent women from being retained in ARV care once they have given birth?
  - What health service changes could be made to improve retention in care?

19. What is your opinion on infant feeding?
20. What are the factors which influence an HIV-positive mother's choices on infant feeding?  
Probe
  - Explore provider's views on the logistics around breast feeding, formula feeding etc

|                   |
|-------------------|
| Retention in care |
|-------------------|

21. In your mind, what obstacles prevent women from continuing in care?
22. What do you think works, or doesn't work in terms of ensuring retention in care during pregnancy?  
Probe
  - For what kinds of reasons are women lost to follow up?
  - What could be done to keep women in care?

**4. Conclusions, suggestions, recommendations**

23. What aspects would you add to health services policy or health system design to improve maternal health and ART treatment services?  
Probe
  - If this clinic was given R1m, what would you spend it on to make a difference?
  - If this clinic was given R5000, what would you spend it on to make a difference?