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**The effectiveness of PMTCT programmes through the measurement  
of NVP coverage in populations of women delivering in designated  
areas in the Western Cape region of South Africa**

**By**

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## Declaration

I, **Hanani Tabana**, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

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## Abbreviations

3TC	lamivudine
AIDS	Acquired Immune Deficiency Syndrome
ARV	Antiretroviral
ANC	Antenatal care
BF	Breast Feeding
CD4	The absolute CD4 cell count measures the number of CD4-T-cells in each cubic ml of blood
CDC	Centres of Disease Control and Prevention, Atlanta, United States of America
EBF	Exclusive Breastfeeding
EDTA	Ethylenediaminetetraacetic acid
HAART	Highly Active Anti-Retroviral Therapy
HIV	Human Immunodeficiency Virus
MTCT	Mother to Child Transmission of HIV
MOU	Midwife-run Obstetric Units
NIH	National Institutes of Health
NVP	Nevirapine
SDNVP	Single dose-Nevirapine
NSP	National Strategic Plan
NRTIs	nucleoside analogue reverse transcriptase inhibitors
NNRTI	non-nucleoside reverse inhibitor
PACTG	Paediatric AIDS Clinical Trials Group

PCR	Polymerase Chain Reaction
PMTCT	Prevention of Mother to Child Transmission of HIV
RCT	Randomised Control Trial
RNA	Ribonucleic Acid
STD	Sexually Transmitted Diseases
UCT	University of Cape Town
UNAIDS	The Joint United Nations Programme on HIV/AIDS
UN	United Nations
USA	United States of America
WHO	World Health Organization
ZDV	Zidovudine

## **Definitions**

### **Nevirapine (NVP) uptake**

The proportion of HIV-positive women in the population who ingested single-dose Nevirapine (SD-NVP).

### **NVP coverage**

NVP coverage was defined as the proportion of HIV-infected mothers and HIV-exposed infant pairs that received both the maternal and infant SD-NVP doses where the maternal NVP was indicated by high performance liquid chromatography (HPLC) of cord blood collected at delivery while the infant dosing was indicated in the clinic records.

## **Abstract**

### **Objective**

The objective was to assess the uptake and coverage of SD-NVP to prevent mother-to-child transmission of HIV in women of unknown HIV status presenting in labour at a sample of delivery sites in the Western Cape. This monitoring activity also accurately measures the prevalence of HIV among pregnant women and ascertains the proportion of HIV exposed infants delivered to these mothers, who received NVP prophylaxis to prevent MTCT.

### **Design**

Anonymous, unlinked specimens of cord blood from discarded placentas were tested for HIV antibodies to determine population-level information on HIV infection and NVP coverage among all women delivering in the facilities. Uptake was measured by counting the number of women who were recorded to have accepted NVP when offered while coverage was measured by using the cord blood NVP assay.

### **Results**

A total of 2198 (96.5%) cord blood specimens were collected from women at delivery. From these, 1876 (85.4%) women received pre-test counselling. Of those who were counselled, 1851 (84.2%) were tested for HIV and 365 (19.3%) tested positive. Amongst those who were infected, 229 (62.7%) received SD-NVP and but only 57.8% adhered to SD-NVP according to the cord blood. Of the infants born to HIV-infected mothers, 311 (85.2%) were recorded as

having received SD-NVP. There was no significant difference in SD-NVP uptake between the two facilities. The overall NVP coverage (mother and infant doses) was 55.3%.

### **Conclusions**

The NVP coverage of 55.3% is poor. In order for PMTCT services to be successful, each mother-infant pair should go through a rigorous cascade of events that include HIV testing, receipt of results, diagnosis and drug adherence. The attrition cascade in this study was described using a new cord blood surveillance methodology. Coverage fails for a number of reasons and interventions are likely to differ from one facility to another. Appropriate interventions should be introduced to reduce the transmission to infants.

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## CHAPTER 1:

### 1 INTRODUCTION

AIDS is an acronym for Acquired Immune Deficiency Syndrome and is the end stage disease manifestation of an infection with the human immunodeficiency virus (HIV) as a result of the body's immune system being compromised. HIV is a retrovirus that infects cells of the immune system, destroying or impairing their function. As the infection progresses, the immune system therefore becomes weaker and the person becomes more susceptible to additional infections.

Although HIV has been isolated from most body fluids such as blood, cerebrospinal fluid, saliva, semen, vaginal secretions and breast milk, it is usually transmitted through blood, vaginal fluid and semen. Most individuals are infected with HIV through sexual contact, *in utero*, during delivery, during breastfeeding and through blood and blood products, via transfusions or needles contaminated with HIV-infected blood.

#### 1.1 *The virus-HIV*

HIV belongs to an unusual class of viruses called *retroviruses*. The family of retroviruses (Retroviridae) is defined by the presence of the unique enzyme, reverse transcriptase which

facilitates the production of a DNA copy from an RNA genome. There are two strains of HIV: HIV-1, which is responsible for the worldwide pandemic and HIV-2. The geographic distribution of HIV-2 virus is confined to West African countries as well as the former Portuguese colonies of Angola and Mozambique (Schoub, 1994). Both strains affect the immune system in a similar way and both have similar mechanisms of transmission. HIV-2 nonetheless, appears to be less virulent than HIV-1 and is not transmitted as easily as HIV-1 especially from mother to child (Hubbly J, 2002).

## **1.2 History of AIDS**

The HIV/AIDS epidemic became apparent in 1981 when doctors in three different hospitals in Los Angeles noticed previously rare diseases in five young men under their care. All five were diagnosed with *pneumocystis carinii pneumonia (IP)*. They were also found to have been infected with cytomegalovirus (CMV), a virus common in immunosuppressed patients. The five men were all sexually active homosexuals. It was only in 1983 that the syndrome AIDS was first defined and HIV was identified as the cause of AIDS and the first HIV antibody test became available (Schoub, 1994).

In 1983, there was evidence of a heterosexual epidemic emerging on the African continent. The epidemic has since increased dramatically in the sub-Saharan region of Africa and particularly, southern Africa. In 1987 the first therapy for AIDS called Zidovudine was approved for use in the USA. The first treatment regimen to reduce mother to child transmission was developed in 1992 (UNAIDS, 2006).

### 1.3 ***Epidemiology of HIV/AIDS***

HIV/AIDS, however, still remains the most prevalent epidemic worldwide despite efforts to improve access to antiretroviral treatment in most countries. In 2005 about 3.1 million people died of HIV/AIDS. More than half a million of that number were children. At the end of 2006, 2.3 million children under the age of 15 were estimated to be living with HIV with 15 million already orphaned due to HIV/AIDS. Of the 2.3 million new infections, 530 000 were children, with 90% being infected through mother-to-child transmission (Richard *et al.*, 2007).

In 2008, there were 2.7 million (95% CI: 2.4 million-3.0 million) incident cases of HIV worldwide. Young people between 15-24 years accounted for half of all new infections. In sub-Saharan Africa, the incident cases were estimated at 1.9 million (95% CI: 1.6 million–2.2 million) people. The estimated number of people living with HIV worldwide in 2008 was 33.4 million (95% CI: 31.1 million-35.8 million). The prevalence of people living with HIV has increased as a result of the ongoing number of new infections each year and the benefit of more widely available antiretroviral therapy (UNAIDS/WHO, 2009). The estimated number of deaths due to AIDS in 2008 was 2.0 million (95% CI: 1.7-2.4million) worldwide, of which 76% occurred in sub-Saharan Africa (UNAIDS update, 2009).

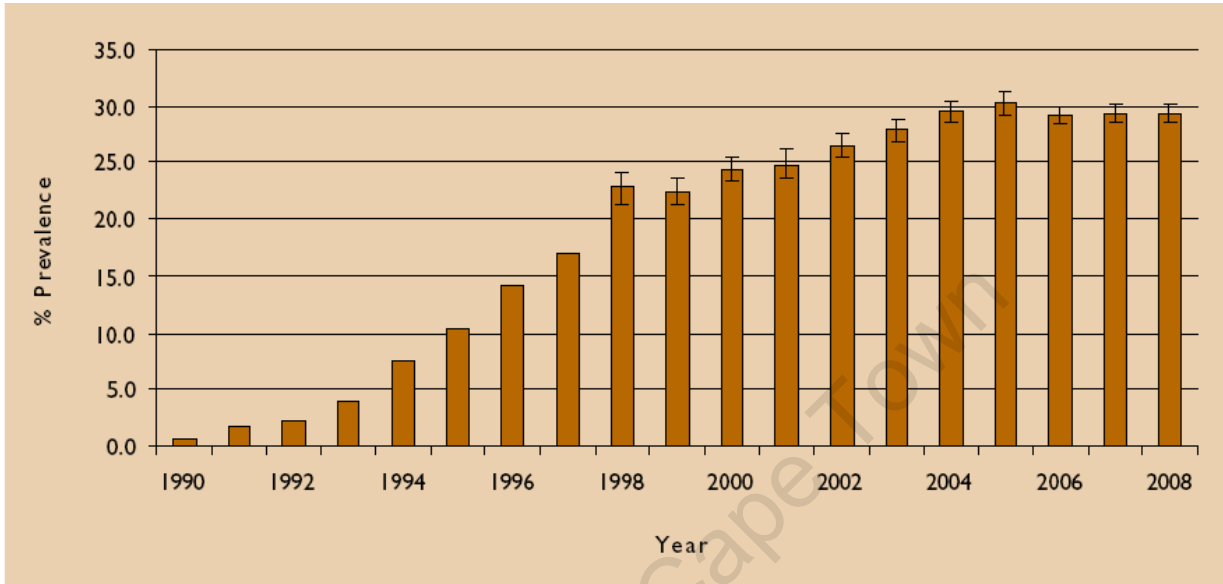
Sub-Saharan Africa still remains the area most affected by the epidemic with approximately 22.4 million people living with HIV and yet the region only makes up just 10% of the world's

population. In 2008, an estimated 1.9 million people in sub-Saharan Africa were newly infected with HIV with 61% being women.

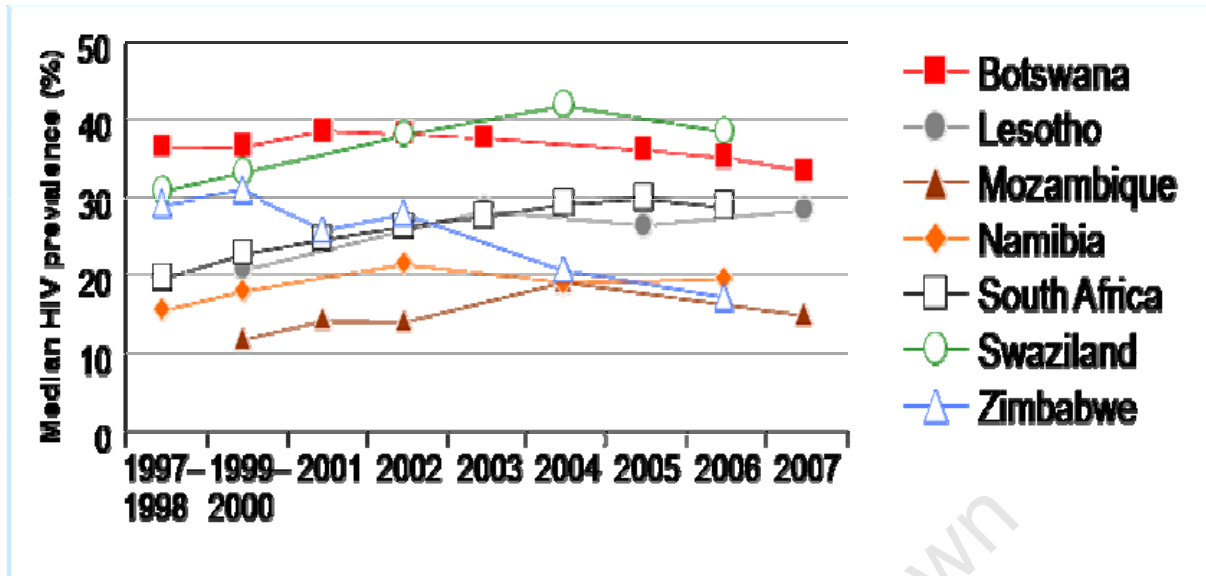
Mother to child transmission (MTCT) is the primary means by which children become infected with HIV (UNAIDS update, 2009, WHO, 2005, Sperling et al., 1994). The majority of infections occur at delivery and through breast feeding.

#### **1.4 HIV/AIDS in South Africa**

South Africa has the largest number of people infected with HIV in the world (UNAIDS/WHO, 2008). Data collected from antenatal clinic surveillance at public sector services suggest that HIV infections might be levelling off (Figure 1). The prevalence among pregnant women was 30.2% (95% CI: 29.1-31.2) in 2005, 29.1% (95% CI: 28.3%-29.9%) in 2006 and 29.4% (95% CI: 28.5–30.1) in 2007 and 29.3% (95% CI: 28.5%–30.1%) in 2008 (Department of Health South Africa, 2009). A decline in the prevalence might be due to increased mortality but not necessarily a drop in new infections, while an increase in prevalence may be due to, increased access to antiretrovirals. The epidemic varies greatly among the nine provinces of South Africa, with the prevalence amongst pregnant women being 16.1% (CI: 12.6%–20.2%) in the Western Cape and 38.7% (95% CI: 37.2%–40.1%) in the KwaZulu-Natal province (Department of Health South Africa, 2009). The overall prevalence in South Africa is similar to other southern African countries (Figure 2).



**Figure 1:** HIV prevalence trends among women attending antenatal services in the public sector in South Africa from 1990 to 2008 with 95% confidence limits since 1998.



**Figure 2:** Median HIV prevalence in 7 southern African countries (including South Africa).

*Source: National surveillance reports and UNAIDS/WHO/UNICEF, Epidemiological Fact Sheets on HIV and AIDS. July 2008.*

In response to the AIDS pandemic in South Africa, the National Strategic Plan (NSP) for HIV/AIDS and STD was initiated by the late Dr. Manto Tshabalala Msimang in 1999. The NSP was implemented in 2000 for the period 2000-2005 and recently revised for the period 2007-2011. The main aims of the NSP are; to reduce the number of new HIV infections by 50%, reduce the impact of HIV/AIDS on individuals, families, communities, and society by expanding access to appropriate treatment, care and support to 80% of all people diagnosed with HIV. Incidence reduction will be specifically targeted at people in the 15-24 year age group as this is the group with the highest incidence of HIV (Williams et al., 2003).

In response to the HIV epidemic worldwide, the UN General Assembly in 2001, set a target of ambitious goals for reducing the proportion of infected infants by 20% in 2005 and 50% in 2010

and the provision of PMTCT services to 80% of all those in need by 2010 (UN General Assembly, 2001, Tabitha *et al.*, 2006).

## **1.5 Epidemiology of Mother-to-child transmission of HIV**

### **1.5.1 Major risk factors for MTCT**

Recent sero-conversion or advanced maternal disease during pregnancy and in the breastfeeding period resulting in high HIV-1 viral load and low CD4 cell count, breast abscess, cracked nipples and associated factors such as mastitis that increase breast milk HIV viral load, are known maternal related factors for HIV transmission from mother to child (Coovadia *et al.*, 2007).

Mofenson *et al.*, 1999 showed that the mean CD4 cell count was lower among women who transmitted infection to their infants compared to those who did not transmit the infection. Other studies have shown that, advanced maternal immune suppression and high HIV viral load were also associated with increased risk of perinatal HIV transmission (Mayaux *et al.*, 1995; Sperling *et al.*, 1996; McGowan J & Shah S, 2000).

#### **1.5.1.1 Breastfeeding and MTCT risk**

Breast feeding results in over 200,000 paediatric HIV infections annually and is one of the ways through which MTCT occurs. In South Africa alone, breast feeding accounts for one third to half of all MTCT cases (Weaver *et al.*, 2000). According to a meta-analysis, the cumulative postnatal transmission was estimated to be 8.9 transmissions/100 child-years of breast-feeding (95% CI, 7.8–10.2 transmissions/100 child-years of breast-feeding) with a cumulative percentage

probability of 9.3% (95% CI 7.8 – 10.2 transmissions/100 child - years of breast feeding) after eighteen months of breast feeding (Coutsoudis et al., 2004). Transmission through breast feeding was reported to be even higher in places where malnutrition and infectious diseases are common (Semba et al, 1995, Landers et al., 1996). Table 1 shows the percentages of HIV 1 infection acquired by different routes.

**Table 1:** Percentage of HIV-1 infection acquired by different routes in the absence of any MTCT intervention

	<b>Partially-breastfed/ breastfed infants</b>	<b>Non-breastfed infants</b>
<b>Intrauterine</b>	20%	30%
<b>Intrapartum</b>	45-50%	70%
<b>Postpartum, by breastfeeding</b>	30-35%	0

These rates are observed in the absence of interventions to reduce MTCT

Adapted from Bertoli J et al. J Infect Dis 1996; 174:722

Mechanisms that may influence breast milk HIV-1 viral load and the relationship between breast milk HIV-1 viral load and MTCT of HIV are unknown (Kreiss J.,1997). Mastitis is an inflammatory process in the breast and has been implicated in the exacerbation of MTCT because of the presence of plasma derived components and inflammatory cells in breast milk during mastitis. HIV-1 infected lymphocytes could raise HIV-1 viral load in breast milk and add to the risk of HIV-1 transmission from mother to child (Morton JA, 1994; Semba et al., 1999). Recent HIV infection or re-infection is an important risk factor for transmission through breast milk as it doubles the risk when compared to a woman with established infection due to the high viral load associated with new infection (Dunn et al, 1992; Eaton & Kalichman, 2009).

In 1999, Semba and colleagues in Malawi showed that mastitis could be detected by elevated breast milk sodium concentrations. Mastitis occurred in 16 % of HIV-infected lactating women 6 weeks postpartum. Elevated breast milk sodium concentrations, maternal plasma HIV-1 viral load and breast milk lactoferin were associated with increased risk of MTCT of HIV-1 by 6 weeks and 12 months of age. They also found a correlation between breast milk HIV-1 viral load and plasma HIV-1 viral load. The median breast milk HIV-1 viral load was 700 copies/ml among women with HIV infected infants compared with less than 200 copies/ml among women with HIV negative infants at 6 weeks of age ( $P < 0.001$ ) (Semba et al., 1999). A study by John et al., 2000 conducted in Kenya confirmed that breast abscess and mastitis are strongly associated with postnatal transmission.

Replacement feeding with formula milk or exclusive breastfeeding has therefore been recommended. In many developing countries formula feeding is unaffordable and there is often a lack of clean water and proper hygiene resulting in greater risk of infection in the infant. The nutritional and immunological benefits of breastfeeding should be weighed against the risk of MTCT of HIV. Women who do not breastfeed may be identified as HIV infected and stigmatized by the community. In the ZEBS study by Kuhn and colleagues, the authors concluded that infants born to HIV-infected women who have high CD4 cell counts are at high risk if breastfeeding is stopped at any time before 16 months and that when maternal CD4 cell count exceeds 300cells/ $\mu$ L, there is a net benefit of continued breastfeeding for HIV-free survival of infants (Kuhn et al., 2009).

There is insufficient data on the risk of HIV acquisition through different infant feeding practices and the associated risks and benefits (Rollins et al., 2004). Interventions are therefore needed urgently to reduce MTCT of HIV among breastfeeding populations in developing countries (Semba et., 1999; John et al., 2000, Kumwenda et al., 2008).

## **1.6 *Prevention of Mother-to-child transmission (PMTCT) of HIV***

### **1.6.1 Antiretrovirals (ARVs) for reducing the risk of mother-to-child transmission (MTCT) of HIV infection**

Antiretroviral (ARV) drugs, including nucleoside analogue reverse transcriptase inhibitors (NRTIs) such as zidovudine (ZDV) and lamivudine (3TC) and the non-nucleoside reverse inhibitor (NNRTI) nevirapine (NVP), either alone or in combinations have been shown in a number of studies, to be effective in reducing MTCT of HIV. These regimens reduce the risk of MTCT by decreasing viral replication and through prophylaxis of the foetus and infant during and after exposure to the virus (WHO, 2004). In high income countries, highly active antiretroviral therapy (HAART) has reduced the transmission rates to less than 1%, but HAART is not yet widely available in low and middle income countries.

In 2003, WHO published guidelines for scaling up HAART in resource-limited countries for persons infected with HIV. By the end of 2007, 3 million people worldwide were estimated to be on HAART, yet less than a third of those needing HAART actually received it and there was a wide variation in coverage (WHO, 2008). Provision of HAART in resource poor settings has been a challenge. In Africa, there are both supply and demand problems. Health system capacity

is grossly inadequate. Key challenges include a lack of human resources and skills, infrastructure and technology barriers, system deficits, and structured health care financing obstacles accompanied by a vertical programme mindset where programmes are run in isolation instead of having integrated services. Even in settings where resources are available, there is a tendency towards small-scale stand alone initiatives rather than large scale system approaches, resulting in poor results, inconsistency in quality and high cost (Gazzard et al., 2006).

On the demand side, the main challenge is the high burden of disease in most developing countries. The current technologies for monitoring critical parameters such as CD4 cell count and viral load are expensive and dependent on electricity and specialist operators. In most African countries, this has led to logistical problems associated with laboratory testing and long delays in the reporting of results (Gazzard et al., 2006). Ekong et al., 2004 in Nigeria, highlighted some of these challenges including the shortage of clinicians with adequate relevant skills on use of HAART.

There are long-term challenges in the provision of HAART in sub-Saharan Africa, the region with the highest HIV prevalence in the world (UNAIDS/WHO, 2007). More than three in four (76%) AIDS deaths in 2007 occurred in sub-Saharan Africa, indicating the unmet need for antiretroviral therapy in the region. Various simpler and less costly ARV regimens have thus been offered to pregnant women and to their new born babies in developing countries because of the challenges with the implementation of HAART programmes (Volmink et al., 2007).

## 1.6.2 PMTCT Programmes

Programmes to prevent mother-to-child transmission (MTCT) of HIV have been successfully implemented in a number of developing countries. These programmes have had a major impact on paediatric HIV prevalence (WHO, 2006). The risk of MTCT can be reduced to less than 2% by interventions that include ARV prophylaxis given to women during pregnancy and labour, to the baby in the first few weeks of life and obstetrical interventions that include elective caesarean delivery (prior to onset of labour and rupture of membranes), (Dorenbaum et al., 2002, Read et al., 2005, Coovadia et al., 2007 and Kumwenda et al., 2008). In many resource-constrained settings, elective caesarean delivery is not feasible and it is often neither acceptable nor safe for mothers to formula feed. In such settings efforts to prevent HIV infection in infants are initially focused on reducing MTCT during labour and delivery. In order to increase the effectiveness of PMTCT programmes, many countries with high HIV prevalence have adopted simpler regimens that are less effective, beginning in the third trimester of pregnancy (Lallemant et al., 2004).

ARV prophylaxis has thus become one of the most important interventions in the prevention of the transmission of HIV. A number of studies have been conducted to demonstrate the efficacy of various short-course regimens including SD-NVP alone (single dose for mother and infant) and SC-ZDV plus SD-NVP (maternal and infant) (Zaba et al., 2005). Available data from trials show that regimens using a combination of ARV drugs such as SC-ZDV plus SD-NVP (maternal and infant) were more efficacious than single drug regimens in reducing MTCT and that longer courses were more efficacious than shorter courses (Dabis F et al., 2003; Kumwenda et al., 2008). If the goal of eliminating HIV infection in children is to be achieved, all women eligible for HAART (as outlined in the WHO guidelines, see Table 2) must have access to HAART, and

countries must adopt more efficacious ARV regimens for preventing MTCT among pregnant women who do not yet require HAART (WHO, 2006). For a pregnant HIV-infected woman, such treatment reduces maternal mortality and morbidity and is an effective method of preventing MTCT of HIV since the well being of the mother would ideally improve survival chances of her baby. Treating a pregnant HIV woman should therefore be seen as a way of not only improving her health but also reducing the risk of MTCT especially for those women with advanced stage disease (Newell et al., 2004; Zaba et al., 2005).

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**Table 2:** Antiretroviral protocols for pregnant women and Infants

CLINICAL DECISION	REGIMEN FOR WOMAN	REGIMEN FOR INFANT
<b>PMTCT regimen for ALL groups of women from 28 weeks of pregnancy unless already on HAART</b>		
CD4 cell count >200, continue with this PMTCT regimen  CD4 cell count ≤200 continue AZT up to point HAART initiated.	<ul style="list-style-type: none"> <li>▪ AZT started from 28 weeks onwards AND</li> <li>▪ sd NVP + AZT at onset of labour on a 3 hourly basis</li> <li>▪ If in false labour continue with AZT</li> </ul>	<b>Sd-NVP + AZT for 7 days*</b>  <b>AZT for 28 days if</b> <ul style="list-style-type: none"> <li>• Mother received &lt; 4 weeks AZT during pregnancy</li> <li>• Mother received &lt; 4 weeks HAART or</li> <li>• Mother only received sdNVP</li> </ul>
<b>HAART regimens (1a and 1b). If on AZT as above need to switch to regimens below</b>		
CD4 cell count ≤200 or WHO stage IV HAART group	<ul style="list-style-type: none"> <li>▪ d4T + 3TC + NVP (Regimen 1b)</li> <li>▪ Preferred regimen for pregnant women</li> <li>▪ Begin at any gestation</li> <li>▪ d4T + 3TC + EFV (Regimen 1a),</li> <li>▪ For pregnant women on regimen 1a, switch EFV to NVP in the first trimester</li> <li>▪ If presenting after first trimester, continue regimen 1a</li> <li>▪ Continue through labour, delivery and postnatal periods</li> <li>▪ After the first trimester, if women develop NVP-associated toxicity, then NVP should be substituted with EFV</li> </ul>	<b>Sd-NVP + AZT for 7 days*</b>  <b>AZT for 28 days if</b> <ul style="list-style-type: none"> <li>• Maternal HAART &lt; 4 weeks</li> </ul>
<b>Unbooked woman presents in labour</b>	Also includes women of known status who have had no ARVs during pregnancy. Do not require testing.	
Consent and test for HIV only in stage 1 labour.  If in advanced stage of labour, defer maternal testing until after delivery.	<b>If HIV positive</b> <ul style="list-style-type: none"> <li>• sd NVP + AZT at onset of labour and on AZT at 3 hourly basis</li> </ul> If she is in false labour continue with AZT.	<b>Sd-NVP + AZT for 28 days</b>

**Table 2:** Guidelines for the implementation of the PMTCT programme adapted from policy and guidelines for the implementation of the PMTCT programme, South African National Department of Health, *February 2008*

In 2009, the WHO produced new PMTCT guidelines. The WHO now recommends earlier initiation of ART for pregnant women, delivery of more patient friendly ARVs and prolonged use of ARVs to reduce the risk of MTCT. Once these new recommendations are implemented, HIV positive mothers or their infants will have to take ARVs during breastfeeding to prevent HIV transmission (WHO, 2009). WHO now recommends the initiation of ART at a CD4 cell count of less than 350cells/mm<sup>3</sup> for HIV positive pregnant mothers and those HIV positive

patients co-infected with tuberculosis (TB). In the previous guidelines, HIV positive mothers were provided with ARVs only in the third trimester (beginning at 28 weeks). However, the new guidelines encourage HIV positive mothers to begin ARV treatment at 14 weeks of pregnancy and exclusively breastfeed their infants for the first twelve months of life. This will ensure a reduction in transmission and an increase in the infant's chances of survival. These recommendations have the potential to reduce MTCT transmission to 5% or lower (WHO, 2009).

### **1.6.3 Review of evidence from PMTCT studies of ARV prophylaxis**

Randomised Controlled Trials (RCTs) to evaluate the efficacy of perinatal ARV prophylaxis regimens have been conducted since the early 1990s. The PACTG076 trial was the first to be conducted in the USA and France. The trial evaluated the efficacy of antenatal and intrapartum SC-ZDV to the mother from 14 weeks and every 3 hours in labour and 6 weeks of postnatal SC-ZDV to infants versus placebo. In this study all mothers gave their infants replacement feeding. Transmission was 7.6% in the SC-ZDV arm and 22.6% in the placebo group at 18 months.

Following the publishing of the PACTG076 trial results, numerous RCTs providing ARVs to reduce MTCT were conducted in Africa and Thailand to make out less complex regimens that would be feasible in developing countries. Most of these studies made use of a placebo arm and this led to a debate among researchers on the use of placebos in these trials as the PACTG076 study had shown that SC-ZDV decreases MTCT and that this should now be regarded as the standard of care. The first results released were from the Thai trial that assessed a short course regimen of SC-ZDV given orally in the last four weeks of pregnancy and during labour

compared to placebo. All infants were formula fed. This study revealed a transmission rate of 9.4% at 6 months in the SC-ZDV group and 18.9% in the placebo group. The results of this trial led to the discontinuation of the placebo arm for other trials that were ongoing at that time including the PETRA study that was being conducted in South Africa, Uganda and Tanzania.

The HIVNET012 trial in Uganda provided SD-NVP to mothers during labour and to infants within 72 hours of birth in the treatment arm and SC-ZDV was given during labour and for 7 days thereafter to infants in the control arm in a breastfeeding population (Guay et al., 1999). This trial revealed a transmission rate of 11.8% in the treatment arm and 20.0% in the control arm at 6-8 weeks. This reduction was sustained at 18 months, with a rate of 15.7% compared to 25.8% in the treatment and control arms respectively (Jackson et al., 2003). The World Health Organization thus recommended this cheaper and more feasible intervention in developing countries in 2004.

The perinatal HIV prevention trial-2 (PHPT-2) equivalence trial in Thailand compared three treatment regimens in Thai women who were receiving SC-ZDV therapy at 28 weeks of pregnancy. In one group, mothers and their infants received SD-NVP (NVP-NVP regimen): in another, mothers and infants received SD-NVP and placebo (NVP-placebo regimen): and in the last group, mothers and infants received placebo (placebo-placebo regimen). The infants were also given 1 week ZDV therapy and were formula-fed. At the first interim analysis, the placebo-placebo group was stopped. Among those women who delivered before the interim analysis, the as-randomized Kaplan-Meier estimates of the transmission rates were 1.1% (95% CI: 0, 3-2.2) in the NVP-NVP group and 6.3% (95% CI: 3.8-8.9) in the placebo-placebo group ( $P < 0.001$ ). The

final per-protocol analysis transmission rate in the NVP-NVP group was, 1.9% (95% CI: 0.9-3.0), was not significantly different from the rate in the NVP-placebo group (2.8%, 95% CI: 1.5-4.1). The authors of this study concluded that, SD-NVP given to the mother with or without a dose of NVP to the infant, added to oral ZDV prophylaxis starting at 28 weeks' gestation, is highly effective in reducing MTCT of HIV (Lallemant et al., 2004).

A further study on the efficacy of SC-ZDV plus SD-NVP was conducted in a population in which 60% of the infants were breastfed in Cote d'Ivoire (Dabis et al., 2003). Women in the DITRAME plus study received SC-ZDV from 36 weeks plus SD-NVP to the mother and infant at delivery (Dabis et al., 1999) and in a similar population, another study assessed the efficacy of SD-NVP added to SC-ZDV and 3TC (Dabis et al., 2003).

These studies from Thailand and Cote d'Ivoire indicated that SC-ZDV plus SD-NVP at delivery to the woman and infant was highly efficacious and suggested that SC-ZDV from 28 weeks gestation is more efficacious than SC-ZDV started at a later stage in pregnancy (WHO, 2004)

Other trials were conducted to assess a variety of short course regimens (Wiktor et al., 1999, Dabis et al., 1999). The PETRA study assessed the efficacy of different regimens of SC-ZDV and 3TC, and the SAINT study compared a combination of SC-ZDV and 3TC (Moodley et al., 2003). The studies are summarised in Table 3 which shows a comparison of Western Cape interventions with other trials conducted in other parts of the world from 1998 until 2007. HIV transmission rates for each of the studies are presented. The comments column indicates when each intervention was implemented in the whole Western Cape Province.

The efficacy of different interventions was tested under ideal trial conditions and the effectiveness of PMTCT programmes in the field may not be the same (Alioum et al., 2001, 2003). Barriers to the uptake of services are poor quality health services and inadequate community support for programmes to prevent MTCT. Some women may not attend ANC or may deliver at home and therefore may not receive adequate antepartum or intrapartum ARV prophylaxis (WHO, 2004). Many challenges remain with the implementation of effective interventions to reduce mother to child transmission of HIV.

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**Table 3:** Western Cape PMTCT interventions introduced following evidence from trials conducted.

Year	Evidence milestones	Transmission rate (%)	Western Cape interventions	Transmission rate (%)	Comments
1994	PACTG 076	7.6%			
1998-1999			AZT from 34 weeks in Khayelitsha	8-9	
1999	1.CDC SC-AZT, Thailand	9.4			
	2.HIVNET 012 SD NVP IP	11.8			
2000-2001			NVP (SD) in Gugulethu and Paarl	8-9	
2002-2003			Dual Therapy introduced (AZT from 34weeks, referred for HAART if eligible). PCR for infants	6.0	Intervention was available throughout the province. Replacement feeding>80%
2003	DITRAME+	6.5			
2004	PHPT2 LC AZT	2.0			
2005	TOPS	2.0			
2006-2007			AZT from 28 weeks		

Adapted from Boule, 2009

### **1.6.3.1 A review of the PMTCT programmes in the Western Cape Province in South Africa**

The Western Cape was the first province to initiate a PMTCT programme in South Africa. In January 1999, the Khayelitsha sub-district was selected as a pilot site to initiate a PMTCT programme in the province. The programme offered HIV counselling and testing, AZT from 34 weeks gestation (300mg twice a day) and during labour as well as infant HIV testing. Replacement feeding was offered until 9 months to mothers who chose not to breastfeed. At 9 months of age, children were tested and those who were positive were retested at 18 months. After delivery, women attended one of the eight local authority clinics every two weeks for 9 months. Support groups played an important role in services offered both antenatally and postnatally (Abdulla et al., 2001).

In 2001, the programme was extended to five more sites using NVP as a single-dose regimen for mothers and infants. The Khayelitsha sub-district continued to provide short course treatment with AZT. At the end of 2002, the South African Department of Health (DOH) implemented a pilot PMTCT programme nationally. Two pilot sites were purposively selected from each province (total of 18 sites) for the implementation of a PMTCT protocol developed by the DOH. The selected sites represented urban and rural sites. In addition, an evaluation of the pilot sites was conducted. The evaluation assessed the provision of VCT to pregnant women, appropriate counselling and support for safe infant feeding practices and follow up care to mother-infant pairs after delivery (McCoy et al., 2002). Doherty et al., 2005 found low coverage, with only 55% of eligible women recorded as being dispensed SD-NVP in the 18 pilot programmes, this is

consistent with other studies showing low uptake of PMTCT services in Africa (Dabis & Ekpini., 2002). Access to PMTCT was variable.

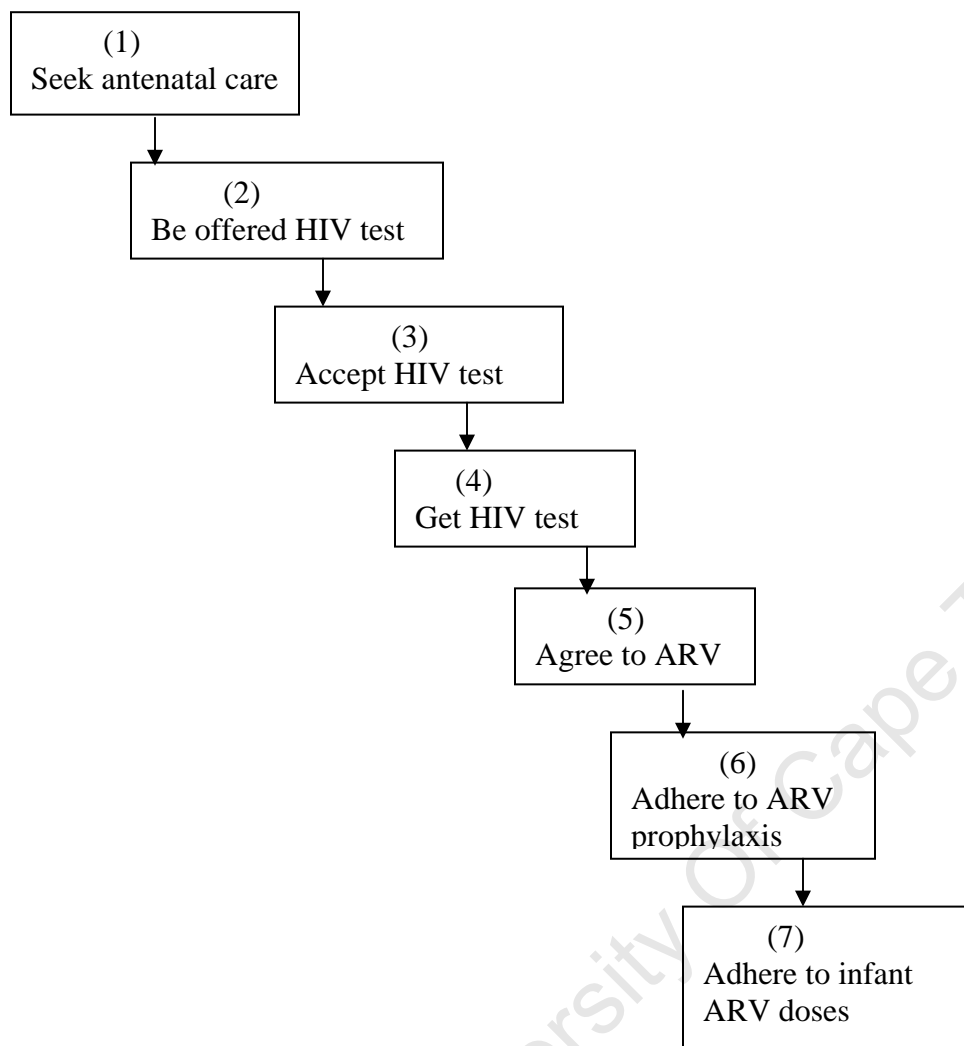
The PMTCT programme in the Western Cape province was amended in July 2003 and mothers were given in addition to AZT from 34weeks, SD-NVP at the onset of labour and a weight adjusted single dose NVP to the infant within 72 hours after birth and 7 days of AZT, following the evidence from the study by Dabis F et al., 2003. Pregnant women were referred for HAART if eligible and PCR was provided for exposed infants. The current policy and guidelines (2008) for the implementation of the PMTCT programme include dual antiretroviral prophylaxis consisting of SD-NVP plus SC-AZT initiated at 28 weeks of pregnancy for women with a CD4 cell count greater than 200 cells / mm<sup>3</sup> (WHO stage I-III) or CD4 cell count unknown and HAART for women with a CD4 cell count less than 200cells/mm<sup>3</sup> or with WHO stage IV disease. In instances where the mother has less than 4 weeks of AZT or a HAART regimen, the infant should be given SD-NVP and 28 days of AZT following the results of the study by Kumwenda et al., 2008 (Policy and guidelines for implementation of the PMTCT programme, National Department of Health, 2008).

#### **1.6.4 Methods for measuring effectiveness**

Researchers and policymakers often distinguish between the *efficacy* and the *effectiveness* of an intervention. Efficacy trials (explanatory trials) determine whether an intervention produces the expected result (effective) under ideal circumstances. Effectiveness trials (pragmatic trials) measure the degree of beneficial effect under 'realistic situations' i.e. clinical settings. Hence, hypotheses and study designs of an effectiveness trial are formulated based on conditions of

routine clinical practice and on outcomes essential for clinical decisions. The best method for evaluating efficacy and effectiveness is with randomized trials (Joubert & Ehrlich, 2007).

Programme coverage or the proportion of HIV infected-exposed mother-infant pairs in a population that receives a PMTCT intervention (Stringer *et al.*, 2003) is an important measure of effectiveness. However, a complex pathway, with a sequence of events needs to be covered before a mother-infant pair receives a PMTCT intervention. This pathway has been described as the PMTCT “cascade” (Figure 3) and can be constructed from process indicators collected routinely by PMTCT programmes and health care facilities (Stringer *et al.*, 2007). It is extremely important that every pregnant HIV-positive mother goes through all the steps of this cascade in order for the intervention to be effective. The sequence of steps that a mother has to follow are: 1) she must seek antenatal care; 2) she must be offered HIV testing; 3) she must accept HIV testing; 4) she must receive her test result; 5) she must be offered prophylactic antiretroviral therapy; 6) she must accept prophylactic antiretroviral therapy; 7) services must supply and she must adhere/comply with the prophylactic antiretroviral therapy.



**Figure 3:** PMTCT -“cascade”. Steps 1, 2, 3 and 4 would apply to any women presenting in an antenatal institution while steps 5, 6 and 7 apply only to HIV-positive women.

### **1.7 Challenges of measuring effectiveness of PMTCT programmes**

In most countries PMTCT programmes fail because pregnant HIV positive women miss one or more of the events outlined in figure 3. One in four HIV-infected pregnant women in Lusaka, Zambia did not adhere to SD-NVP that had been distributed antenatally for self administration at the onset of labour (Sinkala *et al.*, 2003). In studies in Burkina Faso, Cote d’Ivoire and Kenya, up

to 60% of HIV-infected women declined SC-ZDV prophylaxis (Meda *et al.*, 2002; Songok *et al.*, 2003). Reasons for women rejecting prophylaxis included lack of education, not understanding the purpose of ARV prophylaxis, denial and fear of stigma from members of the community (Painter *et al.*, 2004).

Effectiveness of PMTCT programmes has been measured in several ways in different countries. In Zambia, Stringer *et al.*, 2005, estimated the effectiveness of a city-wide PMTCT programme using anonymous cord blood surveillance to determine HIV serology and NVP levels. In this study, 10 public sector delivery centres in Lusaka participated with a total of 10 194 women delivering over a three month period. The study identified three crucial areas of programme effectiveness that were not measured by PMTCT-cascade indicators (Stringer *et al.*, 2007). Women who did not accept an HIV test were more likely to be infected compared to those who accepted it. Secondly, some women were misclassified as negative when in fact the laboratory result at the time of delivery confirmed they were positive and therefore did not receive ARV prophylaxis. The proportion of women who were infected during pregnancy was not known and this may account for some of the discrepant results. Finally, one third of women who were given NVP for self administration did not swallow the tablet. Thus, even in a well implemented PMTCT programme, effectiveness may be diminished.

One of the ways of evaluating the effectiveness of PMTCT programmes is to have exposed infants born to HIV-infected women tested at 6 weeks using polymerase chain reaction (PCR) tests. Antibody testing using the ELISA technique is inaccurate as maternal antibodies may persist in the child until 18 months of age (Peltier *et al.*, 2009). Routine antibody testing of

infants is only informative before the age of 18 months if the test result is negative. With virologic assays including HIV-1 DNA or RNA assays, the diagnosis can be established within several weeks of birth among non-breastfed infants (Read, 2007). This can only be used to assess intrapartum and peripartum transmission effectiveness of programmes (Reithinger *et al.*, 2007) and later testing is required to assess transmission through breast feeding. In many developing countries PCR is not available.

## **1.8 Rationale and Justification**

Intrapartum and perinatal transmission of HIV account for a large part of paediatric HIV incidence in developing countries. In clinical trial settings studies showed that simple, short-course ARV regimens and HAART are effective in reducing vertical transmission of HIV (Lallemant *et al.*, 2000).

PMTCT coverage appears low in many developing countries and the population effectiveness of the PMTCT programmes has not been estimated. It was thus decided to estimate the coverage of PMTCT and compare this to data that is collected on the PMTCT cascade.

## **1.9 Aim and Objectives**

This study aimed to estimate the effectiveness of the PMTCT programme by determining SD-NVP coverage at delivery in HIV-infected pregnant women and their infants from Mitchell's Plain and Gugulethu and coverage according to the PMTCT cascade as recorded on the clinical records.

## ***1.9.1 Objectives:***

### ***1.9.1.1 Primary objective***

The primary objective was to measure PMTCT coverage in pregnant women and their infants delivering at Gugulethu and Mitchell's Plain public sector Midwife-run obstetric units (MOUs) and in women referred from these units to Mowbray Maternity Hospital in the Western Cape region in South Africa.

### ***1.9.1.2 Secondary objectives***

The secondary objectives were:

- To determine the prevalence of HIV in pregnant women at delivery in the two communities
- To determine NVP coverage in the study population
- To determine maternal adherence to NVP
- To construct the PMTCT cascade in order to estimate missed opportunities for the prevention of vertical transmission of HIV and to determine predictors of coverage to SD-NVP by HIV positive mothers and their exposed infants.

## **CHAPTER 2:**

### **2.1 METHODS**

#### **2.1.1 Study design**

This was a cross-sectional study. It was part of a larger study conducted in six communities in four countries (South Africa, Zambia, Coted'Ivoire and Cameroon). This study was conducted between November 2007 and May 2008 and only included public sector delivery units in Mitchell's Plain and Gugulethu in the Western Cape province of South Africa.

#### **2.1.2 Population and Sampling**

The population was all pregnant women delivering at Mitchell's Plain and Gugulethu Midwife-run Obstetric Units (MOU) and those who were referred from these Units to Mowbray Maternity Hospital.

The study sample was all women delivering at these MOUs between 12 November 2007 and 30 May 2008. Presuming SD-NVP coverage of 60% in the population, we required a sample size of 365 HIV positive women to detect this proportion with 95% confidence and a 5% margin of error. The sample size was calculated for a 2-sided test.

## **2.1.3 Measurement**

### **2.1.3.1 Outcome measures**

Coverage was defined as the proportion of infected mother and exposed-infant pairs that received both the maternal and infant SD-NVP. Infant HIV-exposure was ascertained by cord blood antibody testing. Maternal SD-NVP dosing was determined by cord blood chromatography and infant SD-NVP dosing from the clinical records. It has been shown that maternal dosing on its own may fail to achieve a long-lasting infant prophylactic level, especially if the mother ingests the SD-NVP an hour or less before delivery and hence infant prophylaxis was measured as well (Mirochnick et al, 2003 ). Infant dosing on its own has been shown to have modest prophylactic efficacy (Taha *et al*, 2003). Maternal and infant SD-NVP coverage as the primary indicator for PMTCT program performance was therefore a more accurate measure.

### **2.1.3.2 Instruments**

A surveillance form was used to collect demographic and PMTCT related data from the clinical records. After every delivery cord blood was anonymously collected from the discarded placenta of all live-born deliveries. Approximately 5cm<sup>3</sup> of cord blood were obtained in an anticoagulated EDTA tube fixed with a unique number. In the event of a failed attempt to obtain specimens the reason was noted. In the case of twins, two cord blood specimens were obtained from each placenta. Specimens were sent to the laboratory together with surveillance forms with information collected from the patient's folder. Information collected included the health facility where the woman received antenatal care and where she delivered, whether she accepted testing, if the HIV test result was written in the patient's chart, the result of the test, ART provided to the

mother and infant, whether it was a normal delivery or caesarean section, and the baby's birth weight (data collection forms attached in Appendix B). Cord blood specimens were then analysed at the laboratory for HIV antibodies via an Abbott Determine® HIV-1/2 Test. Every tenth specimen was retested by a second observer for quality purposes. Dried blood spot (DBS) specimens were tested for SD-NVP presence via chromatography if the cord blood tested positive for HIV.

### **2.1.3.3 Detection of nevirapine in dried blood spots using tandem mass spectrometry**

Detection of SD-NVP in dried blood spots (DBS) was carried out by a validated method using minor modifications of the method of Koal et al., 2005. SD-NVP was extracted from the DBS with 80% methanol, 20% 0.2M zinc sulphate containing neostigmine as internal standard. HPLC was carried out on a Phenomenex Fusion RP column (5x2x4um) using a methanol/10 mM ammonium acetate gradient to effect elution. Detection was achieved using an Applied Biosystems API 3200 tandem mass spectrometer in the MRM detection mode.

For qualitative assessment, blank and quality control cut-off samples were included with each run. The limit of detection for SD-NVP drug was set at 0.1 ug/ml. Values detected above this limit were reflected as positive and those below as negative. For quantitative assessment, standard curves were run in the range 0.1 – 10 ug/ml and appropriate quality control samples run with each batch. The limit of quantification was 0.1 ug/ml. Inter and intraday coefficients of variation were less than 10% for all controls.

## CHAPTER 3

### 3.1 ETHICS AND DISSEMINATION

#### *3.1.1 Ethical Review*

This protocol was reviewed and approved by the University of Cape Town Ethics committee REC REF: 038/2007. The Ethics approval letter is attached in Appendix A.

##### **3.1.1.1 Informed consent**

Since blood was collected anonymously informed consent was not obtained. All women attending antenatal clinics at these delivery units were informed of the study.

Informed consent was not obtained for the following reasons:

1. There were no risks to the patient as blood was taken from discarded placentas
2. The rights of the patients were not violated and access to health care was not affected since all patients in the study facilities had access to PMTCT and HIV services during antenatal care and delivery. The HIV tests were conducted anonymously and there was no link to the names of patients. In this way, confidentiality was assured.
3. If consent was asked, certain women might not have agreed and this may have led to systematic bias. In a study conducted in Lusaka, Zambia, it was shown that women who refused HIV testing in pregnancy were more likely to be HIV infected (29% vs. 24%;  $p < 0.001$ ).

### **3.1.1.2 Risks**

The collection of cord blood specimens was conducted in an unlinked, anonymous manner to protect the confidentiality of patients. Specimens were coded according to the facility from which they were collected.

### **3.1.1.3 Benefits**

There was no direct benefit to participants in the study. However, findings from this study may assist with improving PMTCT programmes in these areas.

### **3.1.1.4 Confidentiality**

Blood was collected anonymously and no data was linked to patient identities. All surveillance data were stored securely. Study collection forms and laboratory specimens were identified by a coded number. Specimens were stored for the period of the study to test for HIV seropositivity and NVP levels. All data bases were secured with password-protected access systems.

## CHAPTER 4:

### **4.1 DATA MANAGEMENT AND ANALYSIS**

Data from all questionnaires were coded and double entered into an MS Access database and exported to STATA, version 10 software for cleaning and analysis. Data was transformed into a format suitable for logistic regression analysis. String variables were converted into numeric variables and vice versa.

Data were analysed using STATA. The first step was to check for multi-collinearity effect between variables. Statistical tests (correlation test and chi-square test) and clinical knowledge were used to identify variables with multi-collinearity effect. Some of the variables that were found to be collinear were; whether the mother was precounseled or not and whether they accepted the HIV test. HIV result and NVP result were also collinear and finally HIV result and maternal NVP ingested. Whether or not a mother was on HAART was correlated with mode of delivery and test acceptance. Therefore, these variables cannot be both included in the same model as using them together would create a multi-collinearity effect. These variables are collinear because the later variable is a direct consequence of the former.

Univariate data were analysed according to the MOU attended. In the first step, exploratory data analysis was carried out to compute distributions and summary statistics of individual variables. Bivariate data analysis was the next step to identify any correlation between variables to identify significant influential variables of SD-NVP coverage. Variables found statistically significant at significance level 0.05 or strong evidence in the literature of their significant importance were selected and included for binary logistic regression analysis.

In the second step, binary logistic regression was used to identify and measure the influence of the predictor variables identified from the first step. Two approaches were used to carry out logistic regression in order to arrive to a model that best describes SD-NVP coverage. The first approach entailed building the model by starting off with an empty model, which is a model containing only the independent variable, then all dependent/explanatory variables were added to the model, in a stepwise fashion, in order of significance (statistically/biologically). A p-value of  $< 0.05$  (less than 5% chance of random error) was used as a cut-off point for significance level to identify independent factors. In all model development processes, the log likelihood ratio and Akaike's information criterion AIC were used to select the best-fit model.

The second approach used was the backward elimination variable selection where, all variables were initially brought into the model equation. The coefficient of the least significant variable was then tested for significance at probability 0.1 (pre specified level of significance), that is giving a 10% chance of random error. When the least significant variable was found to be significant, then all variables were included in the model and the process stopped. If it was not significant, the variable was excluded; the model refitted without this variable and the process was repeated. The process stopped when all regression coefficients were significant at a 10% level of significance. The two approaches used identified the same predictor variables, but only results from the first model are presented (results section) as the second approach was used for confirmation purposes.

### **4.1.3 Statistical methods**

All data was analysed using STATA, version 10 software developed by StataCorp LP, USA (Copyright 1985-2001). To assess comparisons of age, gravidity, birth weight of infants and other continuous variables between groups, unpaired two-tailed Student t-tests, ANOVA for the comparison of mean differences and 95% confidence intervals around the mean difference were used. Categorical variables were analysed by chi-squares, and 95% confidence intervals for the odds ratios were computed. Proportions on the HIV prevalence and ARV coverage were calculated. Multivariate logistic regression analysis was used to examine the determinants of SD-NVP coverage.

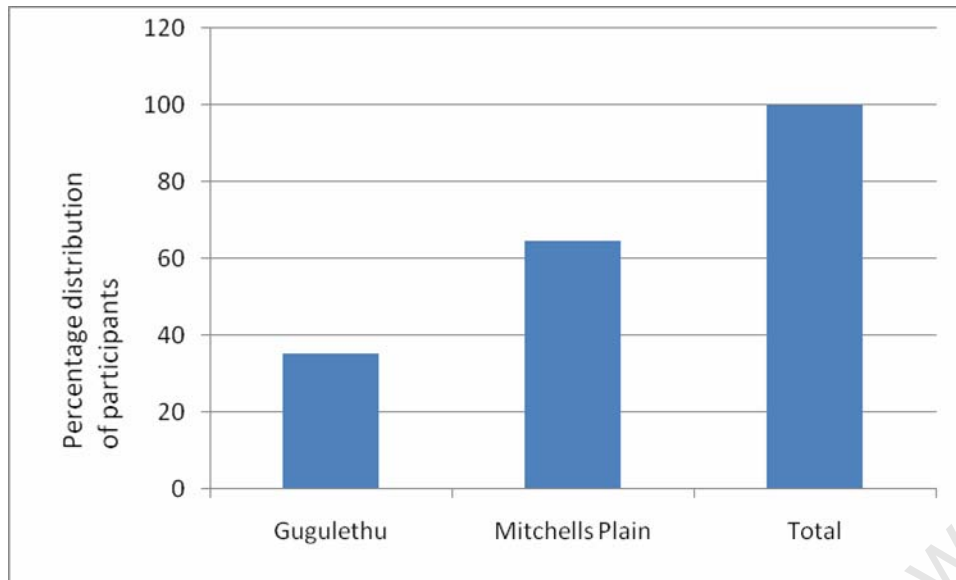
## CHAPTER 5:

### 5 RESULTS

#### *5.1 Baseline characteristics*

##### **5.1.1 Specimen collection rate**

At the Mitchell's Plain, Gugulethu MOUs and at the referral hospital at Mowbray, 2278 women gave birth to live infants between November 2007 and May 2008. From these deliveries, we obtained 2198 specimens and thus the collection rate was 96.5% (Fig 4.2) and 64.8% (1425) of these were from Mitchell's Plain while the rest were from Gugulethu (Fig 4.1). Women from whom we were unable to obtain cord blood specimens did not differ from those from whom the cord blood was obtained with regards to age, gravidity, or whether they had been offered HIV testing in antenatal care (reasons for cord blood not collected are illustrated in Fig 4.4). The results presented here are for the 2198 women from whom cord blood was obtained.



**Figure 4.1 Percentage of participants in the two maternity obstetric units**

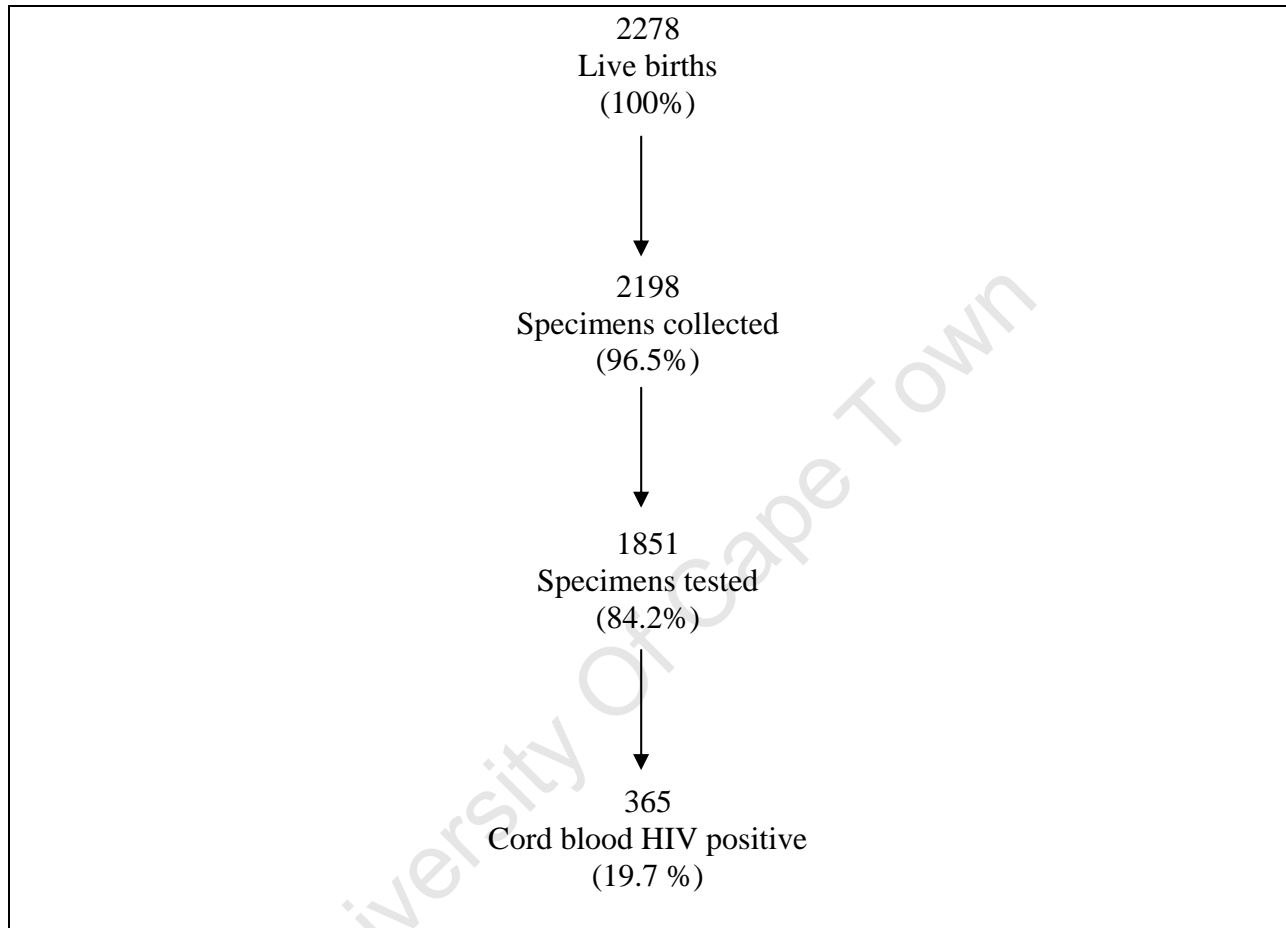
**Table 4.1:** Demographic characteristics of women from Mitchell’s Plain and Gugulethu MOUs

Facility	Baseline characteristics		
		Age	Gravidity
Mitchell’s plain (N=1472)	Mean	25.0	2.0
	Range	13-45	1-13
	SD	5.7	1.2
Gugulethu (N=803)	Mean	25.6	2.1
	Range	12-47	1-7
	SD	5.9	1.1
<b>*P-value</b>		<b>0.0304</b>	<b>0.1760</b>

\*p-value tests for the equality of means for the specific characteristics in the two samples

The 2198 women from whom blood was collected had a mean age of 25.2 years (range, 12-47 years) and standard deviation 5.8. Their mean gravidity (including the current pregnancy) was 2.0 (range, 1-13) (Table 4.1). Most of the women (94.6%) had a normal (vaginal) delivery and 5.4% had a caesarean delivery for both facilities combined. On analyzing mode of delivery by facility, the same proportions of women delivering normally (vaginal) and those having a

caesarean delivery were observed. Less than 10% of women had had an HIV test before the current pregnancy. Amongst those women who had previously tested, only 39 (1.8%) had tested HIV positive at that time.



**Figure 4.2:** Collection rate and HIV prevalence amongst women who had a specimen collected.

Of the 2198 (96.5%) specimens collected, 1851 (84.2%) were tested for HIV (Fig.4.2) and 365 (19.7%) tested HIV positive. Of the women who tested positive on the cord blood, 20.6% had tested negative at their first antenatal clinic visit. A detailed description of the demographic characteristics of women from whom blood specimens were collected is illustrated in Table 4.2.

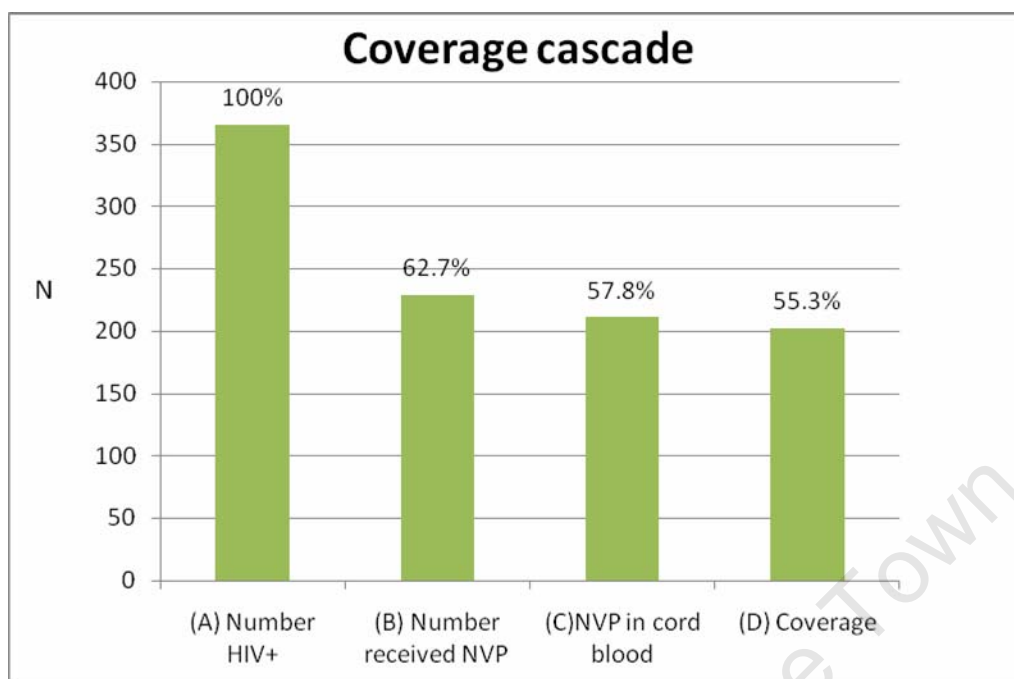
**Table 4.2:** Key characteristics of the women who delivered at Mitchells Plain and Gugulethu during the study

Characteristics		Sites		
		Mitchell's Plain	Gugulethu	Total
Number of women attending first ANC visit at the clinic at which they delivered		1249 (89.0%)	660 (87.4%)	1909 (88.5%)
Number of women with ≤2 ANC visits		269 (18.9%)	185 (23.9%)	452 (20.7%)
Number of women with >2 ANC visits		1156 (81.1%)	588 (76.1%)	1744 (79.3%)
Mode of delivery	caesarean	58 (4.1%)	60 (7.8%)	118 (5.4%)
	normal (vaginal)	1362 (95.9%)	708 (92.2%)	2070 (94.6%)
Number of women who had an HIV test before this pregnancy		120/1425 (8.4%)	69/773 (8.9%)	189/2198 (8.6%)
Number pre-counselled		1254/1425 (88%)	622/773 (80.5%)	1876/2198 (85.4%)
Number of women tested for HIV during the study		1254/1425 (88%)	596/773 (77.1%)	1851/2198 (84.2%)
% HIV prevalence		<b>11.8</b> (149/1255)	<b>34.5</b> (216/596)	<b>19.3</b> (365/1851)
Number of HIV-infected women who received NVP		<b>90 (60.4%)</b>	<b>139 (64.4%)</b>	<b>229 (62.7%)</b>
Number of infants recorded as receiving NVP		128/149 (85.9%)	183/216 (84.7%)	311/365 (85.2%)
Number of women positive for AZT as above		106/149 (71.1%)	161/216 (74.5%)	267/365 (73.2%)
Number of women positive for HAART as above		12/149 (8.1%)	11/216 (5.1%)	23/365 (6.3%)
Number of HIV infected women with evidence of NVP in cord blood		86/149 (57.7%)	125/216 (57.8%)	211/365 (57.8%)

Note: Row percentages were used

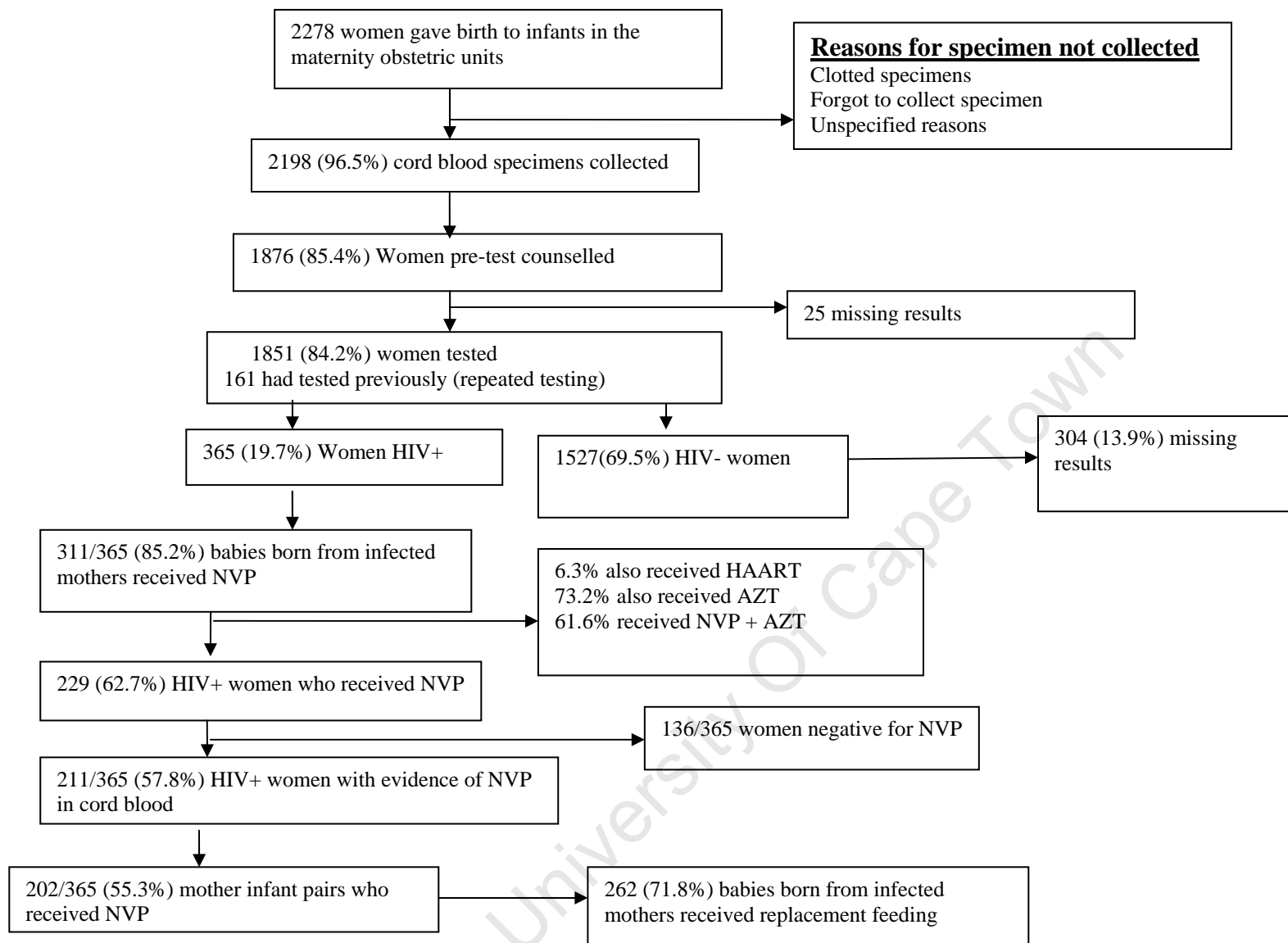
Table 4.2 illustrates key characteristics of the two sites of the 2,198 women who delivered at these facilities during the study, 1,909 (86.9%) had gone for their first ANC visit at that facility. and 1,744 (79.3 %) of the women had been for more than two ANC visits before they delivered.

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**Figure 4.3:** SD-NVP coverage for pregnant women delivering in Mitchell’s Plain and Gugulethu MOUs between November 2007 and May 2008.

Of the 1851 specimens collected 365 (19.7%) tested HIV positive and 229 (62.7%) of mothers received SD-NVP according to the clinical records but only 57.8% had evidence of NVP in the cord blood quantified by HPLC. According to the clinical records 85.2% of infants born to HIV-infected mothers were given ARV prophylaxis (Figure 4.4). Coverage, defined as the proportion of infected-exposed mother-infant pairs that received both the maternal and infant NVP doses was 202/365 (55.3%, Fig 4.3). There was no significant difference in SD-NVP uptake by infants between the two facilities. The cascade was similar for the two sites. These statistics are summarised in figure A2 in Appendix A.



**Figure 4.4** Surveillance study profile. Missing data for variables; mother's age 6 (0.36%), gravidity 12 (0.55%), attended first ANC visit at the facility 40 (1.82%).

**Table 4.3:** Variables identified from the chi-square test to be important predictors of NVP coverage

<b>Variable</b>	<b>Chi2 (1)</b>	<b>Chi2 p-value</b>
<b>Mode of delivery</b>	<b>9.6235</b>	<b>0.002</b>
<b>Maternal NVP</b>	<b>29.6825</b>	<b>&lt;0.001</b>
<b>Mother accepted HIV test</b>	<b>86.1417</b>	<b>&lt;0.001</b>
<b>Gravidity</b>	<b>9.9872</b>	<b>0.041</b>
<b>Attended 1<sup>st</sup> ANC visit in current facility</b>	<b>57.9133</b>	<b>&lt;0.001</b>
<b>Maternal HAART</b>	<b>11.3166</b>	<b>0.003</b>

Factors that were identified from the chi-square as important predictors of NVP coverage are presented in table 4.3 with the corresponding Chi-square and p-values.

### **5.1.2 Predictors of NVP coverage**

Factors associated with NVP coverage (selected from the logistic regression model) are presented in table 4.4.

**Table 4.4:** Factors associated with NVP coverage

<b>Variable</b>	<b>Crude OR</b>	<b>Adjusted OR</b>	<b>P-value</b>
ANC visits	1.23(0.67-2.23)	2.02 (1.04-3.91)	0.04
First ANC visit in current facility	5.62 (3.14-25.67)	4.82 (1.29-18.01)	0.02
Normal vaginal delivery	0.31 (0.10-0.91)	0.39 (0.12-1.30)	0.13
Gravidity = 2	0.83 (0.63-1.08)	0.56 (0.32-0.98)	0.04

Factors associated with NVP coverage included, firstly, the number of ANC visits, secondly, where the first ANC was obtained, and lastly, parity, including the current pregnancy. Women

who had 2 or more ANC visits prior to delivery were more likely to adhere to SD-NVP compared to those who made less than two visits, OR 2.02 (P= 0.04). Having the first ANC visit in the current facility was associated with improved SD-NVP coverage, OR 4.82 (P= 0.02). Women who had at least two pregnancies in their lifetime were more likely to adhere to prophylaxis compared to mothers who had less than two pregnancies, OR 0.56 (P=0.04).

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## **CHAPTER 6:**

### **6 DISCUSSION**

This study was conducted about five years after the implementation of the PMTCT programme throughout the Western Cape in 2001 and nationally since 2002. The programme in the Western Cape was based on the HIVNET 012 NVP regimen and the provision of replacement feeding to all infants whose mothers chose to formula-feed. In 2002-2003 dual therapy (SD-NVP plus AZT) was introduced. However, the impact of the PMTCT programme in South Africa has not been significant (Jackson et al., 2007). Although the HIV testing rate had reached 69% in 2006/2007 (Barron et al., 2007), a third of HIV positive women did not obtain NVP regardless of the national antenatal coverage rate of above 90% and 84% of births attended to by trained health professionals (Day & Gray, 2006).

This study assessed HIV prevalence and NVP coverage at two Midwife-run Obstetric Units in the Western Cape. The prevalence of HIV in Gugulethu (34.5%) and in Mitchell's Plain (11.8%) was similar to the 2008 antenatal surveys conducted in these MOUs at the time of the study. Findings from this study demonstrate that despite a seemingly robust PMTCT programme in the Western Cape Province, not all HIV-exposed infants are getting the appropriate prophylaxis and a minority of HIV positive women are receiving the treatment they need.

Compared to other provinces in South Africa the Western Cape has a well functioning PMTCT programme and yet in the current study, only 62.7% of HIV-infected women received at least SD-NVP, according to the clinic records. There was a large proportion (37.3%, Fig.4.4) of HIV infected women whose blood did not have NVP present according to cord blood chromatography. This could mean that, either, the infected women did not actually ingest the SD-NVP given to them in ANC or they were not tested and never received SD-NVP. The observed low NVP coverage (55.3%, Fig.4.3) calculated as the proportion of infected mother and exposed-infant pairs that received both the maternal and infant SD-NVP, could perhaps be attributed to the short duration between ingestion of SD-NVP and delivery and hence the absence of NVP in the cord blood specimens. Unfortunately no information was collected on the interval between maternal dosing and delivery.

Evidence from previous studies showed that there was an association between time of maternal dosing and NVP plasma concentrations. Stringer *et al.*, 2003, illustrated that women who delivered less than an hour after NVP ingestion had a lower mean NVP cord blood concentration compared to those who delivered at least two hours after they ingested NVP ( $p < 0.001$ ). Lower NVP concentrations were associated with lower cord blood concentrations and a shorter interval between maternal dosing and delivery (i.e. women delivering less than 1 hour after ingesting NVP).

Jackson *et al.*, 2006 also assessed the association of length of time between ingestion of SD-NVP and delivery and concentration of NVP in cord blood. The median NVP cord blood concentration was 1238ng/ml (IQR, 905-1474ng/ml) and 122ng/ml (IQR, 64-321ng/ml) for

women who reported taking NVP more and less than 1 hour before delivery respectively ( $P < 0.001$ ). The results demonstrated that cord blood NVP concentrations correlated well with report of NVP administration and timing of dose before delivery.

The fact that 20.6% of women tested negative at their first antenatal clinic visit and yet tested positive on cord blood indicates that seroconversions may have occurred later in pregnancy or an incorrect HIV test result was recorded in the folder and this may contribute to the PMTCT programme failure. There may also have been false negative cord blood results. Similar findings were reported by Stringer et al., 2005 who found that 13 of the 134 'seroconverters' (9.7%) were also NVP positive and hence concluded that, around 10% of the apparent seroconversions can be attributed to errors in the surveillance exercise. Stringer et al., 2005 emphasized that, whether false- negatives in ANC derive from laboratory errors, clerical errors at the level of the antenatal clinic, or from actual recent infection, the result is the same-failed coverage (Stringer et al. 2005).

More efficacious PMTCT regimens such as triple therapy and HAART have been advocated to prevent PMTCT in developing countries. Although not as efficacious, the provision of single dose NVP is the simplest and most feasible intervention available. The low NVP coverage in this study indicated that it may be more important to improve coverage before extending programmes to include more complex regimens, even though they are more efficacious.

Failures occurred at each stage of the PMTCT cascade (Fig.4.3 and Fig A2). Interventions are required at each stage of the PMTCT cascade in order to improve programme coverage, and consequently programme effectiveness.

Three important predictors of NVP coverage were identified in this study. Having more than two ANC visits increased the number of opportunities for women to enter the PMTCT programme as health workers would have had more time to reinforce the importance of being part of the PMTCT programme and had another opportunity to counsel and test them. Women with at least two previous pregnancies were more experienced and more sensitized to PMTCT and the importance of testing during pregnancy. Thirdly women who had their first ANC visit at the facility where they delivered were easier to follow up and there was greater continuity of care. These women were also likely to be less mobile and of higher socio-economic standing.

The current study findings are consistent with findings from previous studies. A number of factors have been implicated in low maternal adherence to SD-NVP prophylaxis and consequently low coverage. In Rwanda, Delvaux *et al.*, 2009, found that women who had less than two ANC visits, who were unmarried, less educated and those offered testing after their first antenatal clinic visit were more likely to be non-adherent to SD-NVP prophylaxis. In other studies women who were less than 20 years of age, single, having their first pregnancy, and who were less educated and of low socio economic status were less likely to undergo HIV testing and hence would not receive PMTCT prophylaxis if HIV-infected (Thierman *et al.*, 2006). Similar findings have been reported in other studies (Albrecht *et al.*, 2006; Kasenga *et al.*, 2007).

Another critical thing would be to emphasize recognition of labour onset (i.e. it is crucial to take SD-NVP at the correct time, and hence, it is better to give mothers NVP beforehand so that they can take it when they start labour at home rather than only when they get to the MOU, to allow the drug to reach its peak concentrations before delivery) to mothers enrolled in PMTCT programmes and this could be done during counselling sessions.

There are limitations to this study. This was a cross-sectional study and a longitudinal study would have been a better study design since it would have been possible to follow study participants and obtain transmission rates. It was not possible to conduct a longitudinal study for ethical reasons as all women who were identified as HIV-infected would have had to be referred for the best care available, and thus it would not have been possible to observe the cascade. Another limitation of this study was that the timing of the maternal dose was not documented and this limited the ability to correlate maternal adherence with duration since ingested. Demographic information such as marital status, socio-economic status and level of education was not collected and this could possibly have provided more information on variables associated with failed coverage in the PMTCT cascade. Cord bloods were anonymously collected and only information from the clinical chart was collected.

HAART is recommended as standard of care for women with CD4 cell counts less than 200cells/ $\mu$ L in the Western Cape. No information on CD4 cell counts of HIV-infected women was available and thus it was not possible to assess the proportion of women who should have been initiated on HAART. Lastly, the study only included women who delivered at MOUs. Data

from HST shows that about 87.2% of pregnant women in the Western Cape deliver in health facilities (District Health Barometer, 2007/2008).

## **CHAPTER 7:**

### **7 CONCLUSION**

In conclusion, only 62.7% of HIV-infected women in the Western Cape received at least SD-NVP. For PMTCT services to be successful, each mother-infant pair should go through a cascade of events. Coverage was low in this study and different interventions need to be introduced at each stage of the cascade in order to improve PMTCT coverage.

Policy makers should first focus on ensuring that HIV testing rates increase. The findings from this study demonstrate that increasing the effectiveness of a PMTCT programme depends on a number of factors and resources should be better spent in maximizing coverage of simple and moderately effective interventions such as SD-NVP, and later use more efficacious drug regimens when programme effectiveness has been established. Key to improving PMTCT programme are, increasing the uptake of the programme, using more efficacious regimens compared to SD-NVP, and ensuring that women with CD4 cell counts  $< 200$  cells/ $\mu$ L are placed on HAART and appropriate monitoring and evaluation of the programme.

## CHAPTER 8:

### 8 References

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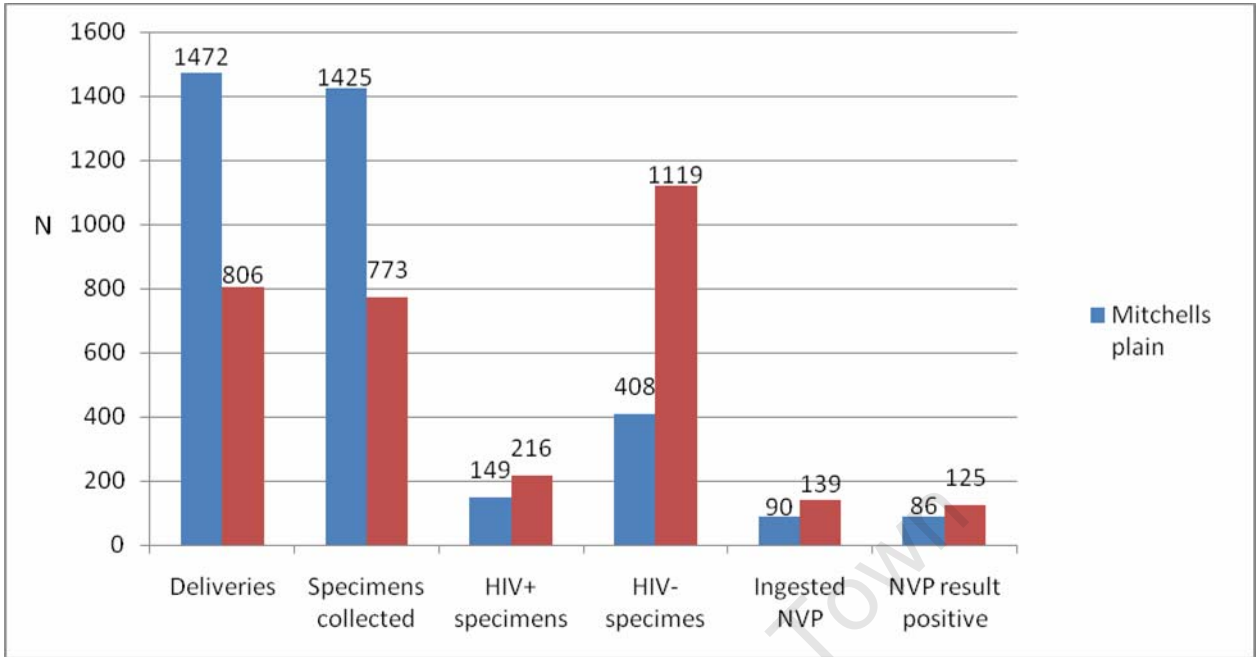
## CHAPTER 9

### 9 Appendix A

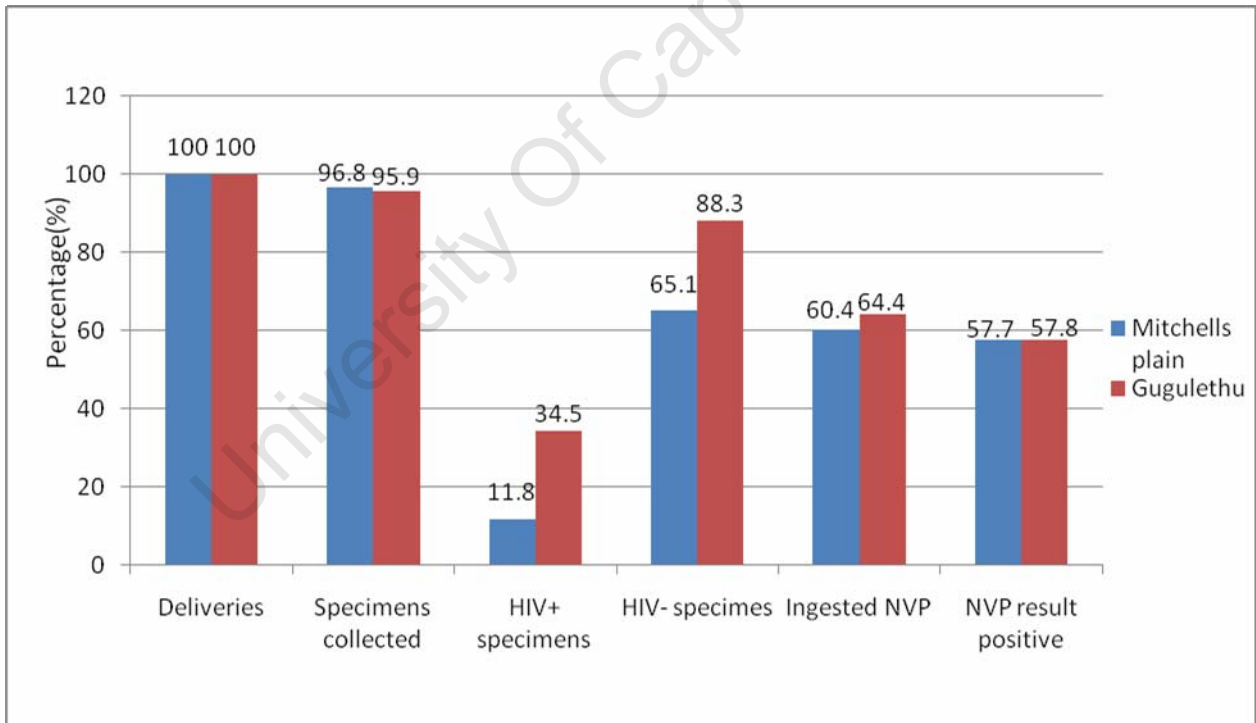
**Table A1:** ARV coverage rates among women in the surveillance population

ANC Facility	Number of deliveries	Specimens collected	HIV+ specimens	HIV- specimens	Proportion ingesting NVP	Proportion with NVP present
Mitchell's Plain	1472	1425(96.8%)	149/1255 (11.8%)	408 (65.1%)	90/149 (60.4%)	86/149 (57.7%)
Gugulethu	806	773(95.9%)	216/596 (34.5%)	1119 (88.3%)	139/216 (64.4%)	125/216 (57.8 %)

The ARV coverage rates were calculated from the proportion of HIV positive women in the sample who had NVP detected in the cord blood. Figure A1 (a) and A1 (b) depict the rates in Table A1. NVP coverage was 57.7% for Mitchell's plain and 57.8% for Gugulethu.



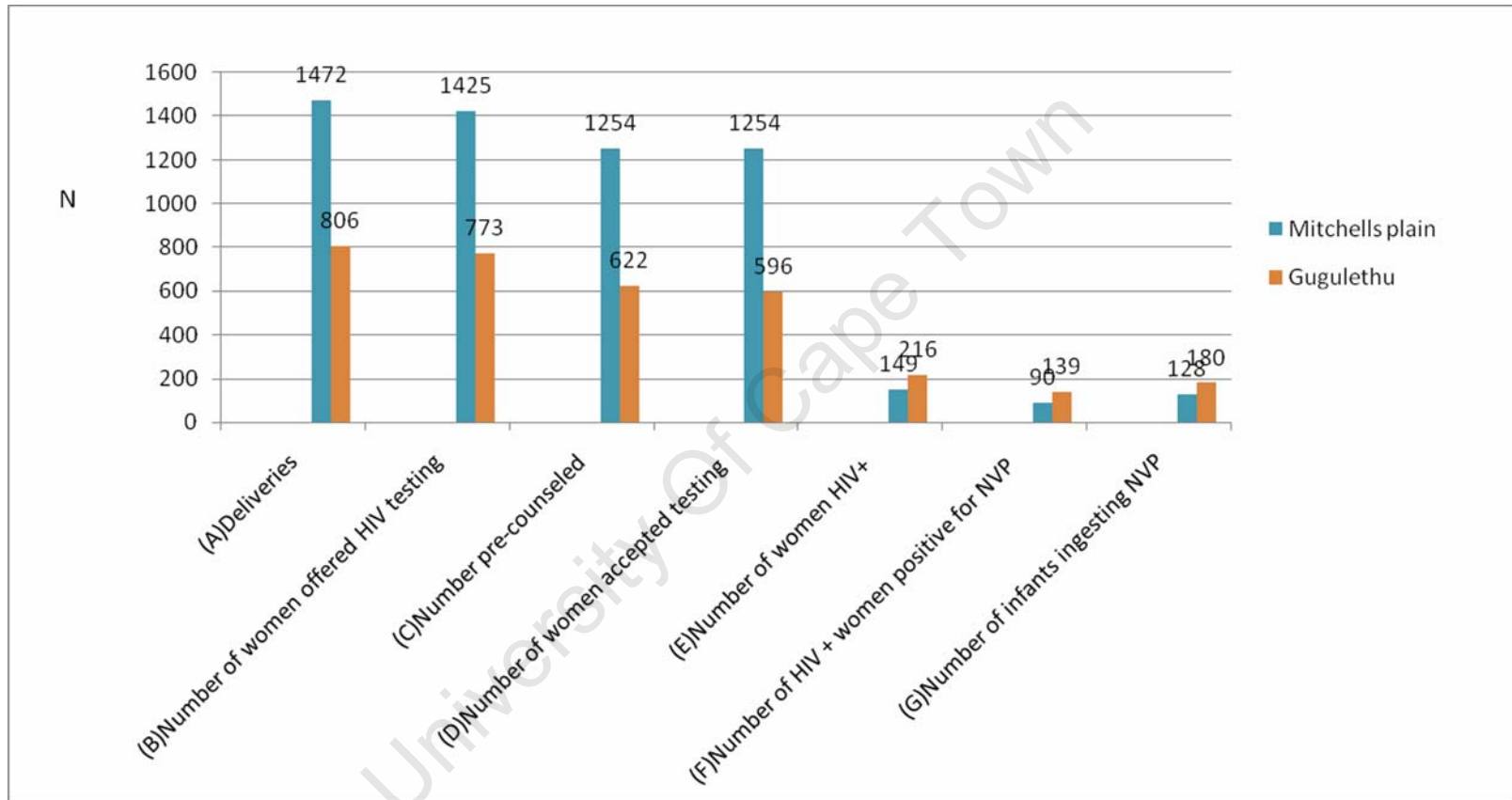
**Figure A1 (a)** Uptake of ARV prophylaxis for HIV-positive pregnant women



**Figure A1 (b)** Percentage uptake of ARV prophylaxis for HIV-positive pregnant women in the surveillance population. . \*NVP result positive indicates the number or percentage of women who adhered to SD-NVP.

Figure A1 (a) and A1 (b) demonstrate uptake of NVP by pregnant women in crude numbers and percentages respectively. The two figures represent all the women in the surveillance population stratified by facility.

Cord blood specimen collection was very high, with 96.8% and 95.9% specimens collected at Mitchell's plain and Gugulethu MOUs respectively. The prevalence of HIV in Gugulethu was 34.5% while in Mitchell's plain it was 11.8%. The HST barometer results for the city of Cape Town indicate that the HIV prevalence among ANC clients for 2006/7 was 16, 8% while the HIV survey showed a prevalence of 17% (CI: 15.5%-18.4%). The Mitchell's plain prevalence falls within the HIV survey prevalence range, while the prevalence in Gugulethu is much higher.



**Figure A2 Attrition cascade among women in the surveillance population.** This figure demonstrates the sequence of events that women in the surveillance population went through in-order to attain prevention of MTCT of HIV service coverage. Step A represents all women delivering in each of the two facilities in the surveillance population. In Mitchell’s plain, 60.4% (90/149) women were positive for NVP while in Gugulethu, 64.4 % ( 139/216) women were positive for NVP

## APPENDIX B: Ethics approval letter & Study forms



UNIVERSITY OF CAPE TOWN

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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 I: 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

*Asley Denley*  
pr **PROF. M BLOCKMAN**  
**CHAIRPERSON, HSF HUMAN ETHICS**

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