Preventing HIV in infants in eastern and southern Africa by improving access to HIV testing, maternal health and quality services

Matthew F Chersich

Doctoral thesis submitted to the Faculty of Medicine and Health Sciences, Ghent University

Promoter: Prof. Dr Marleen Temmerman
Dept of Obstetrics and Gynaecology, Ghent University
For my parents, whose love and support has no limits

Preventing HIV in infants in eastern and southern Africa by improving access to HIV testing, maternal health and quality services
Matthew F Chersich

Promotor: Prof. Dr. Marleen Temmerman
Dept of Obstetrics and Gynaecology, Ghent University Hospital

Deze publicatie is verschenen binnen de reeks “ICRH Monografieën”/ This title has been published in the series “ICRH Monographs”
ISBN 978 90 382 1198 5

International Centre for Reproductive Health Ghent (ICRH)
Ghent University (UGent)
De Pintelaan 185 P3
B- 9000 Ghent (Belgium)
www.icrh.org
Preface

Initiatives to prevent HIV infection in infants need to address the best interests of both the woman and child. This is not only for moral and ethical reasons, but essential for ensuring such services make a substantial impact on the health of children and women. Without direct benefits for a woman, acceptability of antiretroviral prophylaxis and adherence is low, and programmes will leave a legacy of orphans and vulnerable children. Ultimately, an HIV-uninfected child, with an infected mother who has an unmet need for care, is a poor outcome for prevention of mother-to-child transmission programmes. While it is attractive to highlight the pressing need for saving vulnerable fetuses and newborns from HIV, if this results in neglecting the woman involved, such efforts will fail. By necessity, the interests of both the woman and child need protection and direct benefits must accrue to both. Saying a woman benefits indirectly by having an HIV-uninfected child is insufficient. Addressing purely medical needs is also not going far enough – a woman’s health and wellbeing are determined by a complex interplay between economic, gender, cultural, sexual and medical factors.
Contents

Preface ........................................................................................................................................... 1
List of figures and tables .................................................................................................................. 5
Chapter 1. Introduction .................................................................................................................. 7
  1.1. HIV increases maternal mortality, undermining child survival ........................................... 7
  1.2. Effects of HIV infection in infants and young children .............................................................. 9
  1.3. Strategies for securing maternal health and preventing HIV in infants ................................. 10
  1.4. Coverage of services for preventing HIV in infants and young children ............................... 13
  1.5. Opportunities for increasing coverage and effectiveness of services for preventing HIV in infants ....................................................................................................................... 16
Chapter 2. Objectives and Methods .............................................................................................. 23
  2.1. Objectives ............................................................................................................................... 23
    General objectives ....................................................................................................................... 23
    Specific objectives ...................................................................................................................... 23
  2.2. Study settings .......................................................................................................................... 24
    Kenya ......................................................................................................................................... 24
    South Africa .............................................................................................................................. 26
  2.3. Study design ............................................................................................................................ 29
  2.4. Ethical considerations .............................................................................................................. 33
  2.5. Data management and analysis ............................................................................................. 33
  2.6. Data dissemination .................................................................................................................. 34
Chapter 3. Results .......................................................................................................................... 37
  3.1 Improving effectiveness of PMTCT services during pregnancy .............................................. 37
    Article 1: Acceptability and utilisation of voluntary HIV testing and nevirapine to reduce mother-to-child transmission of HIV-1 integrated into routine clinical care 37
    Article 2: Integration of antiretroviral treatment within antenatal care in Gauteng Province, South Africa ......................................................................................................................... 45
  3.2 Identifying HIV exposure in newborns and providing interventions to reduce transmission shortly after birth ........................................................................................................ 53
    Article 3: A randomized trial of two post-exposure prophylaxis regimens to reduce mother-to-child HIV-1 transmission in infants of untreated mothers ........................................ 53
    Article 4: The ethical and legal case for identifying newborn exposure to HIV and providing antiretroviral prophylaxis ......................................................................................... 65
    Article 5: HIV-testing and antiretroviral prophylaxis for a newborn without its mother's consent: case report ............................................................................................................. 89
  3.3 Identifying HIV infection in women attending child health clinics ......................................... 95
    Article 6: HIV testing and counselling for women attending child health clinics; an opportunity for entry to PMTCT and HIV treatment ........................................................................ 95
  3.4 Effects of HIV on disease patterns and health needs in the first year after childbirth .............. 109
    Article 7: Morbidity in the first year postpartum among HIV-infected women in Kenya .................. 109
Chapter 4. Discussion and conclusions ......................................................................................... 119
  4.1 Summary of key findings ........................................................................................................ 119
    4.1.1 Securing maternal health is essential for improving child survival ............................... 120
4.1.2 Interventions in childbirth and child health clinics can complement antenatal PMTCT services ................................................................. 122
4.1.3 Improving quality of PMTCT services .................................................. 126
4.2 Contribution of this work to the field and research agenda at study sites .... 129
4.3 Limitations ................................................................................................ 129
4.4 Priorities for future research ................................................................. 130
4.5 Final remarks ........................................................................................... 132
Summary ........................................................................................................ 135
Samenvatting ............................................................................................... 137
Acknowledgements ....................................................................................... 141
Annexes ........................................................................................................... 143
Annex 1: Vertical HIV transmission in South Africa: translating research into policy and practice (Article 8) ............................................................... 143
Annex 2: Progress and emerging challenges in preventing mother-to-child transmission (Article 9) ................................................................. 147
Annex 3: Increasing the scope and intensity of interventions to prevent HIV infection in infants: best interests of women and children (Article 10) ........ 157
Annex 4: Efavirenz use during pregnancy and for women of child-bearing potential (Article 11) ................................................................. 163
Annex 5: Dandy-Walker variant in an infant exposed to antiretroviral medication (Article 12) ................................................................................ 171
References ................................................................................................. 175
List of abbreviations

AIDS: Acquired Immunodeficiency Syndrome  
ANC: Antenatal care  
ARV: Antiretroviral  
ART: Antiretroviral treatment  
AZT: Azidothymidine  
CI: Confidence interval  
DHS: Demographic and health survey  
EFV: Efavirenz  
HIV: Human Immunodeficiency Virus  
KSPA: Kenya Service Provision Assessment  
MCH: Maternal and child health  
MTCT: Mother-to-child transmission  
NNRTI: Non-nucleoside reverse transcriptase inhibitor  
NRTI: Nucleoside reverse transcriptase inhibitor  
NVP: Nevirapine  
PMTCT: Prevention of mother-to-child transmission  
Sd-NVP: Single-dose nevirapine  
STI: Sexually transmitted infection  
TB: Tuberculosis  
UN: United Nations  
UNGASS: United Nations General Assembly Special Session  
WHO: World Health Organization

List of figures and tables

<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 1: Total and regional number of adult women (≥15 years)</td>
<td>15</td>
</tr>
<tr>
<td>estimated to be living with HIV in 2006</td>
<td></td>
</tr>
<tr>
<td>Figure 2: Total and regional estimated number of children (0-15 years)</td>
<td>15</td>
</tr>
<tr>
<td>newly infected with HIV during 2006</td>
<td></td>
</tr>
<tr>
<td>Figure 3: Expanding entry to comprehensive PMTCT: the role of</td>
<td>15</td>
</tr>
<tr>
<td>antenatal, childbirth and child health services</td>
<td></td>
</tr>
<tr>
<td>Figure 4: Research papers within the PMTCT systems approach to</td>
<td>32</td>
</tr>
<tr>
<td>antenatal; childbirth and child health services</td>
<td></td>
</tr>
<tr>
<td>Table 1: HIV and selected indicators in Kenya and South Africa</td>
<td>26</td>
</tr>
</tbody>
</table>
Chapter 1. Introduction

HIV has increased the already heavy burden of disease and death among women and children in low- and middle-income countries. In many of these countries, AIDS has become a leading cause of illness and death among women of reproductive age and their children. This has undermined the modest gains made in recent decades in maternal and child survival [1-4] and has had devastating effects on families, households and communities. In 2006 an estimated 39.5 million people were living with HIV worldwide, including about 17.3 million women (Figure 1) and 2.3 million children [5]. The epidemic bears the scars of prevailing gender inequities, which continue to drive its transmission. In sub-Saharan Africa, the hardest-hit region, for every 10 men living with HIV, there are about 14 women infected with the virus [5].

New HIV infections continue to occur at high rates. More than 10 000 adults and 1400 children under 15 years of age become infected with HIV every day [5]. Children, therefore, constitute about 15% of all new infections. The majority of these infections occur through mother-to-child transmission (MTCT), which can take place in pregnancy, during childbirth or through breastfeeding. In the absence of any intervention the risk of such transmission is 15–30% in non-breastfeeding populations. Breastfeeding by an infected mother increases the risk by 5–20% to a total of 20–45% [6]. The risk of MTCT can be reduced to under 2% by interventions which include antiretroviral (ARV) prophylaxis given to a woman during pregnancy and labour, and to the infant in the first weeks of life; obstetrical interventions particularly elective caesarean delivery (prior to the onset of labour and rupture of membranes); and complete avoidance of breastfeeding [7-10]. High-income countries, by focusing on women’s health and using triple-combination regimens for pregnant women with or without indications for ARV treatment, have virtually eradicated paediatric HIV. By contrast, only limited progress has been made in reducing HIV in infants in resource-constrained settings.

1.1. HIV increases maternal mortality, undermining child survival

In addition to risks for children, HIV is a major cause of maternal mortality in heavily affected areas. In countries most severely affected by HIV, such as Malawi, Zimbabwe, and South Africa, the AIDS epidemic is thought to have reversed previous gains in
maternal survival [11-14]. Some evidence indicates HIV is now the single largest cause of maternal death in parts of sub-Saharan Africa [15].

The contribution of HIV to mortality estimates does, however, vary with data source and definition of maternal mortality. In routinely collected vital registration of maternal deaths, HIV (an indirect cause of maternal death) forms a relatively low proportion of deaths [3]. There are several reasons that routinely-collected statistics in resource-constrained settings may underestimate deaths attributable to HIV. With these reporting systems, the contribution of maternal deaths from diseases that are not unique to pregnancy is largely unknown. This is partly due to poor diagnostic capability, but also results from underreporting and misreporting of such causes [16]. The inclusion or exclusion of causes that are not unique to pregnancy (e.g. HIV infection) can substantially affect the estimated magnitude of maternal mortality [3]. HIV may also be a relatively more important cause of late maternal deaths (from day 42 to one year after the end of pregnancy). Further, the HIV status of many pregnant women who die is unknown [3, 17]. Therefore, based on data from routine reporting systems alone, the contribution of HIV to maternal mortality is difficult to quantify.

Studies that specifically examine the effects of HIV on maternal mortality may provide more valid estimates. For example, health facility-based data from some hospitals in sub-Saharan Africa found that HIV has become a leading cause of pregnancy-related death in those sites [18-21]. Studies in Uganda and the Republic of Congo showed that maternal mortality ratios among women with HIV were four to five times higher than among uninfected women [11, 14]. Further, in a confidential enquiry into maternal deaths in South Africa between 2002 and 2004, AIDS was the biggest single cause of death [17]. Deaths directly attributable to AIDS accounted for 662 of the 3406 recorded maternal deaths (19.4%). The second largest cause was hypertension (628/3406; 18.4%). Substantial under-reporting was still likely as about half the women in the enquiry had an unknown HIV status.

Several mechanisms may be responsible for a higher mortality among HIV-infected women, such as increased risk for obstetric complications [22, 23]; and HIV-related illnesses such as anaemia or tuberculosis which can be aggravated by pregnancy. Moreover, it is possible that the quality of care received by women who are known to be HIV positive might also be worse than that received by other women, either due to
health-worker stigma or to more severe socioeconomic vulnerability, limiting access to services due to user fees and indirect costs.

In addition to the inherent tragedy of any maternal death, in many settings a mother's death compromises the survival of her children. Also, those children who survive as orphans have substantial vulnerability, often curtailing their life opportunities. Data from several African countries indicate that there is an increase in child mortality in the year before and after a mother's death [4]. A pooled analysis of seven prevention of mother-to-child transmission (PMTCT) trials in Africa showed that child mortality is associated with maternal death, regardless of whether the child is infected with HIV [24]. Among children not infected with HIV, mortality was five times higher among those whose mother had died compared with children whose mother was alive. This finding is consistent with a study in rural Uganda in which death or terminal illness of a mother was an independent predictor of mortality among children [25]. Rates of child death were associated with a mother's terminal illness and death, and were higher in the year immediately following the death of the mother (hazard ratio=5.5; 95% CI=2.6-11.9) than the year before the mother's death (hazard ratio=3.2; 95% CI=1.7-6.2). Taken together, available evidence indicates that improvements in child survival are closely linked to improvements in maternal health and with efforts to address maternal health. Indeed, it has been argued that the provision of ARV prophylaxis for MTCT alone is unlikely to have a marked impact on child survival in the absence of a broad integrated approach with strengthening of the existing health infrastructure and initiatives to address the health and wellbeing of women with HIV infection [26, 27].

1.2. Effects of HIV infection in infants and young children

Without ARV treatment, one quarter of HIV-infected children die in infancy, up to 60% die before reaching two years and almost all die by five years of age [4, 24]. In high HIV prevalence countries, a substantial proportion of children seen at health facilities, either as outpatients or inpatients, are HIV infected [2, 28, 29]. These children have higher rates of hospital readmission and stay longer as inpatients. ARV treatment for children is progressively becoming available [30], but is complicated by: few treatment options with limited syrup formulations; dosage changes as children gain weight; and the unique challenges of adherence and monitoring in children. The burden of clinical care for sick HIV-infected children and for provision of ARV treatment for these children requires marked human and funding resources. Inevitably, to a lesser or greater degree in
different contexts, resources will be directed away from traditional non-HIV initiatives for improving child survival. It is also important to note that mortality is higher among uninfected but HIV-exposed children compared with children born to HIV-negative women [24, 31, 32]. It is uncertain whether this excess mortality is due to maternal death; decreased ability of an ill woman to care for her child; family poverty due to sickness or underlying vulnerability; from an increased mortality due to exposure to opportunistic infections; or immunological mechanisms.

1.3. Strategies for securing maternal health and preventing HIV in infants

WHO and other international bodies promote a comprehensive strategic approach for preventing HIV infection in infants and young children, consisting of four components:

1. primary prevention of HIV infection;

2. prevention of unintended pregnancies among women living with HIV;

3. prevention of HIV transmission from mothers living with HIV to their infants; and

4. care, treatment and support for mothers living with HIV, their children and families [33].

All four components are key for optimizing the effectiveness of PMTCT programmes and reaching the overall goal of improving maternal and child health. Throughout this thesis, the acronym PMTCT is used to refer to comprehensive programmes, which include treatment, care and support for women. The comprehensive approach is built around the routine offer of HIV testing for all pregnant women, ARV prophylaxis for PMTCT, and counselling and support for infant feeding; and is strengthened by ARV treatment, care and support for women living with HIV, their children and families. In this strategy, special attention is given to the provision of primary prevention services for women identified as HIV negative (the majority of women in almost all settings) and strengthening linkages with other sexual and reproductive health services, particularly family planning [34]. Access to essential primary prevention services remains critical during pregnancy and lactation, as both biological and behavioural factors may increase a woman’s risk of acquiring HIV at this time [35, 36].

Insufficient attention has been given to the potential impact of each of the four components of the WHO PMTCT strategy. Evaluation is also needed of their potential
for synergistic contribution. A study using cost-effectiveness modelling, based on data from actual field implementation in eight African countries, demonstrated the importance of family planning services in reducing HIV infection in infants. Sweat et al estimated that reducing unintended pregnancies among women with HIV by 16% would have the equivalent impact in averting HIV infection in infants as ARV prophylaxis using single-dose nevirapine (NVP) [37].

Provision of family planning counselling and services is especially important during the postpartum period for women living with HIV who choose not to breastfeed or who stop breastfeeding early. WHO recommends that, after a live birth, the interval before attempting the next pregnancy is at least 24 months, as this reduces the risk of adverse maternal, perinatal and infant outcomes [38]. Although HIV infection is associated with a reduction in fertility [39, 40], with an abbreviated period of breastfeeding, women with HIV may be at high risk for pregnancy in the postpartum due to a reduction in lactational amenorrhea. Ovulation may occur as soon as four weeks after delivery in women who do not breastfeed. In addition to infant-feeding practices, several factors may influence fertility in the postpartum, including the physiological processes of the puerperium; the return of ovulation; and the women's resumption of sexual activity. Women may be unaware of the complex interrelationship between these factors and fertility, and thus may require repeated counselling on fertility choices and effective postpartum contraception, as well as condom promotion and provision [26, 41, 42].

For pregnant women with indications for ARV treatment, triple-drug ARV regimens benefit their health, are the most effective means of reducing MTCT, and, by improving maternal health, are likely to increase child survival [27]. Current guidelines for PMTCT in Europe, South America, the United Kingdom and United States also recommend the use of triple-combination regimens for MTCT prevention in women not requiring ARV treatment for their own health, albeit at different immunologic and/or virologic levels [9, 43-47]. In these settings, long-course, triple-drug prophylaxis is initiated during pregnancy and discontinued after childbirth for women who do not have indications for ARV treatment. By achieving undetectable plasma viral loads during pregnancy and childbirth, the use of triple-drug ARV prophylaxis has led to a marked reduction in numbers of children with HIV infection in high-income countries and South America [7, 9, 48]. In general, combination regimens are more efficacious than single-drug regimens in reducing MTCT and longer regimens are more efficacious than shorter ones. With the
exception of the particularly pronounced effects noted with NVP, no differences have been detected in the efficacy of individual ARV drugs in reducing MTCT. However, owing to variable drug action and crossing of the placental barrier, in theory, such differences may occur.

Use of triple-drug prophylaxis has increased substantially in high-income countries the last few years. By 2002, the European Collaborative Study reported that about 90% of pregnant women taking ARV drugs during pregnancy received triple combination regimens (either as ARV treatment or solely for MTCT prophylaxis) [7]. Similarly, in the United States, only 10% of pregnant women with HIV were given single-drug MTCT prophylaxis as early as 2001 [49]. Almost all pregnant women in these settings in the last 10 years, and more recently in South America receive triple-combination ARV prophylaxis, discontinued after childbirth in women without indications for ARV treatment.

Most studies in resource-constrained settings have assessed the efficacy of shorter ARV regimens, with either single or dual drug prophylaxis. HIVNET012 is considered a landmark trial, which demonstrated that a single dose of NVP for women in labour and for infants shortly after childbirth can reduce the risk of MTCT by about 50% [50]. These results became available in 1999. More recently, studies have shown that zidovudine (AZT) given from 28 weeks of pregnancy, combined with single-dose (maternal and infant) nevirapine, is even more effective in reducing both in utero and intrapartum transmission [51, 52]. Single-dose NVP remains the most commonly used regimen for MTCT prophylaxis in resource-constrained settings, though in 2006, WHO recommended that more effective regimens be used wherever possible [27].

Efficacy of ARV prophylaxis given during pregnancy and around childbirth is diminished over time in breastfeeding populations due to postpartum HIV transmission through breast-milk [53, 54]. ARV drugs, given during the breastfeeding period to women and/or infants could potentially reduce this mode of transmission [55]. This offers a promising alternative for a problem that causes tremendous difficulties wherever replacement feeding is not feasible. ARV drugs have been shown in randomised trials to reduce MTCT during pregnancy, labour and shortly after childbirth, and in observational studies to reduce HIV acquisition after sexual [56] or occupational exposure [57, 58]. Results will be available in the next few years of randomised trials and observational cohort studies.
that are currently investigating whether ARV drugs also reduce transmission through breastfeeding.

The fourth component of the WHO strategic approach to PMTCT is care, treatment and support for mothers living with HIV, their children and families. This highlights the point that increasing efforts to prevent HIV in infants are vital, but that these efforts need to be accompanied by care for women and ARV treatment for pregnant women who require it. HIV-infected women constitute up to a third of pregnant women in several countries and service delivery models need to be configured to ensure their specific needs for care and treatment are met. This is likely to reduce maternal mortality but also to have indirect benefits for a woman’s children and family. Based on results from PMTCT trials, between 6% and 16% of pregnant women with HIV in Africa have a CD4 cell count below 200 cells/mm$^3$ and require ARV treatment [59]. Some initiatives, in particular MTCT-Plus, have specifically promoted the provision of services for women and their partner’s health within PMTCT programmes in low- and middle-income countries [60]. The MTCT-Plus initiative specifically mentions the importance of involving male partners in PMTCT services, especially in ensuring they access ARV treatment thus obtaining direct benefit from such services.

Women’s needs and autonomy form a central focus of policies such as testing and counselling, fertility choices, termination of pregnancy and breastfeeding. Yet, to a large extent, this has not occurred within PMTCT programmes. Only by supporting a comprehensive set of activities that address the needs of women and children can PMTCT programmes best achieve the fundamental goal of improving the AIDS-free survival of women and their children.

1.4. Coverage of services for preventing HIV in infants and young children

Since the late 1990’s, the international community has recognized the magnitude of the burden of childhood HIV and sought to reinforce countries’ efforts to scale up PMTCT programmes [61-63]. As one of the first HIV interventions to be implemented in resource-constrained settings, PMTCT programmes have helped to create infrastructure for the later roll-out of ARV treatment and to galvanize political support for the broadening of the global response to the HIV epidemic.
In most high-income countries, near-universal coverage with a package of interventions built around the use of triple-combination ARV regimens, the avoidance of breastfeeding and elective caesarean section has virtually eliminated new HIV infections among children. With the low levels of MTCT in many of these countries, elimination targets could be set (reduction of cases of MTCT to a predetermined very low level [64]). It is estimated that in 2006, only about 700 children were infected with HIV in North America, and western and central Europe combined (Figure 2) [48]. The vast majority of HIV infections in children (<15 years) are acquired vertically, from mother-to-child transmission of HIV. The contrast in effectiveness of PMTCT services in the various regions of the world can be clearly illustrated by comparing the numbers of HIV-infected adult women and the numbers of children newly infected with HIV in each region (Figure 1 and 2). For instance there were an estimated 1.6 new HIV infections per 1000 HIV-infected women in North America, compared with 34.8 per 1000 in sub-Saharan Africa. This is more than 20 fold higher.

Compared with high-income countries, progress in scaling up effective and comprehensive PMTCT services has been slow in most resource-constrained settings. Coverage falls far short of internationally-agreed targets [61]. Globally, about 11% of pregnant women living with HIV received ARV drugs for PMTCT in 2005 [30]. This is lower than community ARV treatment coverage, a more recent and complex service.
Figure 1: Total and regional number of adult women (≥15 years) estimated to be living with HIV in 2006 (UNAIDS and WHO estimates [48])

<table>
<thead>
<tr>
<th>Region</th>
<th>Number (2006)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western &amp; Central Europe</td>
<td>200 000</td>
<td>[150 000 – 290 000]</td>
</tr>
<tr>
<td>North Africa &amp; Middle East</td>
<td>700 000</td>
<td>[330 000 – 13 000]</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>460 000</td>
<td>[360 000 – 500 000]</td>
</tr>
<tr>
<td>Eastern Europe &amp; Central Asia</td>
<td>420 000</td>
<td>[270 000 – 660 000]</td>
</tr>
<tr>
<td>Latin America</td>
<td>480 000</td>
<td>[340 000 – 760 000]</td>
</tr>
<tr>
<td>Caribbean</td>
<td>160 000</td>
<td>[100 000 – 220 000]</td>
</tr>
<tr>
<td>North America</td>
<td>310 000</td>
<td>[170 000 – 550 000]</td>
</tr>
<tr>
<td>Total</td>
<td>530 000</td>
<td>[410 000 – 660 000]</td>
</tr>
</tbody>
</table>

Total: 17.3 (95% confidence interval: 14.8 – 20.6) million

Figure 2: Total and regional estimated number of children (0-15 years) newly infected with HIV during 2006 (UNAIDS and WHO estimates [48])

<table>
<thead>
<tr>
<th>Region</th>
<th>Number (2006)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western &amp; Central Europe</td>
<td>280 000</td>
<td>[1600 – 4700]</td>
</tr>
<tr>
<td>North Africa &amp; Middle East</td>
<td>43 000</td>
<td>[23 000 – 73 000]</td>
</tr>
<tr>
<td>South &amp; South-East Asia</td>
<td>430 000</td>
<td>[230 000 – 780 000]</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>13.2 million</td>
<td>[11.4 – 15.1 million]</td>
</tr>
<tr>
<td>Latin America</td>
<td>4900</td>
<td>[3500 – 7800]</td>
</tr>
<tr>
<td>Caribbean</td>
<td>2400</td>
<td>[1400 – 3600]</td>
</tr>
<tr>
<td>North America</td>
<td>500 (&lt;1000)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>530 000</td>
<td>[410 000 – 660 000]</td>
</tr>
</tbody>
</table>

Total: 530 000 (95% confidence interval: 410 000 - 660 000)
Although PMTCT coverage levels are low, encouraging trends have been noted as national programmes increasingly move beyond pilot projects and begin more widespread implementation of these services. In three of the most severely-affected countries – Namibia, South Africa and Swaziland – maternal ARV prophylaxis uptake more than doubled from 2004 to 2005 [65]. The increased availability of ARV drugs and infrastructure supporting the expansion of ARV treatment has provided impetus to the scale up of PMTCT services. The WHO 3by5 Initiative and the United States President’s Emergency Plan for AIDS Relief (PEPFAR) has led the way in expanding HIV treatment and prevention services, including PMTCT programmes. An increase from 7% global PMTCT coverage in 2004 to 11% in 2005 occurred at the same time as these initiatives [65]. Further, by 2006 about six million pregnant women had been provided with PMTCT services through the PEPFAR plan [66]. It is anticipated that future expansion and consolidation of ARV treatment centres will be accompanied by improved PMTCT coverage. With further improvements in coverage and quality of services, PMTCT programmes could prevent: HIV infection among women and men of reproductive age; unintended pregnancies among women living with HIV; and mother-to-child transmission from women living with HIV. This would avert hundreds of thousands of new HIV infections among children; and lead to entry to services for women who could benefit from ARV treatment. Expansion of PMTCT services also provides an opportunity to strengthen other services, particularly sexual and reproductive health services. To achieve this, innovative approaches are needed, tailored to local epidemiological and socioeconomic contexts.

1.5. Opportunities for increasing coverage and effectiveness of services for preventing HIV in infants

Although, health systems are generally weak in many countries with the highest burden of HIV, maternal and child health clinics form the backbone of existing primary health care services in these countries and are relatively well established. More than 70% of all pregnant women in sub-Saharan Africa attend at least one antenatal care (ANC) visit [67]. This provides an opportunity for delivering PMTCT interventions and entering these women and their children within a comprehensive continuum of HIV prevention, care and treatment services. However, in some settings with high coverage of antenatal services, many women deliver without a skilled birth attendant, hindering provision of PMTCT interventions around childbirth. A WHO report showed that in 2007, only 46.5% of
women in Africa gave birth with the help of a skilled attendant. A skilled attendant was present at an even lower proportion of births in eastern Africa (34.2%) and western Africa (39.6%) [68]. If PMTCT programmes are to be successful, women require expanded access to high-quality antenatal, childbirth and postpartum care, and must use these services more frequently and earlier in pregnancy than they currently do.

Optimally, a full comprehensive package of PMTCT interventions would be provided as an integrated component of existing sexual and reproductive health services [27]. In turn, sexual and reproductive services should function seamlessly within broader health services. Sexual and reproductive health services, like other health services, require strong functioning health systems. In particular this involves strengthening of procurement and distribution of essential medicines through an efficient logistics system, as well as planning and management processes for human resources (i.e. staffing patterns, remuneration and motivation, training and supervision) [69]. Both technical and managerial capabilities of service providers must be increased. The rationale for integration is to increase the effectiveness and efficiency of the health system and to meet people’s needs [70]. At national planning level, integration should involve linkages between sexual and reproductive health and health sector planning processes taking place across other sectors, such as education, agriculture, youth, women’s affairs, environment and finance [69]. At the point of service delivery in primary health care systems, integration means bringing together service components and establishing strong linkages with other health-care and related social services [71]. This could be summarized as: providing services in the same facility, by the same provider and at the same visit, as far as possible. Therefore, reproductive health services need to have sufficient capacity to provide basic, quality services to individuals with different needs. For example, maternal health services need to be able to provide prevention, care or referral to other services for women with HIV. Similarly, if special ARV treatment services are in place, providers must be able to respond (either by providing care directly or through referral) to sexual and reproductive health needs of women, including family planning, care of reproductive tract infections and cervical cancer prevention and treatment, as well as counselling on domestic abuse, nutrition and child care. In the same vein, additional resources for PMTCT could also serve as an opportunity to strengthen key aspects of maternal health services, such as increased use of skilled birth attendants.
Analysing service delivery using a systems approach allows for a systematic assessment of the quality and coverage of interventions at each step of the sequence of care for women and infants. Berwick describes the central law of quality improvement as: ‘every system is perfectly designed to achieve the results it achieves’ [72]. In a systems approach to improvement of services, emphasis is placed on learning from mistakes and on modifying systems of care to make mistakes due to programmatic weaknesses less likely to occur [73]. Using a systems approach to quality improvement, the limitations noted with antenatal-focused entry to PMTCT care, indicate that additional points of entry need to be identified (Figure 3). Constructing a flowchart or cascade of potential entry points and consequent interventions provides one means of systematically analysing process systems. Several authors have previously discussed a cascade of PMTCT interventions, though largely applying this in an ANC and childbirth context [74, 75]. The cascade could be broadened to include the pregnancy, childbirth and postpartum periods. This approach facilitates the systematic identification of opportunities for PMTCT entry and service provision, as well as assessment of barriers to highly-effective services.

Across Africa, there have been many reports of high rates of losses occurring at each step of the MTCT cascade, with the majority of women and infants lost to care after childbirth [75-78]. There is much value in identifying the causes of patient attrition at each step of this cascade. Aspects of this are summarized here. Barriers to HIV testing limits the potential effectiveness of PMTCT services in almost all settings [79, 80]. However, point-of-care HIV testing with rapid tests has improved the proportion of women who test for HIV who receive their test results. A randomized trial provides evidence supporting this assertion [81]. As already mentioned in this section, patterns of health care seeking behaviour complicate provision of ARV drugs and entry into PMTCT services during pregnancy, around childbirth and in the postpartum. In settings where a large proportion of women do not deliver in health facilities, it may be optimal to provide ARV prophylaxis at the first ANC visit (such as the maternal NVP pill and infant NVP syrup in a leuer lock syringe) [82]. An important study in Zambia assessed adherence to single-dose NVP by measuring NVP drug levels in women who had been given a NVP pill to take during labour. This study showed that substantial fall-off can also occur at the cascade at this time point due to poor adherence to ARV prophylaxis [83].
Recent WHO guidelines stratify pregnant women into those requiring ARV treatment and those not [27]. While this creates an opportunity to re-focus PMTCT services on improving women’s health, it also necessitates the addition of two further steps (a maternal CD4 cell count and a decision about ARV treatment eligibility) to an already poorly functioning cascade of PMTCT interventions. Little evidence is available of how PMTCT programmes, which are already struggling to come to scale, have responded to these changes.

Although single-dose NVP is seemingly a simple regimen to implement, there have been several reports of difficulties in timing the administration of the maternal dose, suboptimal adherence, repeated doses due to false labour, missed NVP dosing of the newborn, and difficulties in ensuring the long-term continuity of care for the woman-infant pair [77, 83-86]. Given this, not surprisingly, population-level impact of single-dose NVP provision on HIV infection in infants has been low in some studies [75, 85]. A recent study at seven immunization clinics in South Africa [1] assessed the effectiveness of PMTCT interventions by determining the prevalence of HIV infection in six-week old infants with HIV RNA polymerase chain reaction tests. All participating clinics had a PMTCT programme based around provision of single-dose (maternal and infant) NVP. In total, 37.4% (931/2489) of infants had evidence of HIV exposure (HIV-antibody positive), of which 20.2% (188/931) were HIV infected. The authors conclude that, even where PMTCT coverage exists, transmission rates are high, reflecting a series of health system failures.

NVP itself is inexpensive, but the substantial investments in health system enhancements, and in HIV testing and counselling make PMTCT interventions more costly. Paradoxically, the low effectiveness of single-dose NVP may make the overall package less cost effective than use of a more expensive, but more effective regimen. In a study of the cost effectiveness of single-dose NVP, health system costs accounted for most of the programme expenses, followed by HIV testing and counselling; an extremely small proportion of total costs were for ARV drugs for MTCT prophylaxis [37]. The authors of the study concluded that by using an ARV regimen that increases the efficacy of prophylaxis from 50% to 70%, one could spend up to $152 per client on ARV prophylaxis and have a programme as cost effective as a single-dose NVP programme.
Figure 3: Expanding entry to comprehensive PMTCT: the role of antenatal, childbirth and child health services

Women who are tested, have a positive result and receive the result. X women who decline or are not offered testing. *Antenatal clinics, childbirth services and child health clinics refers to existing services which could potentially provide PMTCT entry.

ARV antiretroviral; ART antiretroviral treatment; √ women who are tested, have a positive result and receive the result. X women who decline or are not offered testing.
Most programmes have focused on establishing interventions to prevent transmission to infants, with a relative neglect of the other three components of the WHO strategic approach to PMTCT. In particular, many PMTCT programmes have not paid adequate attention to services for women themselves, especially the strengthening of linkages between PMTCT and ARV treatment services. Initiating ARV treatment during pregnancy for women with indications for such treatment, or later when they become eligible for ARV treatment is essential for avoiding maternal deaths.

The WHO four-component strategy defines a comprehensive standard of care for PMTCT to which all women of reproductive age should have access. This standard emphasizes the importance of enrolling women and children in PMTCT programmes within a continuum of care, including long-term follow up. Optimizing the impact of PMTCT programmes requires that women of reproductive age, and especially pregnant women, as well as their partners, receive HIV prevention services; that pregnant women and mothers living with HIV receive longitudinal care, treatment and support, including sexual and reproductive health services for their own needs; that HIV-exposed children (all children born to HIV-infected mothers) receive essential postpartum care to optimize their overall survival; and that children who become infected despite PMTCT interventions can access care and treatment. Improved infant feeding counselling, which begins during pregnancy and continues during the breastfeeding period, would also make a vital contribution to reducing HIV infection in infants. Community- and individual-level promotion of exclusive breastfeeding, as opposed to mixed feeding, is especially critical as this feeding mode has been shown to reduce risk of HIV transmission to infants, in addition to several other infant and maternal benefits [87]. Infant feeding counselling and support interventions also provide a key opportunity for entry into PMTCT services.

The effects of high levels of stigma and of gender-based violence on uptake of PMTCT services are difficult to quantify, but are likely to be substantial. In many areas heavily-affected by HIV, women face alarming levels of intimate-partner violence, which may be even further heightened during and after pregnancy, or following disclosure of HIV status [88-90]. Other challenges to expanding comprehensive PMTCT services in resource-constrained settings include overburdened health care workers, poor quality of HIV counselling and low levels of perceived risk for HIV among women [91-93]. Moreover, in
many settings, implementing HIV-related services that are grounded in public health principles remains subject to substantial political and ideological barriers [94, 95].
Chapter 2. Objectives and Methods

2.1. Objectives

General objectives

1. To evaluate interventions to improve effectiveness of PMTCT services during pregnancy, which directly benefit both women and their children in eastern and southern Africa; and

2. To investigate the potential role of PMTCT services shortly after childbirth and in the first year postpartum in eastern and southern Africa

Specific objectives

1. To investigate ways of increasing effectiveness of PMTCT services during pregnancy, in particular use of repeated audit to identify programmatic weaknesses and inform targeted actions;

2. To assess the feasibility of identifying HIV exposure in newborns shortly after birth as well as to determine the efficacy of ARV prophylaxis given to newborns whose mother had not received ARV drugs;

3. To investigate uptake and acceptability of provider-initiated HIV testing among women bringing their child for immunization or acute paediatric services; and

4. To assess effects of HIV on disease patterns and health needs among women in the first year after childbirth
2.2. Study settings

Research activities took place in two parts of sub-Saharan Africa: Mombasa in the Coast Province of Kenya and Johannesburg in Gauteng Province, South Africa. This section provides background information about the HIV epidemic and country-level responses in both settings. This overview is summarized in Table 1.

Kenya

In East Africa, where HIV infection levels have been lower than in the south of the continent, a general trend of a declining HIV prevalence appears to be continuing. HIV prevalence among pregnant women has dropped in Kenya, as it has in Tanzania and, to a lesser extent, in Rwanda [5]. In recent years, a steep decrease in infection levels among pregnant women has occurred at the majority of antenatal surveillance sites in Kenya. At five sites, mean HIV prevalence fell from 25.1% in 1998 to 7.9% in 2004, while in three other sites it declined from a mean of 14.7% in 2001 to 4.3% in 2004 [96]. Importantly, in Kenya, HIV prevalence among young pregnant women less than 20 years (used as a proxy for recent infection) declined by more than 25% in both urban and rural areas [5]. This trend is largely attributed to behavioural changes resulting from large-scale prevention efforts that began in 2000, including delayed sexual debut, increased condom use and reduced rates of sex with multiple partners [97]. Nevertheless, Kenya is still contending with a serious AIDS epidemic, with an estimated 1.3 million people currently living with HIV of a total population of 34 million [5, 98]. Moreover, the declines in HIV among the general population may not be occurring among high-risk groups. A survey in Mombasa among female sex workers in 2000 found 30.6% (151/493) of women were HIV-infected, while the HIV prevalence was 33.3% (166/498; \( P=0.36 \)) in 2005, measured using identical methodology as the initial survey [99, 100]. Most-at-risk populations like female sex workers form bridging groups, a source of ongoing HIV transmission to the general population.

A population-based survey in 2003 found that about 14% of Kenyan men and women had ever had an HIV test [101]. By the end of 2006, it was estimated that some 125 000 people were receiving ARV treatment through public and private facilities, 44% of those who require this treatment in Kenya [65]. However, in 2005, only about 20% of HIV-infected pregnant women received ARV prophylaxis to prevent MTCT [65].
The 2003 Kenya demographic and health survey (DHS) found that 88% of pregnant women in Kenya make at least one visit to antenatal clinics, 31% two or three visits, and about 52% make four or more visits [101]. Women who attended ANC were a median 5.9 months pregnant at their first ANC visit, almost in the third trimester of pregnancy. Coverage of ANC in the Coast Province was the same, with 88% of pregnant women attending ANC at least once. Data have been presented on health seeking behaviours of pregnant women at the study site in Mombasa [82]. From January to December 2005, data were collected from ANC and childbirth records at five public facilities in the urban Mombasa district and adjacent rural Kwale district. These data showed that first ANC visits occurred at median 6.4 months (IQR-5.1-7.4) and 6.0 months (IQR-5.1-6.7) of pregnancy in Mombasa and Kwale respectively. Of women attending ANC in Mombasa, 63.7% (5097/8008) attended more than once, compared with only 51.3% (1056/2058) in Kwale (P<0.001). About a quarter of women attending ANC in Mombasa (23.6%; 1886/8008) completed the WHO recommended four-visit schedule, while 13.5% (277/2058) did so in Kwale.

Based on information from the 2003 DHS survey, only two out of five births (40%) in Kenya are delivered in a health facility. Levels of skilled birth attendance are even lower in the Coast Province (34%). Attendance at child health and immunization clinics is, however, higher. According to information from both the vaccination card and the mothers’ reports, 89% of children aged 12-23 months have received the first dose of DPT-HepB-Hib, while 91% have received the first dose of polio. Overall, 57 percent of children are considered fully immunized (one dose of BCG, three doses each of DPT-HepB-Hib and polio, and one dose of measles vaccine).

The Kenya Service Provision Assessment of 2004 (KSPA 2004) survey provides information about the general performance of health facilities [102]. Performance is assessed at a representative sample of facilities, using a Facility Inventory Questionnaire (information on the availability of resources, support systems and infrastructure), a health provider interview, observation of patient-provider consultations and exit interviews with clients. The KSPA 2004 found that about two thirds of facilities charge some form of user fees for ANC, while 74% of all facilities offering delivery services charge some form of user fee. Almost all hospitals and maternities, and all private for-profit and faith-based facilities charged user fees for delivery services. A further finding was that only one quarter of first-visit ANC clients were assessed for all of the relevant
medical history items (age, last menstrual period, any prior pregnancy, complications in prior pregnancy and medications currently taken). Partographs and protocols to support quality delivery standards are available in only 39% and 7% of facilities, respectively.

### Table 1: HIV and selected indicators in Kenya and South Africa

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Kenya</th>
<th>South Africa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>34 256 000</td>
<td>47 000 000</td>
</tr>
<tr>
<td>Per capita gross national income</td>
<td>US $1050</td>
<td>US $10 960</td>
</tr>
<tr>
<td>Number living with HIV</td>
<td>1 300 000 (3.8% of population)</td>
<td>5 500 000 (11.7% of population)</td>
</tr>
<tr>
<td>Number who have initiated ARV treatment</td>
<td>125 000 (44% of need)</td>
<td>325 000 (32% of need)</td>
</tr>
<tr>
<td>Women ≥15 years living with HIV</td>
<td>740 000</td>
<td>3 100 000</td>
</tr>
<tr>
<td>Proportion of all HIV-infected women who receive ARV prophylaxis in pregnancy</td>
<td>20%</td>
<td>30%</td>
</tr>
<tr>
<td>Proportion of general population ever tested for HIV</td>
<td>14% of women, 13% of men</td>
<td>31% of women, 25% of men</td>
</tr>
<tr>
<td>Antenatal care coverage^</td>
<td>88%</td>
<td>94%</td>
</tr>
<tr>
<td>Gestation at first ANC visit (median)</td>
<td>5.9 months</td>
<td>5.2 months</td>
</tr>
<tr>
<td>Proportion of births attended by skilled health personnel</td>
<td>40%</td>
<td>83%</td>
</tr>
<tr>
<td>Proportion attended child health services at least once</td>
<td>89%</td>
<td>&gt;90%</td>
</tr>
</tbody>
</table>

^Proportion of women attended, at least once during their pregnancy, by skilled health personnel for reasons relating to pregnancy. ARV: antiretroviral; ANC: antenatal care

### South Africa

South Africa has a unique history, and is a young democracy, facing marked challenges. Not least of the challenges faced is, in sheer numbers, one of the world's largest HIV epidemics, with an estimated 5.5 million people living with HIV (total population: 47 million) [48]. A recent study showed the first evidence that HIV prevalence and incidence are declining in South Africa. This evidence is from the 2006 antenatal survey, which used standard unlinked anonymous methodology, and obtained prevalence estimates for each district in the country [103]. The national HIV prevalence among pregnant women decreased from 30.2% to 29.1%, a statistically significant reduction. A small reduction was also noted among pregnant women <20 years old, from 15.9% to 13.7%, which implies a decline in incidence in the general population. The prevalence among the pregnant women sampled in Gauteng province was 30.8%. Among the general
population, according to a 2005 national HIV household survey, one in three women aged 30–34 years were living with HIV in 2005, as were one in four men aged 30–39 years [104].

The latest official mortality data show total deaths (from all causes) in South Africa increased by 79% from 1997 to 2004 (from 316,505 to 567,488) [105]. Death rates from natural causes for women aged 25–34 years increased fivefold between 1997 and 2004, and for males aged 30–44 they more than doubled over that period. A large proportion of this rise in death rates has been attributed to the AIDS epidemic [106, 107], and the increasing death toll makes South Africa one of only 21 countries in which life expectancy at birth has declined by four years or more between 1990 and 2001 [106].

Despite these levels of infection and mortality, a large proportion of South Africans do not believe they are at risk of acquiring HIV infection. Half of respondents who were found to be infected with HIV in a 2005 national household survey, had reported that they felt they were at no risk of acquiring HIV [104]. In the same survey only 31% of women and 26% of men had previously been tested for HIV.

Access to treatment and care for people living with HIV has increased in the past few years. South Africa introduced ARV treatment in the public sector in 2004. Treatment scale-up initially began slowly, but expanded rapidly in 2006, with an estimated 325,000 people having received treatment by the end of 2006 [65]. This represents 32% of those who presently require ARV treatment. Progress has also been made in the provision of PMTCT services, with about 30% of HIV-infected pregnant women receiving ARV prophylaxis for PMTCT in 2005.

Findings of the DHS survey from 2004-2006 are expected in late 2007. The previous DHS was in 1998, which reported a very high utilisation of antenatal care (94%), with levels of 95% in Gauteng Province [108]. The median pregnancy gestation of the initial antenatal visit was 5.2 months. The report showed that 83% of births occurred in a health facility, with higher levels noted in Gauteng Province (93%). Similar patterns were noted in the proportion of deliveries accompanied by a skilled birth attendant: 84% for all of South African and 94% in Gauteng. Over 90% of children had received the first doses of DPT and polio; however, only 63% of children age 12-23 months were fully immunized. At the Coronation Women and Children Hospital, the median gestation at first antenatal clinic visit was about 25 weeks in one report [109].
South Africa has a complex political environment which has markedly influenced HIV policies. HIV lays bare issues of gender, race, societal norms, economic inequities and north-south tensions. The rapidly evolving, but still racially-charged atmosphere in South Africa creates considerable difficulties in negotiating these issues. Even in the period when the global icon Nelson Mandela had most influence in South Africa, HIV prevalence among pregnant women rose from 0.7% in 1990 to 24.5% in 1999 at the end of his presidency [103]. When Thabo Mbeki became president in 1999, he sought an African understanding of the country’s problems, including HIV/AIDS [95, 110]. A recurrent theme in his scrutiny of the causes of HIV/AIDS is the disparity between heterosexual transmission of HIV in Africa and in the Western world, and the connotations this infers about African sexuality, particularly sexuality of African males. This is well illustrated in the following quote of President Mbeki:

> And thus does it happen that others who consider themselves to be our leaders take to the streets carrying their placards, to demand that, because we are germ carriers and human beings of a lower order that cannot subject their passion to reason, we must perforce adopt strange opinions to save a depraved and diseased people from perishing from a self-inflicted disease [111].

Clear answers are needed to the ‘Why Africa?’ question. Adequate answers to this question will need to include, not only biological and behavioural rationale, but also the dynamic interplay of these factors with socioeconomic, economic-migratory, cultural and historical influences. While attempting to seek answers to this question, the South African government has adopted controversial HIV policies. A leading activist, Zackie Achmat, head of the Treatment Action Campaign in South Africa has referred to these policies as “a Holocaust against the poor” [112]. A constitutional court ruling in 2002 was necessary before PMTCT programmes were scaled up in South Africa. The details of this court case and its implications for implementation of the PMTCT programme in South Africa are discussed in additional detail in Annex 1. The government has since adopted more conventional policies, but has been criticised by international bodies for its slowness in providing ARV treatment [65]. Outcomes of HIV research and programme implementation in South Africa need to be interpreted within the above socio-political context.
2.3. Study design

In the Coast Province of Kenya, a cross-sectional study took place with 500 women who were within one year of childbirth. Study activities occurred at a provincial-level hospital, the Coast Provincial General Hospital, Mombasa. Women attending an immunization and acute care paediatric clinic participated. The study formed part of the Uzazi Bora five-year safe motherhood project funded by the European Union (grant number KE/AIDCO/2001/460). A cross-sectional study design was used to determine health needs and to compare women with HIV infection and those uninfected (specific objective 4; article 7). A lay counsellor offered women HIV counselling and rapid HIV testing. Attitudes to HIV testing in child health clinics were assessed by asking women whether they thought testing should be offered in such facilities and to explain their opinion. This study aimed to address specific objective 3 and its findings are presented in article 6.

To address specific objective 1, PMTCT services at Coronation Women and Children Hospital were evaluated on two occasions, firstly from 2000-2002, and then between 2004 and 2005. Coronation is a public sector facility providing secondary-level paediatric, and obstetric and gynaecology services in Johannesburg, Gauteng Province, South Africa. In the first evaluation, ARV treatment was not yet available and research activities assessed process indicators and uptake of PMTCT services built around single-dose (maternal and infant) NVP (article 1). The second evaluation, presented in article 2, evaluated the provision and outcomes of ARV treatment for pregnant women with indications for such treatment. Outcomes among women who initiated ARV treatment were compared with those receiving single-dose NVP. In addition, a randomized trial was conducted in South Africa to assess the efficacy of ARV prophylaxis in newborns whose mother had not received ARV drugs. By determining efficacy of ARV prophylaxis given to newborns whose mother had not received ARV drugs, the study aimed to address specific objective 2. In addition to Coronation Hospital, two other sites participated, namely: Chris Hani Baragwanath Hospital, Soweto, in Gauteng Province and Mowbray Hospital in Cape Town, Western Cape Province. Further discussion of the methods used in this randomized trial and its results are in article 3.

Several steps were used to evaluate and inform targeted improvements in PMTCT service delivery at Coronation Women and Children Hospital. These steps were similar in the two studies presented in chapter 3.1. A baseline audit evaluated several
indicators, such as time from HIV diagnosis to ARV treatment initiation, and proportion of HIV-exposed infants who received single-dose NVP. Data were extracted from hospital records over a two-week period in the initial study and a six-week period in the second study. After collating and analyzing the findings of the audit, changes in service delivery were made to address weaknesses identified. Two repeat audits were used to provide data to assess whether service delivery had improved in the first study. Different methods were used to assess changes in service delivery in the second study. Routine ongoing monitoring systems were established to allow for more frequent and systematic assessment of programme effectiveness and weaknesses. To determine the effectiveness of these interventions, service delivery outcomes were compared before and after intervention. Mostly process indicators were used to assess service performance, but MTCT rates are also available, showing overall effectiveness of PMTCT services.

Ethical and legal considerations were used to assess the advantages and disadvantages of mandatory testing of newborns for HIV exposure. This article (number 4) which focuses on specific objective 2, also considers a hypothetical case where a doctor tests a newborn for HIV exposure and provides ARV post-exposure prophylaxis to the newborn against the mother’s wishes. This case was placed on an online HIV Policy and Ethics Discussion Forum. The views of health professionals who commented on the case are summarized in a case report for a regular ethics column in the Southern African Journal of HIV medicine (article 5).

A narrative review paper was also written critiquing the widely-held view that efavirenz is a human teratogen. Common clinical scenarios are considered, such as women receiving efavirenz-based ARV treatment who become pregnant. Also on the theme of safety of ARV treatment during pregnancy, a case is reported of an infant with Dandy-Walker variant who was exposed during the first trimester of pregnancy to stavudine, lamivudine, nevirapine, cotrimoxazole, isoniazid, rifampicin, pyrazinamide and ethambutol. These papers discuss potential effects of in utero exposure to ARV drugs, a vital aspect of safety considerations of these drugs. These safety considerations inform selection of ARV regimens for women of reproductive potential and are used in making decisions about regimen change for women who become pregnant while receiving ARV treatment. These papers are contained within Annex 4 and 5.
In large part, the PMTCT narrative review articles (Annex 2 and 3) summarize the findings of the studies reported in this thesis, and aim to place these findings within the context of existing evidence. For these papers, literature searches were done, both of journals articles and publications of international organisations like WHO.
Figure 4: Research articles within the MTCT systems approach to antenatal, childbirth and child health services

- **Pre-conception**
  - Women receiving ART
  - HIV-infected women not receiving ART

- **Pregnancy**
  - ART continuation or initiation, and infant feeding counselling
  - Determine eligibility for ART

- **Labour and delivery**
  - Infant ARV prophylaxis during pregnancy and/or labour, and infant feeding counselling

- **First year postpartum**
  - Infant feeding counselling and support, family planning services, and care and treatment for women

- **Entry points**
  - Women with unknown HIV status
  - Antenatal clinics*: HIV testing for pregnant women
  - Childbirth services*: HIV testing for women around childbirth or testing newborns for HIV exposure
  - Child health clinics*: HIV testing for women or infants (HIV exposure or diagnosis)

- **Interventions**
  - ART prophylaxis during pregnancy and/or labour, and infant feeding counselling

*Antenatal clinics, childbirth services and child health clinics refers to existing services which could potentially provide PMTCT entry.
2.4. Ethical considerations
For the Kenyan studies, the Kenyatta National Hospital Ethics and Research Committee reviewed and approved study activities. Women gave written informed consent, including for anonymous HIV testing in the Kenyan cross-sectional study. Several efforts were made to ensure that women who participated in the studies obtained direct benefits from participation. Participants were advised to return for HIV and other test results and, if required, received treatment according to local guidelines. Those who had health problems identified during the course of the studies were linked with available local services, as appropriate. For conditions such as syphilis or malaria, women with positive results were contacted and asked to return immediately. All participants were offered same-day HIV testing and counselling. Women identified as HIV positive were taken and shown the onsite chronic HIV care clinic and entered into long-term care services, which include ARV treatment. Women in all studies were explicitly told they could opt out of HIV testing procedures.

All studies in South Africa reported here, obtained approval from the University of the Witwatersrand Human Research Ethics Committee. As with all randomized trials, it is important to ensure that equipoise exists between study arms, to avoid knowingly exposing study participants to sub-optimum interventions. In the randomized trial included in this thesis (article 3), no evidence was available at initiation or during the trial that combination regimens for infants born to women who had not received ARV drugs was superior to single-drug prophylaxis. The trial compared the standard of care at that time (six weeks of AZT for the infant) with an alternative intervention (single-dose NVP for the infant). No additional evidence became available during the trial to indicate that the assumption of equipoise was no longer valid. After completion of the study, results were published from different trial in Malawi which showed that a combination of ARV drugs (single-dose NVP and AZT for one week) was more effective than single-drug prophylaxis for infants born to women who had not received ARV drugs.

2.5. Data management and analysis
Standard data collection tools were used wherever possible, such as the WHO Alcohol Use Disorders Identification Test (AUDIT) for identifying women with hazardous and harmful patterns of alcohol consumption. In the Kenyan cross-sectional study, data were collected using a pre-tested structured questionnaire, administered in Swahili. Medical
conditions were classified according to standard methods, for instance categorizing depression with the ICD-10 codes. Data collected during interviews and laboratory investigations were double entered by separate data entry clerks. Intercooled Stata 8.0 (Stata Corporation, College Station, Texas, USA) was used for statistical analysis.

Mixed quantitative-qualitative methods were used to determine attitudes to HIV testing, described in article 6. An open-ended question was used to collect data on attitudes. Women’s responses to these questions were coded, with code labels that developed as themes emerged. Text was grouped according to common themes and presented in a frequency distribution. Representative quotations are also used to illustrate main themes.

In the South African studies at Coronation Women and Children Hospital, data were extracted from routine hospital records. Intercooled Stata 8.0 (Stata Corporation, College Station, Texas, USA) was used for statistical analysis in the 2006 audit (article 2), while Epi-Info 2000 was used in the earlier study (article 1). For the randomized trial reported in article 3, double data entry was performed using a Microsoft Access database. Case report forms and laboratory results had been checked for accuracy and completeness. Data analyses were performed with SAS version 8.2 (SAS Institute, Cary, North Carolina, USA).

2.6. Data dissemination

The following papers have been published or submitted for publication, and provide the basis for this thesis:


2. van der Merwe K*, Chersich MF*, Technau K, Umurungi Y, Conradie F, Coovadia A. Integration of Antiretroviral Treatment Within Antenatal Care in Gauteng Province, South Africa. *Journal of Acquired Immune Deficiency Syndrome* 2006. December 15. 43 (5); 577-81. *Contributed equally to this article. (Chapter 3.1)*

child HIV-1 transmission in infants of untreated mothers. AIDS 2005.19:1289-1297. (Chapter 3.2)


Besides the research objectives, this work also has developmental goals, such as informing improvements in service delivery at the study sites and other settings. The
results of each component of this research were presented to staff and other interested parties at respective sites. Study findings were also presented at national and international conferences [82, 84, 113-119].
Chapter 3. Results

3.1 Improving effectiveness of PMTCT services during pregnancy

Article 1: Acceptability and utilisation of voluntary HIV testing and nevirapine to reduce mother-to-child transmission of HIV-1 integrated into routine clinical care
Acceptability and utilisation of voluntary HIV testing and nevirapine to reduce mother-to-child transmission of HIV-1 integrated into routine clinical care

M Urban, M Chersich

Objectives. Use of nevirapine for prevention of mother-to-child transmission (PMTCT) of HIV-1 has been routine clinical care at Coronation Women and Children’s Hospital since April 2000. We assessed the effect of regular audit and targeted interventions on the utilisation of the PMTCT programme.

Methods. Review of antenatal cards and hospital records of women discharged following delivery, in three time periods between October 2000 and February 2002. Following the initial audit an intervention was implemented to eliminate weaknesses in our PMTCT service. Following the second audit the hospital became a pilot site for the Gauteng PMTCT programme.

Results. In the initial audit 53.2% of women (159/299) were tested for HIV and received their results, while 56% (14/25) of identified HIV-infected women, and 16% (4/25) of their infants, received nevirapine. By the third audit 74.3% of women (266/358) received their results, and 86% (43/50) of HIV-positive women and 74% (37/50) of newborns were documented to have received nevirapine. In all three audits over 90% of women initiating antenatal care at the hospital were tested for HIV, while women who initiated care at district community clinics were less likely to receive testing.

Conclusions. Ongoing audit has been important for targeting obstacles to detection of HIV-infected women and documented nevirapine uptake by women and infants. Rates of HIV testing and nevirapine use have increased significantly. Voluntary counselling and testing for HIV and use of nevirapine are acceptable to pregnant women in our setting. Roll-out of the pilot programme to district community clinics is essential for further improvement.

whether women received their HIV test result; (iv) whether a rapid plasma reagin (RPR) test for syphilis was done (for comparison purposes); and (v) whether nevirapine use was documented for mother and infant. Antenatal cards and hospital records of those not tested were assessed for missed opportunities for VCT at CWCH.

Women initiating antenatal care at CWCH receive VCT, and if they consent, are tested for HIV at the first visit. At the time audit 1 was conducted a laboratory enzyme-linked immunosorbent assay (ELISA) test was used. HIV-infected women were identified at the second visit and referred to the antenatal HIV clinic. One of the community clinics had a VCT system, but the other clinics tested only sporadically. In the interests of confidentiality results were documented cryptically on the patient-held antenatal card. Each clinic had its own method of documentation. HIV-infected women who presented to the hospital in labour were identified by the nursing staff and given nevirapine. In the postnatal wards, infants were detected and treated in a similar manner.

Problems with the operational aspects identified in the initial audit (Table I) were addressed initially by means of an intervention to increase staff awareness. This included discussions with relevant staff, and a poster campaign in the hospital to target the problems identified. The audit was repeated in April 2001, 2 months after the intervention.

With the implementation of the national PMTCT pilot project (described by McCoy et al4) in October 2001, CWCH became a provincial pilot site. Audit 3 was conducted in February 2002. While the pilot project provided additional resources to the hospital, the community clinics were not included.

Statistical analysis was conducted using Epi-Info 2000. Audit data were compared using a chi-square or Fisher’s exact test as appropriate. Audit 1 was used as a control group for audit 2, and audit 2 for audit 3.

The study was approved by the University of the Witwatersrand Committee for Research on Human Subjects, protocol number M01-04-23.

Results

A total of 965 records were assessed across the three audits. Audit data for the whole group, and for those initiating antenatal care at CWCH, are presented in Tables II and III respectively.

The system for syphilis testing was efficient in all audits, whether antenatal care was initiated at CWCH or elsewhere. A total of 900/965 records (93.3%) had a rapid plasma reagin (RPR) result documented.

The rate of HIV testing differed markedly between women who initiated antenatal care at CWCH and those who did not. In total 424/965 women (43.9%) initiated antenatal care at CWCH, forming a similar proportion in each audit. The rates of testing for HIV among these subjects were above 90% for all the audits, with 401/424 (94.5%) tested.

Of the 965 women, 541 (56.0%) did not start antenatal care at CWCH. Most of these subjects initiated antenatal care at the community clinics, while 71 patients (7.4% of all subjects) received no antenatal care. The rate of HIV testing among these women was poor in audit 1, with only 37.2% (64/172) tested. This improved to 64.1% (109/170) and 74.9% (149/199) in

### Table I. Process of audit and intervention

<table>
<thead>
<tr>
<th>Problems at initial audit</th>
<th>Probable reason/s for problem</th>
<th>Interventions following audit 1</th>
<th>Changes introduced by PMTCT pilot project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to offer VCT at community clinics</td>
<td>Lack of VCT knowledge, skills and resources</td>
<td>Clinic staff informed about availability of VCT training and encouraged to implement VCT</td>
<td></td>
</tr>
<tr>
<td>Failure to test at hospital antenatal clinic visit</td>
<td>Lack of staff awareness</td>
<td>Staff education</td>
<td>Salaried lay counsellors</td>
</tr>
<tr>
<td>Failure to obtain HIV results</td>
<td>Lack of staff awareness OR Women presenting in advanced labour OR Difficulty interpreting encoded results OR Poor documentation</td>
<td>Staff education</td>
<td>‘Rapid’ on-site tests OR Women received nevirapine to take home for self-administration</td>
</tr>
<tr>
<td>No maternal dose of nevirapine recorded</td>
<td>Lack of staff awareness OR Women presenting in advanced labour OR Difficulty interpreting encoded results OR Poor documentation</td>
<td>Staff education</td>
<td>Lay counsellors monitor infant dosing</td>
</tr>
<tr>
<td>No infant dose of nevirapine recorded</td>
<td>Lack of staff awareness OR Difficulty interpreting encoded results OR Poor documentation</td>
<td>Staff education</td>
<td></td>
</tr>
</tbody>
</table>

VCT = voluntary counselling and testing.
audits 2 and 3 respectively. As there may have been missed opportunities for testing at CWCH before the onset of labour, the frequency of missed opportunities in untested women was assessed in audits 1 and 2. There were 51 missed opportunities in audit 1 compared with 24 in audit 2.

The rate at which women received nevirapine increased significantly between audits 1 and 3 ($p = 0.004$, chi-square). The only women who received nevirapine to take home for self-administration were those initiating antenatal care at CWCH in audit 3. None of these women took their nevirapine more than 48 hours before delivery.

### Table II. HIV testing and nevirapine use for all patients

<table>
<thead>
<tr>
<th></th>
<th>Audit 1 October 2000 (N = 299)</th>
<th>Audit 2 March 2001 (N = 308)</th>
<th>Audit 3 February 2002 (N = 358)</th>
<th>p-value * (audit 2 v. audit 1)</th>
<th>p-value * (audit 3 v. audit 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV tested (No. (%))</td>
<td>181 (60.5)</td>
<td>242 (78.6)</td>
<td>300 (83.8)</td>
<td>&lt; 0.001</td>
<td>0.08</td>
</tr>
<tr>
<td>HIV results obtained antenatally (as % of the tested)</td>
<td>159 (82.8)</td>
<td>213 (88.0)</td>
<td>266 (88.7)</td>
<td>0.95</td>
<td>0.81</td>
</tr>
<tr>
<td>ELISA-positive (as % of tested)</td>
<td>27 (14.9)</td>
<td>58 (24.0)</td>
<td>54 (18.0)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Positive results obtained antenatally (% of positives)</td>
<td>25 (93)</td>
<td>51 (98)</td>
<td>50 (93)</td>
<td>0.79</td>
<td>0.41</td>
</tr>
<tr>
<td>Mother received nevirapine (as % of antenatal positives)</td>
<td>14 (56)</td>
<td>39 (76)</td>
<td>43 (86)</td>
<td>0.07</td>
<td>0.22</td>
</tr>
<tr>
<td>Nevirapine 2 - 48 hours before delivery (as % of those receiving nevirapine)</td>
<td>26 (67)</td>
<td>–</td>
<td>30 (70)</td>
<td>–</td>
<td>0.76</td>
</tr>
<tr>
<td>Baby received nevirapine (as % of antenatal positives)</td>
<td>4 (16)</td>
<td>23 (45)</td>
<td>37 (74)</td>
<td>0.01</td>
<td>0.003</td>
</tr>
</tbody>
</table>

* Chi-square, or Fisher’s exact test.

### Table III. HIV testing and nevirapine use for subjects initiating antenatal care at CWCH

<table>
<thead>
<tr>
<th></th>
<th>Audit 1 October 2000 (N = 127)</th>
<th>Audit 2 March 2001 (N = 138)</th>
<th>Audit 3 February 2002 (N = 159)</th>
<th>p-value * (audit 2 v. audit 1)</th>
<th>p-value * (audit 3 v. audit 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV tested (No. (%))</td>
<td>117 (92.1)</td>
<td>133 (96.4)</td>
<td>151 (95.0)</td>
<td>0.13</td>
<td>0.55</td>
</tr>
<tr>
<td>HIV results obtained antenatally (as % of the tested)</td>
<td>101 (86.3)</td>
<td>130 (96.7)</td>
<td>150 (99.3)</td>
<td>&lt;0.001</td>
<td>0.34</td>
</tr>
<tr>
<td>ELISA-positive (as % of the tested)</td>
<td>10 (8.5)</td>
<td>23 (17.3)</td>
<td>24 (15.9)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Positive results obtained antenatally (% of positives)</td>
<td>8 (60)</td>
<td>22 (96)</td>
<td>24 (100)</td>
<td>0.21</td>
<td>0.31</td>
</tr>
<tr>
<td>Mother received nevirapine (as % of antenatal positives)</td>
<td>6 (75)</td>
<td>21 (95)</td>
<td>22 (92)</td>
<td>0.17</td>
<td>1.0</td>
</tr>
<tr>
<td>Nevirapine 2 - 48 hours before delivery (as % of those receiving nevirapine)</td>
<td>Not checked</td>
<td>14 (67)</td>
<td>17 (77)</td>
<td>–</td>
<td>0.44</td>
</tr>
<tr>
<td>Baby received nevirapine (as % of antenatal positives)</td>
<td>1 (12.5)</td>
<td>7 (30)</td>
<td>19 (79)</td>
<td>0.39</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

* Chi-square, or Fisher’s exact test.
Discussion

The study demonstrates significant improvements over time in the rates of testing for HIV. Audit 1 showed that the CWCH antenatal clinic provided an effective VCT and HIV testing programme for those initiating antenatal care at the hospital, and demonstrates that HIV testing is well accepted by women attending antenatal care. Among women not initiating antenatal care at CWCH the rate of HIV testing was low because several community clinics did not have a well-established VCT system. Testing rates improved over time, but remained suboptimal. The fact that RPR testing was provided efficiently suggests that these clinics give competent antenatal care, and that with appropriate support they should be able to implement VCT for HIV. Although there was a reduction in missed opportunities for HIV testing at CWCH, in many cases there were no opportunities for HIV testing at the hospital. We concur with the recommendation of McCoy et al.¹ that the PMTCT programme should be developed and integrated into other related programmes at subdistrict level.

The proportion of HIV tests for which results were obtained did not improve between the audits, except among women who initiated antenatal care at CWCH between audits 1 and 2. For these patients virtually all results were obtained once staff awareness improved, because undocumented results are readily accessible by computer. Thus the introduction of a rapid HIV test yielded no further improvement, contrary to the findings of a previous study² demonstrating increased uptake of testing with a rapid test compared with a laboratory ELISA test. The use of a rapid test would more likely have been useful in the community clinics, where there were persistent problems with obtaining HIV results.

The maternal dose of nevirapine should be taken between 2 and 48 hours before delivery. Nearly one-third of women who received nevirapine did not take it in this time period (i.e. timeously). One might expect that women would tend to take nevirapine too late if it is only dispensed by labour ward staff, and too early if they self-administer it. However, in only one case was the nevirapine taken too early and this was administered by hospital staff. In the small group of subjects who received nevirapine for self-administration there was no significant improvement in the rate at which these women took their nevirapine, or in the rate that they took it timeously. It is likely that self-administration of nevirapine would be more important for women who live further away from the hospital, particularly those attending community clinics. Reasons for failure to self-administer nevirapine at the correct time require further elucidation. Our impression is that some women find it difficult to decide when to take their nevirapine, or may misplace the tablet. It is therefore important that women be counselled on the correct use of nevirapine and that the labour ward staff confirm that nevirapine has been taken.

The emphasis on maternal diagnosis and prophylaxis may result in an underemphasis on giving nevirapine to the infant. However, this is an integral part of the regimen. In addition, post-exposure prophylaxis with neonatal nevirapine may be important if women do not receive nevirapine or do not receive it timeously (G Gray et al. — paper presented at the 14th International AIDS Conference, Barcelona, 2002 (abstract No. LB0R13)). The neonatal dose of nevirapine was infrequently documented at the initial audit. This improved, but by the third audit neonatal nevirapine was still not documented in one-quarter of cases. The neonatal dose is given in the postnatal wards, and requires that the antenatal card and delivery notes be rechecked and nevirapine given accordingly.

The confidential nature of information regarding HIV status unintentionally increases the risk of missed opportunities for nevirapine use. Some women are reluctant to notify staff of their status. This is unlikely to change until stigma related to HIV-positive status reduces. In addition, it has proved difficult to develop a uniform but confidential system of documentation for HIV results.

The fact that almost half of the identified HIV-infected women in audit 1 were not documented to have received nevirapine may reflect poor documentation. The study was limited by the fact that it relied on written documentation in the antenatal cards and hospital records, and it was not possible to differentiate with certainty between medication not given and medication not documented. While we attempted to improve documentation, we feel that for audit purposes it is appropriate to assume that ‘not documented means not done’.

Another limitation was the retrospective collection of data, resulting in an inability to collect information on women who received antenatal care in our service but delivered elsewhere.

It has been noted that public health interventions in developing countries, such as the Expanded Programme for Immunisation, have taken some time to achieve adequate coverage.³ In view of our use of historical control groups, it is not possible to be certain that the improvements documented were due to the interventions applied rather than related to the passage of time. However, it seems very likely that ongoing quality control through audit and intervention has been important in the improvement our PMTCT programme. It is apparent from our results that the incremental effect of drop-offs at several stages in the process of HIV testing, obtaining results and providing nevirapine on the overall efficiency of the PMTCT programme can be very large. Attention to each detail is therefore essential.

Conclusion

The overall efficiency of our PMTCT service improved from audit to audit. Testing for HIV and use of nevirapine were well
accepted. The main shortcomings with HIV testing were
among women who initiated antenatal care outside the
hospital. Roll-out of the PMTCT pilot project to the community
clinics is essential. In addition, significant challenges remain in
the provision of nevirapine to newborns, and in the timing of
the maternal dose. Similar to many other public health
interventions, the PMTCT programme requires ongoing quality
control to ensure effectiveness.

Our thanks to the hospital counselling staff, health workers, and
Professors K Bolton and S Levin.

References

     compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in


3. Eshlemann SH, Misiria M, Guay L, et al. Selection and fading of resistance mutations in
     women and infants receiving nevirapine to prevent HIV-1 vertical transmission (HIVNET


5. Malonza IM, Richardson BA, Kreiss JK, Bwayo JJ, John-Stewart GC. The effect of rapid HIV-1
     testing on the uptake of perinatal HIV-1 interventions: a randomised clinical trial. AIDS
     2003; 17:113-118.

6. Abdullah MF, Young T, Bito L, Couture N, Myers JE. Public health lessons from a pilot
     programme to reduce mother-to-child transmission of HIV-1 in Khayelitsha. S Afr Med J

Accepted 16 January 2004.
Article 2: Integration of antiretroviral treatment within antenatal care in Gauteng Province, South Africa
Integration of Antiretroviral Treatment Within Antenatal Care in Gauteng Province, South Africa

Karin van der Merwe, MBCh,* Matthew F. Chersich, MD, MPH,†‡ Karl Technau, MBCh,* Yvonne Umurungi, MBCh,§ Francesca Conradie, MBCh,§ and Ashraf Coovadia, MBCh, FCPaeds*

Background: Antenatal clinics are a key entry point into HIV treatment and care, together with interventions to reduce mother-to-child transmission (MTCT). Further evaluation is needed of interventions linking antenatal with antiretroviral (ARV) treatment services and effectiveness of triple-ARV regimens for reducing MTCT in resource-constrained settings.

Methods: Data were gathered from HIV-infected women attending antenatal care from June 2004 to July 2005 at Coronation Women and Children Hospital, South Africa. After a patient record review, interventions were implemented to strengthen service linkages and integrate ARV treatment within antenatal care. Laboratory investigations were streamlined, including CD4 cell count testing at the first antenatal visit. MTCT risk for women initiating ARV treatment is compared with that of women-infant pairs receiving single-dose nevirapine (sd-NVP).

Results: In total, 164 pregnant women initiated ARV treatment and 863 received sd-NVP. After changes to service delivery, time-to-treatment initiation was reduced from a median of 56 days to 37 days (P = 0.041). The risk of MTCT for women receiving ARV treatment (5 [4.3%] of 116 women) was lower than for those given sd-NVP (74 [10.7%] of 692 women; P = 0.032).

Conclusions: Strengthening linkages and integrating key components of ARV treatment within antenatal care reduces time-to-treatment initiation. In this setting, among women with a high MTCT risk, triple-ARV regimens are effective in reducing HIV infection in infants.

Key Words: developing countries, disease transmission, vertical, prevention and control, HIV infections, pregnancy, South Africa

(74 [10.7%] of 692 women; P = 0.032). The risk of MTCT for women initiating ARV treatment (5 [4.3%] of 116 women) was lower than for those given sd-NVP (74 [10.7%] of 692 women; P = 0.032).

Conclusions: Strengthening linkages and integrating key components of ARV treatment within antenatal care reduces time-to-treatment initiation. In this setting, among women with a high MTCT risk, triple-ARV regimens are effective in reducing HIV infection in infants.

Key Words: developing countries, disease transmission, vertical, prevention and control, HIV infections, pregnancy, South Africa

© 2006 by Lippincott Williams & Wilkins

Epidemiology and Social Science

Triple-antiretroviral (ARV) regimens for pregnant women reduce maternal mortality and morbidity; are the most effective method of preventing mother-to-child transmission (MTCT) of HIV; and, by securing the health of women, improve child survival. ARV treatment, used in high-income countries for a decade, is increasingly becoming available in resource-constrained settings. It is anticipated that antenatal clinics can provide entry into HIV treatment and care, together with interventions to reduce MTCT.

There is widespread consensus that pregnant women with indications for ARV treatment should start treatment during pregnancy. In high-income countries and, increasingly, in Latin America and the Caribbean, triple-ARV prophylaxis is provided during pregnancy and discontinued after childbirth for an HIV-infected woman without indications for ARV treatment. Data, mostly from high-income countries, have shown that these regimens, initiated as early as 12 weeks of pregnancy, reduce the risk of MTCT to approximately 2%. Almost all pregnant women with HIV in these settings are offered triple-ARV prophylaxis, regardless of their plasma viral load or CD4 cell count. Consequently, in 2005, only an estimated 700 children were newly infected with HIV in North America and Western Europe combined. This near-elimination of MTCT risk has not been achieved in resource-constrained settings, where less effective regimens are used for MTCT prophylaxis—commonly, single-dose maternal and infant nevirapine (sd-NVP) for HIV-infected women without indications for ARV treatment.

Several factors hinder the uptake of ARV treatment for pregnant women in resource-constrained settings. These include weak linkages between antenatal and ARV treatment services and missed opportunities to identify pregnant women with indications for treatment, mostly because of inadequate access to CD4 cell counts. Further, initiation may be delayed, because many women present late for antenatal care and treatment preparation requires several visits. To reduce MTCT maximally, it is necessary for pregnant women to receive ARV treatment for an adequate duration of pregnancy, with consequent virologic suppression, which is particularly important around the time of childbirth.

The study investigated the effectiveness of interventions to increase the uptake of ARV treatment and reduce delays in initiating treatment during pregnancy. Specifically, effects of strengthening linkages and integrating key components of ARV treatment within antenatal care were examined. Findings of this study could inform ongoing initiatives to provide timely ARV treatment for pregnant women.
METHODS

Study Setting
The study took place at Coronation Women and Children Hospital, a public health care facility providing secondary-level pediatric and obstetric and gynecology services in Gauteng Province, South Africa. Approval for the study was obtained from the University of the Witwatersrand Human Research Ethics Committee.

As part of routine care, HIV testing and counseling are offered to all pregnant women at their first antenatal visit. Rapid HIV tests (First Response HIV Card test 1-2.0 [Kachigam, Daman, India] and Pareekshak HIV Triline card test [Bangalore, Karnataka, India]) are used for HIV diagnosis, with results available the same day. Women are considered medically eligible for ARV treatment if they have World Health Organization (WHO) clinical stage 4 conditions or a CD4 cell count <250 cells/mm³, which is determined using a Beckman Coulter (Fullerton, CA) Epics XL MCL cytometer and Beckman Coulter TQ PREP. Women who present late in pregnancy and are medically eligible are started on treatment, irrespective of the gestational age of the fetus. HIV-infected pregnant women without indications for ARV treatment receive sd-NVP.

Gestation is determined from a maternal history of the last menstrual period, clinical assessment, and ultrasound, where available. Elective cesarean section for reducing MTCT risk is not considered part of standard care. Women receive infant feeding counseling and support for their choice, including being offered free replacement feeding.

When ARV treatment in the public sector became available in April 2004, pregnant women with indications for ARV treatment were given a referral letter for the Themba Lethu Clinic, Helen Joseph Hospital, located approximately 1 km away, for preparation and initiation of treatment and long-term follow-up. From the outset of the program, pregnant women presenting at Helen Joseph Hospital have been “fast-tracked” into treatment. During the study period, ARV treatment for adults was not available at Coronation Women and Children Hospital.

Evaluation of Service Delivery
The study includes HIV-infected women attending the antenatal clinic between June 2004 and July 2005. In January 2005, an audit evaluated time between HIV diagnosis and ARV treatment initiation and related aspects of service delivery for pregnant women. Hospital records from the ARV treatment clinic were reviewed as well as the records of all women attending the antenatal clinic in the 6-week period from December 1, 2004 to January 13, 2005. Information was extracted on maternal demographics and the number of days between HIV diagnosis and treatment initiation.

Changes in Service Delivery
Changes in service delivery were made to address weaknesses identified in the audit. These interventions, beginning January 15, 2005, aimed to strengthen linkages between antenatal clinics and ARV treatment and to integrate key aspects of ARV treatment within antenatal care (Box 1).

<table>
<thead>
<tr>
<th>BOX 1. Interventions to strengthen linkages and integrate antiretroviral treatment within antenatal care</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Health workers from the ARV treatment clinic at Helen Joseph Hospital attend a weekly clinic for HIV-infected pregnant women at Coronation Women and Children Hospital.</td>
</tr>
<tr>
<td>• CD4 cell counts are performed at the first antenatal visit for women with HIV.</td>
</tr>
<tr>
<td>• Two weeks later, at the second antenatal visit, women receive CD4 cell count results and women with fewer than 250 cells/mm³ have baseline laboratory investigations for ARV treatment: alanine transaminase, aspartate transaminase, and hemoglobin.</td>
</tr>
<tr>
<td>• For women with indications for ARV treatment, adherence counseling and treatment preparation take place during their second antenatal visit. Thereafter, women are referred to Helen Joseph Hospital for initiation and follow-up of ARV treatment, which, whenever possible, is provided by the same staff members who began treatment preparation.</td>
</tr>
<tr>
<td>• Ongoing monitoring systems are established, allowing frequent assessment of uptake and time between HIV diagnosis and initiation of ARV treatment.</td>
</tr>
</tbody>
</table>

Measures Used
To determine the effectiveness of these interventions, we compared outcomes for women attending the antenatal clinic before and after changes to service delivery. Time-to-treatment initiation before these changes (June 1, 2004–January 13, 2005) is compared with the subsequent 6-month period (January 15, 2005–July 15, 2005). Time-to-treatment initiation is the number of days between HIV diagnosis (made at the first antenatal visit) and initiation of ARV treatment. Other process indicators include time to receiving CD4 cell count results, mean gestation at treatment initiation, and number of weeks ARV treatment is received before childbirth. For the period after changes to service delivery, uptake of ARV treatment is reported (proportion of medically eligible pregnant women who initiate ARV treatment).

Risk of HIV infection among infants born to women receiving ARV treatment during pregnancy is compared with that of woman-infant pairs participating in the sd-NVP program. Using a locally validated protocol,[19] HIV diagnosis was determined in infants aged 6 weeks or older with a DNA polymerase chain reaction (PCR) test (AmpliCloc HIV-1 DNA PCR version 1.5 assay; Roche Diagnostics, Inc., Alameda, CA).

Statistical Analysis
After data checking and cleaning, Intercooled Stata 8.0 (Stata Corporation, College Station, TX) was used for statistical analysis. During analysis, World Health Organization (WHO) clinical stages 3 and 4 were combined. HIV infection in a single or both twins was counted as 1 transmission. Univariate comparisons for categoric variables were tested using a $\chi^2$ test or Fisher’s exact test for trend. For continuous variables, the Student’s $t$ test and Wilcoxon rank-sum test were used for...
RESULTS

In total, 164 women initiated ARV treatment during pregnancy and 863 women-infant pairs received sd-NVP. Women initiating ARV treatment and those receiving sd-NVP had similar gravidity, mode of delivery, and infant weight (Table 1). Differences in maternal age were detected; women receiving ARV treatment were, on average, 1.3 years older (95% confidence interval [CI]: 0.4 to 2.1 years; \( P = 0.005 \)) than women in the sd-NVP program. Most women chose replacement feeding; 95.9% (589 of 614) of women receiving sd-NVP and 99.1% (107 of 108) of women taking ARV treatment (\( P = 0.12 \)).

Most women (88 [76%] of 116) who initiated ARV treatment were asymptomatic (WHO clinical stage 1), 15% (17 of 116) had WHO clinical stage 2 disease, and 9% (11 of 116) had WHO clinical stage 3 or 4 conditions. Of pregnant women who initiated ARV treatment, 9% would have been identified as medically eligible for treatment if the presence of WHO clinical stage 3 or 4 disease were the only criterion for eligibility. The first-line treatment regimen for most women was lopinavir with a ritonavir boost, along with lamivudine and stavudine (155 [94.5%] of 164), with fewer women receiving a combination of NVP (5 [3.1%] of 164) or efavirenz (4 [2.4%] of 164) plus lamivudine and stavudine.

Time-to-Treatment Initiation and Effectiveness of the Program

No differences in baseline maternal characteristics or pregnancy outcomes were detected between women attending the antenatal clinic before and after changes in service delivery. Time-to-treatment initiation, reduced from a median of 56 days before interventions (interquartile range [IQR]: 30–103), was implemented to 37 days thereafter (IQR: 22–63; \( P = 0.041 \); Table 2). The median number of days between HIV diagnosis and receiving CD4 cell count results also decreased (50 vs. 29 days; \( P = 0.047 \)).

### TABLE 1. Baseline Maternal Characteristics, Pregnancy Outcome, and Infant Feeding

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of women (y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>839</td>
<td>32</td>
<td>131</td>
<td>0.005* NS*</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>28.4 (5.3)</td>
<td>29.4 (4.7)</td>
<td>29.7 (5.0)</td>
<td></td>
</tr>
<tr>
<td>WHO clinical stage, n/N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>15/21 (71%)</td>
<td>73/95 (77%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2/21 (10%)</td>
<td>15/95 (16%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3/21 (14%)</td>
<td>6/95 (6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>NA</td>
<td>1/21 (5%)</td>
<td>1/95 (1%)</td>
<td>NA NS‡</td>
</tr>
<tr>
<td>CD4 cell count (cells/mm(^3))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>624</td>
<td>31</td>
<td>131</td>
<td>&lt;0.001† NS†</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>474.5 (337–676)</td>
<td>146 (117–178)</td>
<td>143 (92–186)</td>
<td></td>
</tr>
<tr>
<td>Gravidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>852</td>
<td>7</td>
<td>91</td>
<td>NA NS‡</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>2 (2–3)</td>
<td>2 (1–3)</td>
<td>2 (2–3)</td>
<td></td>
</tr>
<tr>
<td>Gestational age at first antenatal visit (wk)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>88</td>
<td>27</td>
<td>130</td>
<td>NA NS§</td>
</tr>
<tr>
<td>Mode of delivery, n/N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal birth</td>
<td>645/821 (78.6%)</td>
<td>9/14 (64%)</td>
<td>76/98 (77.6%)</td>
<td></td>
</tr>
<tr>
<td>Cesarean section</td>
<td>176/821 (21.4%)</td>
<td>5/14 (36%)</td>
<td>22/98 (22.5%)</td>
<td></td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>838</td>
<td>21</td>
<td>103</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.94 (0.58)</td>
<td>3.01 (0.58)</td>
<td>2.93 (0.57)</td>
<td></td>
</tr>
<tr>
<td>Infant feeding mode, n/N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Replacement feeding</td>
<td>589/614 (95.9%)</td>
<td>17/18 (94%)</td>
<td>87/87 (100%)</td>
<td></td>
</tr>
<tr>
<td>Ever breast-fed</td>
<td>25/614 (4.1%)</td>
<td>1/18 (6%)</td>
<td>0/87 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

All women initiating ARV treatment are compared with women receiving sd-NVP (A vs. \( B + C \)).

*Student \( t \) test.

†Wilcoxon rank-sum test.

‡\( \chi^2 \) test.

NA indicates data not available; NS, not significant.
TABLE 2. Comparison of ARV Treatment Provision Before and After Changes to Service Delivery

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>27</td>
<td>127</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>56</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>IQR (range)</td>
<td>30–103 (7–216)</td>
<td>22–63 (7–168)</td>
<td>0.041</td>
</tr>
<tr>
<td>Days from HIV diagnosis to receiving CD4 cell count result</td>
<td>25</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>50</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>IQR (range)</td>
<td>22–92 (3–206)</td>
<td>11.5–45 (2–167)</td>
<td>0.047</td>
</tr>
<tr>
<td>Gestational age at ARV treatment initiation (wk)</td>
<td>30</td>
<td>130</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>33.5</td>
<td>32.4</td>
<td></td>
</tr>
<tr>
<td>IQR (range)</td>
<td>30.7–36.4 (25.1–43.9)</td>
<td>28.1–34.6 (10.9–40.9)</td>
<td>0.042</td>
</tr>
<tr>
<td>Weeks from ARV treatment initiation to childbirth</td>
<td>22</td>
<td>108</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>5.1</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>IQR (range)</td>
<td>2.0–10.3 (0.6–18.1)</td>
<td>3.9–11.2 (0.3–25.6)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Number of patients in each group varies because of missing data.
*Wilcoxon rank-sum test.
NS indicates not significant.

HIV diagnosis is not available for 21.3% (219 of 1027) of infants in the study. Five (4.3%) of 116 infants born to women receiving ARV treatment were infected with HIV. This risk of transmission was lower than among women-infant pairs in the sd-NVP program (74 [10.7%] of 692 woman-infant pairs; P = 0.032 by χ² test). Infants born to women receiving ARV treatment were 2.66 times less likely to be infected with HIV compared with women-infant pairs in the sd-NVP program.

During the second time period (January 15, 2005–July 15, 2005), 75.4% of eligible women (129 of 171) initiated treatment. Of the 42 women with indications for ARV treatment who declined such treatment, 23 (55%) continued to attend follow-up visits and received sd-NVP. Seventeen percent (4 of 23) of their infants were infected with HIV. To determine whether uptake increased during this period, 2-month intervals were examined; no increase was observed (odds ratio = 1.00; P = 0.78 by χ² test for trend), however.

**DISCUSSION**

In this study, strengthening linkages and integrating key aspects of ARV treatment within antenatal care reduced delays between HIV diagnosis and treatment initiation for pregnant women. Measuring CD4 cell counts at the first antenatal visit seems to be particularly important in reducing delays. Several interventions occurred simultaneously, however, making it difficult to determine the relative importance of each intervention. Inclusion of health workers from ARV treatment services within antenatal clinics aimed to streamline the transition from antenatal care to long-term ARV treatment services, to ensure consistent counseling and messages, and to provide necessary oversight of the program. Despite improvements in service delivery, only three quarters of medically eligible pregnant women initiated ARV treatment. Further improvements in service delivery may be needed to optimize uptake. Similarly, additional attention and resources may be required to achieve high levels of uptake and well-functioning linkages between ARV treatment and other key entry points, such as voluntary testing and counseling sites and clinics for tuberculosis (TB) and sexually transmitted infections. Additional evidence is needed of the specific practical steps necessary for establishing such linkages and reducing missed opportunities for facilitating entry into HIV-related services after an HIV diagnosis.

CD4 cell counts formed a vital link between antenatal and ARV treatment services; approximately three quarters of pregnant women who initiated ARV treatment were asymptomatic, and using clinical criteria alone, few women would have received ARV treatment. To identify pregnant women who require ARV treatment, it may be necessary to include CD4 cell count testing in minimum care packages for pregnant women with HIV. Women with a low CD4 cell count require ARV treatment for their own health as well as having a higher risk for MTCT (even with sd-NVP17 or short-course zidovudine combined with sd-NVP18) and a higher risk of viral resistance after receiving sd-NVP.19 Identifying these women and facilitating their entry into ARV treatment is a high priority for prevention of MTCT programs.1,15,20 In this setting, triple-ARV regimens were highly effective in reducing MTCT among women with indications for ARV treatment. Women with a CD4 cell count ≥250 cells/mm³ and at lower baseline risk for MTCT were given sd-NVP but had a 2.7-fold higher MTCT risk than immunosuppressed women who received ARV treatment.

Initiation of ARV treatment is not a clinical emergency, and adequate preparation is required. For pregnant women, accelerated initiation is necessary to decrease MTCT risk, however. Difficulties with timely initiation of ARV treatment...
during pregnancy are compounded by health-seeking patterns in these settings. In Latin America, the Caribbean, the Middle East, and North Africa, two thirds of women present for antenatal care in the first trimester of pregnancy; in Asia, nearly half of women present for antenatal care at this time. In contrast, most women in sub-Saharan Africa present for antenatal care in the second trimester of pregnancy, and a substantial proportion are only seen in the third trimester. Given these patterns, to ensure timely initiation of ARV treatment, particular attention is needed to optimize each contact with pregnant women.

Data on effectiveness of prevention of MTCT services at Coronation Women and Children Hospital and interventions to improve these services have previously been published.21,22 The findings of this study are consistent with those of previous reports, showing that regular audits and monitoring, accompanied by corrective action, can substantially improve service delivery.22 Inherent limitations of comparing outcomes of service delivery before and after an intervention restrict the ability to interpret and generalize study findings, however. In particular, it is possible that changes observed between the 2 time periods are attributable to improvements that occur naturally over time as new services become established. Nevertheless, given the magnitude of improvements in service outcomes, this seems unlikely to be solely attributable to changes over time. A further study limitation is the amount of unavailable data. Information in hospital records was recorded for other purposes, thus limiting data extraction and resulting in missing information. A substantial proportion of infants have an unknown HIV status. Similar difficulties with infant follow-up have been reported from other settings.23–25

Implementation of ARV treatment is an important opportunity to strengthen existing health systems, including services for HIV-related prevention and care.26 This study further demonstrates that additional inputs available for implementing ARV treatment may, with adequate planning, have positive spin-offs, such as preventing HIV infection in infants.

ACKNOWLEDGMENTS

Study activities took place as part of routine hospital services in collaboration with staff from the Gauteng Province Department of Health. The authors acknowledge Professor K. Bolton and Ms. S. Jordaan for supporting this program and the interhospital collaboration. Dr. S. Luchters and Professor M. Temmerman provided incisive revisions on several manuscript drafts. The authors thank the antenatal clinic staff at Coronation Women and Children Hospital who implemented study activities, particularly Jeffrey Mhlauli, the counselor coordinator.

REFERENCES


3.2 Identifying HIV exposure in newborns and providing interventions to reduce transmission shortly after birth

Article 3: A randomized trial of two post-exposure prophylaxis regimens to reduce mother-to-child HIV-1 transmission in infants of untreated mothers
A randomized trial of two postexposure prophylaxis regimens to reduce mother-to-child HIV-1 transmission in infants of untreated mothers

Glenda E. Gray a, Michael Urban b, Matthew F. Chersich a, Carolyn Bolton a, Ronelle van Niekerk a, Avy Violari a, Wendy Stevens c and James A. McIntyre a for the PEP Study Group*

Background: Single-dose nevirapine (NVP) prophylaxis to mother and infant is widely used in resource-constrained settings for preventing mother-to-child transmission (MTCT) of HIV-1. Where women do not access antenatal care or HIV testing, post-exposure prophylaxis to the infant may be an important preventative strategy.

Methods: This multicentre, randomized, open-label clinical trial (October 2000 to September 2002) in South Africa compared single-dose NVP with 6 weeks of zidovudine (ZDV), commenced within 24 h of delivery among 1051 infants whose mothers had no prior antiretroviral therapy. HIV-1 infection rates were ascertained at birth, and at 6 and 12 weeks of age. Kaplan–Meier survival methods were used to estimate HIV-1 infection rates in an intention-to-treat analysis.

Results: Overall, 6 week and 12 week MTCT probability was 12.8% [95% confidence interval (CI), 10.5–15.0] and 16.3% (95% CI, 13.4–19.2), respectively. At 12 weeks, among infants who were not infected at birth, 24 (7.9%) infections occurred in the NVP arm and 41 (13.1%) in the ZDV arm (log rank $P = 0.06$). Using multivariate analysis, factors associated with infection following birth were ZDV use [odds ratio (OR), 1.8; 95% CI, 1.1–3.2; $P = 0.032$], maternal CD4 cell count < 500 cells/l (OR, 2.5; 95% CI, 1.3–5.0; $P = 0.007$), maternal viral load > 50 000 copies/ml (OR, 3.6; 95% CI, 1.2–10.2; $P < 0.0001$) and breastfeeding (OR, 2.2; 95% CI, 1.3–3.8; $P = 0.006$).

Conclusion: A single-dose of NVP given to infants offers protection against HIV-1 infection and should be a strategy used in infants of mothers with untreated HIV infection.

AIDS 2005, 19:1289–1297

Keywords: Africa, mother-to-child transmission, zidovudine, nevirapine, postexposure prophylaxis, breastfeeding, infant HIV-1 infection

Introduction

In resource-constrained settings, current interventions to reduce mother-to-child transmission of HIV-1 (MTCT) target the peripartum period [1–4]. To date, the most widely used regimen is derived from the HIVNET 012 study, which demonstrated that a single-dose of nevirapine (NVP) given to the mother in labour and a dose administered to the infant soon after birth reduced transmission by half [5,6]. In regimens with an antenatal component, zidovudine (ZDV) is recommended from 28 weeks of gestation [7]. Adding single-dose NVP to antenatal ZDV regimens in Thailand [8] and Africa [9] has reduced transmission rates to levels seen previously only

ISSN 0269-9370 © 2005 Lippincott Williams & Wilkins

55
in the developed world, where triple antiretroviral regimens initiated prenatally have reduced MTCT rates to < 2% among women avoiding breastfeeding [10].

Postexposure prophylaxis [11] is based on the premise that administration of antiretroviral drugs soon after exposure will inhibit viral replication and dissemination, thus enabling the host defence mechanism to clear the inoculum [12,13]. The pathogenesis of transcutaneous, transmucosal, intrapartum and early postpartum infection with HIV has not been fully elucidated. Following intrapartum or early postpartum exposure, a 'window of opportunity' may exist in which antiretroviral treatment may prevent infection.

Several studies have prompted treatment recommendations for postexposure prophylaxis. The Centers for Disease Control and Prevention (CDC) case–control study of occupational HIV infections found that healthcare workers who received ZDV treatment after exposure were 79% less likely [odds ratio (OR), 0.21] to acquire infection than those who did not receive treatment, independent of the other variables affecting the probability of transmission [11]. Further, data from the PACTG 076 study demonstrated that ZDV given to HIV-infected pregnant women from 14 weeks of pregnancy, continued intravenously in labour and given to the infant for 6 weeks could reduce MTCT transmission by 67% [14]. The efficacy of this regimen could not be explained purely on the basis of a reduction in maternal viral load. Experience with the PACTG 076 protocol demonstrates the prophylactic efficacy of antiretroviral therapy if ZDV is administered during pregnancy. It did not, however, address the issue of commencing therapy in the postpartum period to the infant.

Evidence supporting the role of postexposure prophylaxis in reducing HIV transmission among infants whose mothers did not access therapy during pregnancy or labour has been demonstrated in a prospective study in Malawi that investigated postpartum prophylaxis in newborns [15]. This study indicated that dual therapy with single-dose NVP and one week of ZDV given to the infant was superior to single-dose NVP alone. The overall transmission rate at 6–8 weeks of age in the group which received single-dose NVP and ZDV was 15.3% compared with 20.9% in the arm that received NVP alone.

Previously, a retrospective uncontrolled study by Wade et al. [16] demonstrated the use of ZDV prophylaxis in MTCT, even if only administered to the infant for 6 weeks. When ZDV was initiated within 48 h of delivery, the transmission rate was 9.3%, compared with 26.6% if no therapy was given. If ZDV was administered at longer than 48 h after delivery, the transmission rate was 18.4%.

Administration of single-dose NVP is associated with rapid emergence of NVP-resistant variants in both the mother and HIV-infected infants [17–21]. This may be associated with an increased risk of treatment failure among women who subsequently initiate NVP treatment [22]. Single-dose NVP given only to the infant would avoid the risk of maternal NVP resistance.

Postpartum prophylaxis of infants may be an important strategy to prevent MTCT in settings where women do not access antenatal care, are not offered HIV testing and counselling, where babies are born at home, or where health workers wish to avoid maternal NVP dosing. NVP is a potent inhibitor of HIV-1 replication, which, because of its long half-life in babies [23,24], may be as effective as longer therapy with ZDV.

The primary objective of this study was to compare postuterine HIV infection at week 12 in infants who were not infected at birth and were given either a single-dose of NVP or ZDV for 6 weeks [25]. Transmission data were collected up to 12 weeks of age. The secondary objective of this study was to assess how breastfeeding affected the efficacy of the two regimens.

Methods

Participants

The trial was conducted in three hospitals in South Africa: Chris Hani Baragwanath Hospital (Soweto), Coronation Hospital (Johannesburg) and Mowbray Hospital (Cape Town) between October 2000 and September 2002. Women delivering without prior knowledge of their HIV status were offered postpartum voluntary counselling and rapid on-site testing (PP-VCT) within 24 h of delivery. Blood samples were tested with Determine HIV-1/2 tests (Abbott Laboratories, Abbott Park, Illinois, USA), and, if reactive, a second confirmatory test using the Uni-Gold HIV test (Trinity Biotech, Wicklow, Ireland) was performed. Women who tested negative with the initial Determine test were considered uninfected.

Eligible women testing HIV positive were offered enrolment. Infants were excluded if they were preterm weighing < 1200 g, requiring ventilation, unable to take oral medication or with congenital abnormalities. Ineligible infants or infants of mothers unwilling to participate were offered off-study single-dose NVP. Informed consent and randomization occurred within 24 h of delivery. Randomization was by using computer-generated random allocations; enrolled babies were sequentially assigned the next study number and allocation to the study arm was provided to study nurses in sequentially numbered non-transparent sealed envelopes that were only opened after informed consent was obtained.

At enrolment, after obtaining informed consent and randomization, blood samples were collected from infants
A two group study staff within 24 h of delivery. Hourly for 6 weeks). Initial doses were administered by the oral ZDV (10 mg/ml at a dose of 4 mg/kg administered 12-hourly for 6 weeks). Infants of women who had consented to participate were randomized to receive intrapartum antiretroviral therapy. Infants found to be HIV-1 infected received co-trimoxazole prophylaxis from 6 weeks of age.

**Trial design**

The study was a multicentre, two-arm, randomized open-label trial of NVP compared with ZDV when administered postnatally to infants born to HIV-1-infected women who had not received antepartum or intrapartum antiretroviral therapy. Infants of women who had consented to participate were randomized to receive either a single oral dose of NVP (10 mg/ml oral suspension at a dose of 2 mg/kg) within 24 h of delivery or ZDV (10 mg/ml at a dose of 4 mg/kg administered 12-hourly for 6 weeks). Initial doses were administered by the study staff within 24 h of delivery.

A two group $\chi^2$ test with a 0.05 two-sided significance level would have 90% power to detect the difference between a 0.10 proportion (10%) of HIV-infected infants using ZDV and a 0.19 proportion (19%) of HIV-infected infants using NVP (OR, 2.111) when the sample size in each group was 320. To allow for loss to follow-up, infant deaths, withdrawals and unavailable PCR results, 1051 infants were randomized to achieve the study groups needed.

Baseline sociodemographic information, medical and pregnancy history were recorded. Follow-up visits at day 10 and at weeks 6 and 12 for the infant included a clinical examination and a blood sample for HIV-1 diagnosis and haemoglobin estimation. Ongoing HIV-1 testing occurred in breastfed infants at 3-monthly intervals.

Serious adverse events were documented and the Ethics Committee and sponsors received biannual reports.

Standardized operating procedures for enrolment and data collection were used at all study sites. Staff training, site visits and ongoing external monitoring were conducted to ensure uniformity of the study across the sites.

A preliminary analysis of efficacy and safety was reviewed by an independent Data and Safety Monitoring Board in July 2002. A second meeting was held after all infants had been enrolled, where all new data was reviewed.

Approval for the study was given by the Gauteng Department of Health Provincial Review Committee, the University of the Witwatersrand Committee for Research on Human Subjects and the Mowbray Maternity Hospital Research Committee in Cape Town.

**Laboratory procedures**

Laboratory testing was performed at Contract Laboratory Services in Johannesburg, which was certified by both internal and external quality assurance programmes. All blood specimens were collected in ethylenediaminetetraacetic acid-treated tubes, and whole blood was used for HIV-1 RNA (maternal) and DNA (infant) PCR. Infant samples were tested for HIV-1 DNA using the Roche Amplicor Monitor version 1.5 qualitative PCR assay (Roche Diagnostics, Basel, Switzerland).

Definite infant HIV-1 infection was defined as two consecutive blood samples tested positive for HIV-1 DNA by PCR. Infants who had one documented positive result and were then lost to follow-up were considered infected. Infants who tested positive at day 1 or before day 10 were considered to be infected in utero. Infants who tested negative at birth and positive at day 10 or more were considered to be infected postuterine (intrapartum or early postpartum). A child was considered to be uninfected when a week 6 or later result was negative in the absence of breastfeeding. In breastfed infants, retesting occurred 1 month after breastfeeding ceased. These infants were considered uninfected if this sample was negative.

**Statistical methods**

Case report forms and laboratory results were checked for accuracy and completeness. Double data entry was performed using a Microsoft Access database. The datasets were merged using SAS version 8.2 (SAS Institute, Cary, North Carolina, USA) to detect data entry discrepancies. Edit checks were built into the Access database to ensure correction of data errors. A 100% quality control, in which the case report forms and database were cross-checked, was carried out on the following variables: HIV DNA results, treatment groups and infant feeding. Data analyses were performed using SAS version 8.2. Continuous baseline data were summarized using descriptive statistics. Student’s $t$ test was used for continuous baseline variable comparisons, with the exception of CD4 cell count and viral load, for which an analysis of variance (ANOVA) was used. Categorical baseline data were summarized using frequency tables and compared using the $\chi^2$ test, or Fisher’s exact test where applicable.

A 95% confidence level (CI) was used and a $P$ value of 0.05 was considered to be statistically significant; all
statistical tests were two-tailed. Data were collected up to 12 weeks of age (time window defined as 70–100 days), based on scheduled visits. An intention-to-treat analysis was performed.

Kaplan–Meier survival analysis was performed to determine and compare HIV-1 transmission rates, using the log rank test. The HIV-free survival time for infants infected within the 12-week period was defined as the date of birth to the date of the first positive PCR result; for infants not infected within the 12-week period, the HIV-free survival time was defined as the date of birth to the date of the last negative PCR result. Survival time was censored when the survival time was greater than 100 days.

The 95% CI values for this estimate were calculated based on the normal distribution and the 95% CI for the log of the relative risk (RR). The 95% CI for the estimate was calculated as the range between \((1 - \text{lower bound anti-log 95\% CI for RR})\) and \((1 - \text{upper bound anti-log 95\% CI for RR})\).

Infant feeding at week 12 was classified as either exclusive formula feeding or as 'breast milk exposure'. The latter group included exclusively breast feeders, mixed feeders and ever breast feeders. Infants were classified into one of these two groups by taking the feeding practices into account at all visits. Infants who were formula fed from randomization or who were exposed to <2 days of breast milk were classified as exclusive formula fed.

Risk factors included in the logistic regression model for predicting transmission in utero and at week 12 (only postuterine infection at week 12) were treatment, infant feeding exposure, mode of delivery, maternal viral load and CD4 cell count, and time to study drug ingestion.

Deaths with unknown 'date of death' and serious adverse events with unknown 'start date' were included in the 12-week analyses.

**Results**

From October 2000 to September 2002, approximately 12 000 women delivered without HIV results and were offered PP-VCT. Of these 5634 (49.5%) accepted PP-VCT; 1530 (27.2%) were found to be HIV positive and 1051 infants (88.7%) were randomized into the study: 533 in the ZDV arm and 518 in the NVP arm (Fig. 1).

The maternal demographic data were comparable in both groups (Table 1). At enrolment, the median total CD4 cell count was \(467 \times 10^6\) cells/l and the median plasma viral load was 21 800 copies/ml. Mean time of drug ingestion were similar in both groups. There was no difference in birthweight, gender or feeding practices between the groups (Table 1).

**Primary endpoint: efficacy**

A total of 7118 infants had evaluable results at week 12 and loss to follow-up was similar in both groups (Fig. 1). At birth, HIV PCR positivity was observed in 7.0% of the NVP-treated infants and 5.8% of the ZDV-treated infants (log rank test, \(P = 0.5\)). Cumulative HIV-1 transmission rates by Kaplan–Meier estimates at 6 weeks were 11.9% in the NVP arm and 13.6% in the ZDV arm (log rank test, \(P = 0.6\)). At 12 weeks, the cumulative infection rate in the NVP arm was 14.3% and in the ZDV arm was 18.1% (log rank test, \(P = 0.4\)). In infants uninfected at birth, the postuterine MTCT probabilities at week 6 in the NVP and the ZDV groups were 5.3% and 8.2%, respectively. At week 12, the postuterine MTCT probabilities in the NVP and the ZDV groups were 7.9% and 13.1%, respectively (log rank test, \(P = 0.06\)). In multivariate analysis, at 12 weeks, ZDV use was less protective (OR, 1.8; 95% CI, 1.1–3.2) (Tables 2 and 3).

**Primary endpoint: safety**

The rate of serious adverse events were similar in both arms (118 in the ZDV arm and 94 in the NVP arm; \(P = 0.56\)), were deemed to be unrelated to study medication and were mostly caused by infections such as pneumonia (22 in the ZDV arm and 18 in the NVP arm; ZDV, \(P = 0.75\)) and gastroenteritis (20 in the ZDV arm and 15 in the NVP arm; \(P = 0.91\)). Birth-related conditions (14 in the ZDV arm and 6 in the NVP arm; \(P = 0.15\)), physiological jaundice (10 in the ZDV arm and 5 in the NVP arm; \(P = 0.26\)) and neonatal septicaemia (7 in the ZDV arm and 13 in the NVP arm; \(P = 0.09\)) were the next most frequent serious adverse events.

Of these serious adverse events, 17 (18.1%) in the NVP arm and 36 (30.5%) in the ZDV arm were related to HIV (\(P = 0.84\)). There were 165 (15.7%) instances of hospitalization: 73 (14.1%) in the NVP arm, 92 (17.3%) in the ZDV arm (\(P = 0.44\)).

**Primary endpoint: infant mortality**

Twenty-four infants (3.4%) died before 100 days (13 in the ZDV arm and 11 in the NVP arm; log -rank test, \(P = 0.8\)). Five (20.8%) died from respiratory infections, three (12.5%) from gastroenteritis, four (16.7%) from birth-related conditions and 12 (50.0%) from other causes, such as meningitis and septicaemia. Nine (37.5%) infants had negative PCR results; two (8.3%) infants died before day 1 blood was taken and 13 (54.2%) infants were PCR positive. No deaths were attributed to study medication. Four (2.2%) breastfed infants died before 12 weeks of age and 19 (3.8%) formula-fed infants. There was no increased mortality in the formula-fed group (log rank test, \(P = 0.2\)).

**Secondary endpoint: effect of breastfeeding**

Overall, when comparing breastfed with formula-fed infants in the treatment arms (Table 2), the additional infection rate at 12 weeks was 14.8% in the breastfed
Table 1. Baseline characteristics of mothers and infants a.

<table>
<thead>
<tr>
<th></th>
<th>Nevirapine arm</th>
<th>Zidovudine arm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mothers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age [years (IQR)] (n = 1047)</td>
<td>25.0 (22–29)</td>
<td>25.0 (22–30)</td>
</tr>
<tr>
<td>Median HIV RNA [copies/ml (IQR)] (n = 1001)</td>
<td>242.50 (5790–84400)</td>
<td>19700 (4510–74400)</td>
</tr>
<tr>
<td>Median CD4 cell count [× 10⁷ cells/l (IQR)] (n = 964)</td>
<td>480.5 (309.5–661.5)</td>
<td>448.5 (310.5–661.5)</td>
</tr>
<tr>
<td>Mode of delivery [No. (%)] (n = 1021)</td>
<td>466 (92.28%)</td>
<td>478 (92.64%)</td>
</tr>
<tr>
<td>Caesarean delivery</td>
<td>39 (7.72%)</td>
<td>38 (7.36%)</td>
</tr>
<tr>
<td><strong>Infants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median weight (g) (IQR) (n = 1051)</td>
<td>2900 (2600–32000)</td>
<td>2950 (2640–32000)</td>
</tr>
<tr>
<td>Median time to drug ingestion [h (IQR)] (n = 1025)</td>
<td>15.42 (11.3–21.0)</td>
<td>15.00 (10.75–20.3)</td>
</tr>
<tr>
<td>Feeding practices [No. (%)] (n = 991)</td>
<td>398 (82.06%)</td>
<td>436 (86.17%)</td>
</tr>
<tr>
<td>Exclusively formula feeding</td>
<td>78 (16.08%)</td>
<td>68 (13.44%)</td>
</tr>
<tr>
<td>Exclusively breast feeding</td>
<td>9 (1.86%)</td>
<td>2 (0.40%)</td>
</tr>
<tr>
<td>Mixed feeding</td>
<td>243 (47.00%)</td>
<td>261 (49.06%)</td>
</tr>
<tr>
<td>Gender [No. (%)] (n = 1049)</td>
<td>274 (53.00%)</td>
<td>271 (50.94%)</td>
</tr>
</tbody>
</table>

IQR, interquartile range.

aTotals < 1051 are a consequence of missing or unknown data. There were no significant differences between the values for the two groups of treatment.
group compared with 9.4% in the formula-fed group (log rank test, $P = 0.007$). Comparing infant feeding within treatment arms, the additional infection rate in the breastfed infants in the ZDV-treated infants was 20.6% compared with 11.1% (log rank test, $P = 0.004$) in those infants who were not breastfed. The additional infection rate in the breastfed infants in the NVP arm was 9.9% compared with 7.3% (log rank test: $P = 0.3$) in the non-breastfed group (Table 2).

### Discussion

A postexposure prophylaxis regimen of single-dose NVP given to infants whose mothers had received no prior antiretroviral therapy was at least as good as 6 weeks of ZDV in reducing MTCT. Compared with 6 weeks of ZDV therapy, single-dose NVP is easier to implement, is likely to be more cost-effective and adherence would be easier to ensure. Further, in multivariate analysis, the ZDV regimen did not appear to be as effective as single-dose NVP in reducing postnatal transmission.

Although directly comparing trials is difficult, the transmission rate seen in our single-dose NVP arm at 6 weeks (11.9%; 95% CI, 8.8–15.0) of age is comparable to the transmission rate seen in HIVNET 012 (11.8%: 95% CI, 8.2–15.5) [5,6], where both mother and infant received NVP, and to the transmission rate at 6–8 weeks (15.3%) seen in infants who received single-dose NVP in addition to 1 week ZDV in the Malawi study [15]. At 12 weeks of age, the transmission rate seen in our single-dose NVP arm (14.3%) was similar to the transmission rate (13.1%) seen in HIVNET 012 at 14–16 weeks of age. There are no data available on transmission at 12 weeks from the Malawi study.
RNA levels. Their offspring were more likely to have plasma HIV-1 if mothers who transmitted infection to their infants had lower maternal viral loads, consistent with those of Dickover et al. [26], who showed that the risk of transmission with maternal CD4 cell counts less than 500 copies/ml at delivery was 4.4 (2.6–7.5) times higher than those with counts greater than 50000 copies/ml. Our findings, showing the association of maternal viral load with transmission, are similar to other studies [26–29].

As in other studies [26–29], we demonstrated an increase in risk of transmission with maternal CD4 cell counts, especially in the first year of life. The proportion of infections and, as optimal care of this group is available, uptake has been low or variable [33,34]. For this reason, an intervention that targets infants may be an additional important strategy in resource-constrained settings. In richer parts of the world, infants of mothers delivering without prenatal care account for a large proportion of infections and, as optimal care of this group has not been fully elucidated, the results of this trial may also be relevant to these women [35].

Despite proven efficacious and cost-effective interventions for prevention of MTCT [2–6,32], these interventions have only been implemented on a very small scale. In some settings where these interventions are available, uptake has been low or variable [33,34]. For these reasons, an intervention that targets infants may be an additional important strategy in resource-constrained settings. In richer parts of the world, infants of mothers delivering without prenatal care account for a large proportion of infections and, as optimal care of this group has not been fully elucidated, the results of this trial may also be relevant to these women [35].

Table 3. Total HIV-1 transmission rates by treatment and feeding method (Kaplan–Meier analysis).

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Total &lt; day 10^6</th>
<th>Total week 6</th>
<th>Total week 12</th>
<th>P value (log rank)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. [% (95% CI)]</td>
<td>No. [% (95% CI)]</td>
<td>No. [% (95% CI)]</td>
<td></td>
</tr>
<tr>
<td>NVP versus ZDV</td>
<td></td>
<td></td>
<td></td>
<td>0.39</td>
</tr>
<tr>
<td>Total (n = 1030)</td>
<td>63 [6.4 (4.9–7.9)]</td>
<td>111 [12.8 (10.5–15.0)]</td>
<td>128 [16.3 (13.4–19.2)]</td>
<td></td>
</tr>
<tr>
<td>NVP (n = 510)</td>
<td>34 [7.0 (4.7–9.3)]</td>
<td>52 [11.9 (8.8–15.0)]</td>
<td>58 [14.3 (10.6–18.0)]</td>
<td></td>
</tr>
<tr>
<td>ZDV (n = 520)</td>
<td>29 [5.8 (3.7–7.9)]</td>
<td>59 [13.6 (10.3–16.8)]</td>
<td>70 [18.1 (13.7–22.5)]</td>
<td></td>
</tr>
<tr>
<td>NVP: EFF versus BME</td>
<td>0.95</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (n = 416)</td>
<td>31 [8.1 (5.5–10.7)]</td>
<td>51 [13.1 (9.7–16.5)]</td>
<td>57 [15.5 (11.6–19.4)]</td>
<td></td>
</tr>
<tr>
<td>EFF (n = 266)</td>
<td>24 [9.1 (5.7–12.5)]</td>
<td>36 [13.9 (9.7–18.1)]</td>
<td>38 [15.7 (10.7–20.7)]</td>
<td></td>
</tr>
<tr>
<td>BME (n = 140)</td>
<td>9 [6.3 (2.3–10.3)]</td>
<td>15 [11.7 (6.1–17.4)]</td>
<td>19 [15.5 (9.0–22.0)]</td>
<td></td>
</tr>
<tr>
<td>ZDV: EFF versus BME</td>
<td>0.11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (n = 424)</td>
<td>29 [7.0 (4.6–9.5)]</td>
<td>59 [14.8 (11.3–18.3)]</td>
<td>70 [19.4 (14.9–23.9)]</td>
<td></td>
</tr>
<tr>
<td>EFF (n = 302)</td>
<td>21 [7.7 (4.7–10.7)]</td>
<td>40 [13.6 (9.7–17.5)]</td>
<td>46 [17.9 (12.6–23.2)]</td>
<td></td>
</tr>
<tr>
<td>BME (n = 122)</td>
<td>6 [5.1 (1.1–9.1)]</td>
<td>19 [18.9 (11.2–26.6)]</td>
<td>24 [24.6 (15.9–33.3)]</td>
<td></td>
</tr>
<tr>
<td>EFF: NVP versus ZDV</td>
<td>0.81</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (n = 570)</td>
<td>47 [8.3 (6.0–10.6)]</td>
<td>76 [13.8 (10.9–16.6)]</td>
<td>84 [16.9 (13.2–20.6)]</td>
<td></td>
</tr>
<tr>
<td>NVP (n = 268)</td>
<td>24 [9.0 (5.6–12.5)]</td>
<td>36 [13.9 (9.7–18.1)]</td>
<td>38 [15.6 (10.7–20.6)]</td>
<td></td>
</tr>
<tr>
<td>ZDV (n = 302)</td>
<td>23 [7.7 (4.7–10.7)]</td>
<td>40 [13.6 (9.7–17.5)]</td>
<td>46 [17.9 (12.6–23.3)]</td>
<td></td>
</tr>
<tr>
<td>BME: NVP versus ZDV</td>
<td>0.14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (n = 270)</td>
<td>15 [5.8 (2.9–8.6)]</td>
<td>34 [15.0 (10.3–19.8)]</td>
<td>43 [19.7 (14.4–25.1)]</td>
<td></td>
</tr>
<tr>
<td>NVP (n = 148)</td>
<td>9 [6.1 (2.3–10.2)]</td>
<td>15 [11.7 (6.1–17.4)]</td>
<td>19 [15.5 (9.0–22.0)]</td>
<td></td>
</tr>
<tr>
<td>ZDV (n = 122)</td>
<td>6 [5.1 (1.1–9.1)]</td>
<td>19 [18.9 (11.2–26.6)]</td>
<td>24 [24.6 (15.9–33.3)]</td>
<td></td>
</tr>
<tr>
<td>CD4 cell count category (× 10^3 cells/μl)</td>
<td>0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 500 (n = 502)</td>
<td>41 [7.3 (5.0–9.4)]</td>
<td>78 [15.8 (12.5–19.0)]</td>
<td>93 [21.4 (16.9–25.8)]</td>
<td></td>
</tr>
<tr>
<td>≥ 500 (n = 438)</td>
<td>22 [5.2 (3.1–7.4)]</td>
<td>33 [8.7 (5.8–11.6)]</td>
<td>35 [9.4 (6.4–12.4)]</td>
<td></td>
</tr>
<tr>
<td>Viral load category (copies/ml)</td>
<td>&lt; 0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50000 (n = 691)</td>
<td>30 [4.5 (3.0–6.1)]</td>
<td>46 [7.6 (5.5–9.8)]</td>
<td>55 [10.2 (7.4–13.0)]</td>
<td></td>
</tr>
<tr>
<td>≥50000 (n = 339)</td>
<td>33 [10.2 (6.9–13.5)]</td>
<td>65 [23.8 (18.4–28.6)]</td>
<td>73 [28.9 (22.5–35.3)]</td>
<td></td>
</tr>
</tbody>
</table>

No., number of events; CI, confidence interval; NVP, nevirapine; ZDV, zidovudine; EFF, exclusively formula feeding; BME, breast milk exposure.

Table 4. Logistic regression analysis: significant risk factors for additional transmission at week 12 (day 100).

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>OR (95% CI)</th>
<th>P value</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal HIV RNA &gt; 50 000 copies/ml</td>
<td>4.4 [2.6–7.5]</td>
<td>&lt; 0.0001</td>
<td>3.6 [2.0–6.2]</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Maternal CD4 cell count &lt; 500 × 10^3 cells/μl</td>
<td>3.4 [1.8–6.3]</td>
<td>0.0002</td>
<td>2.5 [1.3–4.0]</td>
<td>0.007</td>
</tr>
<tr>
<td>BME</td>
<td>2.1 [1.2–3.5]</td>
<td>0.006</td>
<td>2.2 [1.3–3.8]</td>
<td>0.006</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>1.7 [1.0–2.9]</td>
<td>0.053</td>
<td>1.8 [1.1–3.2]</td>
<td>0.032</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; BME, breast milk exposure.
In countries with a high HIV burden, universal NVP therapy to all newborns could be considered, particularly where HIV testing and counselling is not available [31,36]. This could be viewed as analogous to the universal use of tetracycline eye ointment in newborns for preventing ophthalmia neonatorum. Further research on the effectiveness of this approach is needed.

So far, almost all programmes to prevent MTCT in resource-constrained settings have concentrated on antenatal VCT. PP-VCT has been shown to be feasible and advantageous to programmes that aim to prevent HIV infection in infants [37]. For women who have not accessed antenatal care, PP-VCT, infant-feeding counselling and single-dose NVP could be considered as part of essential care. In areas with high HIV incidence rates, women testing negative during antenatal care may benefit from retesting after delivery.

There is concern that single-dose NVP for prevention of MTCT could result in the selection of drug resistance that would limit future therapeutic options. Several studies have demonstrated that drug-resistance mutations were present in maternal and infant viral sequences following NVP exposure for prevention of MTCT [17–21]. Limited evidence suggests that women exposed to single-dose NVP have a poorer response to subsequent therapy based on non-nucleoside reverse transcriptase inhibitors [22]. Preliminary data from our study suggest that in HIV-infected infants exposed to single-dose NVP there is a lower frequency of resistance compared with those in HIVNET 012 [38].

Although breastfeeding rates were low, multivariate analysis demonstrates that, by 12 weeks of age, breastfeeding was associated with an increased risk of transmission (OR, 2.2; 95% CI, 1.3–3.8). Investigating alternatives to breastfeeding, or minimizing breastfeeding, remain important strategies in preventing MTCT.

Our data demonstrate that a single postpartum dose of NVP administered to infants is a valid additional intervention for prevention of MTCT. As access to antiretroviral therapy becomes a reality in countries heavily affected by HIV, attempts should be made to preserve the efficacy of NVP for the treatment and care of women. Postexposure prophylaxis to infants provides a valuable alternative.

Acknowledgements

The authors would like to acknowledge Professor Herman Schoeman for his input on the statistical analysis; Professor Louise Kuhn for her helpful advice on both the analysis and interpretation of our data, as well as her input into the manuscript and Professor Marie-Louise Newell for her valuable insight into our analysis and for her input into the manuscript.

Sponsorship: This study was funded by a grant from the Bristol-Meyers Squibb Secure the Future Programme (RES 057–02) and by additional funding from the US Agency for International Development (USAIID: 674–0320–G–00–5053) under the terms of Award No 674–0320-G-00-5053.

Note: The opinions expressed herein are those of the authors and do not necessarily reflect the views of the US Agency for International Development.

References


Article 4: The ethical and legal case for identifying newborn exposure to HIV and providing antiretroviral prophylaxis
TITLE: THE ETHICAL AND LEGAL CASE FOR IDENTIFYING NEWBORN EXPOSURE TO HIV AND PROVIDING ANTIRETROVIRAL PROPHYLAXIS

Running head: Mandatory testing for newborn HIV exposure

Authors: MF Chersich, A Egan, A Kleinsmidt, S Luchters, WDF Venter, P Knox, M Temmerman

Corresponding author:
MF Chersich, International Centre for Reproductive Health
Tudor Four Estate, Tom Mboya Avenue
P.O.Box 91109
Mombasa, Kenya
Tel: +254 (0)41 2494 866 or +254 (0)721 83 1518
Mobile: +254 735721251
Fax +254412495025
Email: matthewf.chersich@icrhk.org

Key words: HIV testing, patient autonomy, mother-to-child transmission of HIV, Africa

Total word count (including abstract): 4598 words
ABSTRACT
Continued poor outcomes of programmes to prevent mother-to-child transmission of HIV necessitate critical assessment of current HIV testing paradigms. Where access to HIV treatment is assured, the degree and range of benefits from an early HIV diagnosis differ markedly from those of a late diagnosis when HIV declares itself with severe disease.

We make an ethical and legal case for mandatory testing of newborns to ascertain HIV exposure. Several US states have successfully implemented this policy for almost a decade, providing proof of concept, encouraging safety data and justifying further investigation. In most countries, the state has final responsibility for protecting the child’s health and wellbeing, and must intervene to protect these when necessary. The child’s interests (identifying exposure and receiving antiretroviral post-exposure prophylaxis) are weighed against a woman’s right to autonomy and not to know her status. We conclude that while women still face substantial levels of stigma and discrimination, the right of the child to know they are HIV exposed and receive preventive care takes precedence. This assertion is underscored by legislation stating: ‘in all actions concerning children, the best interests of the child shall be a primary consideration’. Rigorous monitoring of effects of such policies on women’s health-seeking behaviour would be essential. Health workers could seek a court interdict to test a newborn whose mother refused testing. Legal action requesting courts to overrule parental authority may effect policy change, though the lived experience of HIV-infected children and women who care for these children must also determine policy.
INTRODUCTION
Each day nearly 1500 children worldwide become infected with HIV, with the vast majority of these infections occurring in sub-Saharan Africa. This reflects the continued failure in reach and effectiveness of programmes to prevent mother-to-child transmission of HIV (PMTCT). By contrast, with high-quality intervention paediatric HIV has been virtually eliminated in many countries. Worldwide only about 11% of pregnant women living with HIV infection access PMTCT programmes, with HIV testing remaining a major bottleneck to PMTCT entry. Despite these problems, the approach to HIV testing in PMTCT programmes has remained largely unchanged: women are offered HIV testing and counselling during pregnancy, and antiretroviral (ARV) prophylaxis is provided for those identified as infected.

With the overall objective of assisting individuals (and their children) to benefit from knowing their HIV status (or exposure), testing strategies are increasingly viewed as complementary, rather than mutually exclusive. New approaches to identifying newborns exposed to HIV, in conjunction with a strengthening of existing testing strategies, may re-invigorate PMTCT and accelerate its scale up. This is conceptually analogous to how failures with voluntary counselling and testing (VCT) led to

---

development of provider-initiated testing and concurrent efforts to strengthen VCT services, with international mobilisation and recommitment to HIV testing.

Consideration is warranted of expanding the range of testing strategies in PMTCT programmes, especially testing of infants for HIV exposure. Shortly after childbirth, identifying HIV-exposed infants born to women who have not accessed PMTCT services (either because they declined HIV testing, or because these services were unavailable or functioned poorly) would enable these infants to benefit from ARV prophylaxis. Others have previously argued for mandatory testing of newborns6 and several states of the US have successfully implemented such policies since the late 1990s7. In this paper, we make the case that testing of all infants born to women of unknown HIV status serves the child’s best interests, which are of primary importance in international and domestic laws. Specifically, in the context of recent changes to HIV testing policies, we consider the child’s interests (identifying HIV exposure shortly after childbirth and preventing HIV acquisition) relative to the mother’s right to autonomy and to refuse HIV testing.

To illustrate the problem, let us consider the following case:

A paediatrician working in a government hospital in South Africa is called to assess an infant born four hours ago. The child’s mother is 32 years old, severely wasted, has oral thrush and is of unknown HIV status. This is her second child, the first died in infancy after a short illness, which has a history typical of pneumonia. The doctor examines the newborn, who is vigorous, fully grown for age and has no signs of HIV infection. After counselling, the mother declines an HIV test. The paediatrician knows that testing the newborn for HIV exposure and giving ARV prophylaxis is likely to markedly benefit the

child. The doctor recalls that her duty is primarily to protect the child’s health and is unsure what to do. Hospital policy is not to test newborns for HIV exposure unless the mother consents to testing. She decides to make a court application, asking the judiciary for permission to test the child.

SITUATING HIV TESTING OF NEWBORNS WITHIN REVISED TESTING PARADIGMS

Recent years have seen a shift in HIV testing paradigms, as benefits of knowing one’s HIV status accrue. The traditional rights-based approach, built around the need for safeguarding individual autonomy, is increasingly being balanced with public health interests, the interests of partners and children, and by the harms individuals face from only discovering their HIV status when severely ill. Recent WHO and CDC guidelines recommend an opt-out approach to provider-initiated testing, make testing more routine, while acknowledging the right of individuals to decline testing. Shifts in policy are also shown by revised terminology and practices. Both WHO and CDC recommend that abbreviated ‘pre-test information’ replace complex pre-test counselling, which was modelled on counselling modalities for untreatable genetic diseases like Huntington’s chorea. Similarly, post-test counselling for those testing negative has been markedly abbreviated as little evidence supports its utility. CDC goes further, recommending elimination of requirements for specific consent to HIV testing.

---

The consent process for HIV testing remains distinct from processes for identifying other transmissible diseases and other diseases which respond well to chronic treatment\textsuperscript{12}. Identifying maternal HIV infection or newborn HIV exposure may be more important on purely medical grounds than identifying maternal infection and newborn exposure to syphilis or hepatitis B, for example. However, the more severe social implications for women of an HIV diagnosis are given more weight than this medical rationale. This is mostly due to stigma, a key reason for the distinctiveness of HIV testing. The challenge, of course, is to de-stigmatise HIV in the public consciousness. Though there are qualitatively few differences in procedures and benefits of detecting infection with syphilis, hepatitis B or HIV, a gap in popular consciousness remains. From an ethical point of view we should ask whether such a gap should determine policy.

Presently, many HIV-infected people only discover their status when they develop severe diseases, which are often associated with a high mortality or permanent morbidity. Further, those only diagnosed with HIV infection when they develop such diseases and advanced immunosuppression, have poorer outcomes with ARV treatment\textsuperscript{13}. Essentially, changes in current policies are grounded on the fact that HIV infection will declare itself and that a timely diagnosis of HIV has substantial benefits for those infected (and for their children and sexual partners). Consistent with these revised policies, HIV testing is considered part of essential care around childbirth\textsuperscript{14}. Recent WHO guidelines have re-emphasized and strengthened this recommendation\textsuperscript{15}.

\textsuperscript{15} WHO. Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants in resource-limited settings: towards universal access. 2006. Available at: \url{http://www.who.int/hiv/pub/guidelines/pmtct/en/index.html}.
However, where PMTCT programmes are established but women decline testing, several ethical issues are raised.

**From self-initiation to mandatory testing; a spectrum**

HIV testing policies need to optimally balance protection of individual rights with the interests of children, sexual partners and the public. In this context, arguments have been made for mandatory testing: in source patients following incidents of occupational exposure, or sexual assault; before marriage; and even among the general population\(^{16}\).

Previously, a clear dichotomy existed between voluntary and mandatory HIV testing. However, there is considerable variation in the urgency and importance of knowing one’s HIV status or knowing one has been HIV exposed. Volunteerism for HIV testing could therefore be viewed as a spectrum, ranging from individuals who actively self-initiate testing, to the other extreme with involuntary testing of a rape perpetrator, for example. Between these poles are several scenarios where: the *availability of testing is mentioned* during clinical encounters unrelated to HIV (such as eye refraction clinics); patients in sexually-transmitted infection clinics are *informed of the benefits of testing and offered a test*; and patients with signs of advanced HIV disease are *strongly recommended and implored to test* as they have a substantial likelihood of a mortal illness if ART is not initiated in the near future. As opposed to the dichotomous approach, a spectrum model better acknowledges the complexity of this topic. Extending this model to women during pregnancy or around childbirth, suggests that, at a minimum, health workers need to ensure these women are *adequately informed of the consequences of declining testing,*

both for themselves and for their child. As early as 2002, in Thailand’s much-praised PMTCT programme ref, pregnant women were ‘encouraged to consent’ for testing\textsuperscript{17}.

Testing of newborns for HIV exposure needs to be placed within this spectrum. In addition to benefits for infants of identifying HIV exposure and consequent PMTCT interventions, women would decrease their likelihood of having to care and pay for a chronically-ill child, and of experiencing their child’s HIV death. Further, in many communities, having a chronically-ill child can be a source of stigma and is highly suggestive of HIV infection, undermining confidentiality.

POST-EXPOSURE PROPHYLAXIS FOR INFANTS SHORTLY AFTER CHILDBIRTH REDUCES HIV TRANSMISSION

ARV prophylaxis for newborns is conceptually similar to post-exposure prophylaxis following occupational or sexual exposure. Two trials in Africa and an observational study in the United States have demonstrated the efficacy of ARV prophylaxis in reducing HIV infection in infants whose mother had not received ARV drugs\textsuperscript{18}. In a Malawi trial, the risk of HIV transmission was 15.3% with infant single-dose nevirapine (NVP) and one week of zidovudine (AZT), compared with 20.9% in infants who received only single-dose NVP. However, if infant ARV prophylaxis is delayed more than three days after childbirth, it is unlikely to have any benefit\textsuperscript{19}. As NVP has a long half life


(levels detectable up to 21 days after a single dose\textsuperscript{20}) it may also provide additional benefit in preventing transmission from breastfeeding shortly after birth\textsuperscript{21}. Most commonly, in resource-constrained settings, a single dose of NVP is given to HIV-infected women during labour and to their infants shortly after childbirth, to prevent transmission of the virus. This regimen reduces the risk of MTCT to about 12\%, though more effective regimens are progressively being implemented. Based on evidence from previous trials, these reductions in transmission are likely to be sustained, even if the woman breastfeeds for prolonged periods\textsuperscript{22}. Rapid HIV tests, with blood taken from newborns, are especially suited to testing for HIV exposure. The presence of HIV antibodies in infants is indicative of maternal HIV infection and that the infant is HIV exposed.

HIV infection markedly diminishes quality of life for children, and without access to ARV treatment, about half die within two years of birth and nearly all die by five years\textsuperscript{23}. ARV treatment for children is progressively becoming available, but is complicated by: few treatment options with limited syrup formulations; dosage changes as children gain weight; and unique challenges of adherence and monitoring in children. In high-HIV burden settings, a substantial proportion of children seen at health facilities, either as outpatients or inpatients are HIV infected\textsuperscript{24}. Addressing their needs thus requires


substantial human and funding resources, which – to a lesser or greater extent – is likely to detract from initiatives to improve survival of uninfected children. The suffering of HIV-infected children and related public health costs, are preventable.

**BALANCING WOMEN’S AUTONOMY WITH CHILD’S INTERESTS**

Autonomy, the capacity to think, to decide, and to act on the basis of personal freedom\(^ {25} \), is something acquired with difficulty (particularly by women in a patriarchal system) and needs to be protected. However, tensions arise when autonomy is asserted in the face of overwhelming evidence of the advantages of medical treatment, and of manifest and clear harm to a patient or others. While it is within the woman’s autonomy not to test herself for HIV, a decision to test newborns for HIV exposure raises additional complexities. Stated otherwise, women have a ‘right not to know’ their HIV status\(^ {26} \), but this can conflict with a newborn’s ‘right to know’ whether they are HIV exposed.

Strictly speaking, infants do not have autonomy since autonomy implies the capacity to make decisions for oneself, or to instruct a person to act as proxy\(^ {27} \). Although parents or legal guardians usually have power to consent for medical procedures for their children, it is by no means clear that they should have the final word on how their child should be treated.

Literature on the right not to know one’s genetic status could inform discussion of the woman’s right not to know HIV status. Andorno contends that the right not to know can be an expression of autonomy but that this right is limited where ‘there is a serious risk of

---

110; G Walraven et al. The impact of HIV-1 infection on child health in sub-Saharan Africa: the burden on the health services. *Trop Med Int Health* 1996, 1:3-14.


harm to other persons and where there is some reasonable form of cure or therapy\textsuperscript{28}. Similarly, the WHO Guidelines on Ethical Issues in Medical Genetics and the Provision of Genetic Services recommends that ‘The wishes of individuals and families not to know genetic information, including test results, should be respected, except in testing of newborn babies or children for treatable conditions’\textsuperscript{29}. This situation is perhaps analogous to HIV exposure in newborns.

Although privacy and confidentiality are central to health worker-patient relations, limits can be set where third parties lives are at stake. The 1976 Tarasoff case in the US, where a psychotherapist failed to report his client’s intentions to kill a young woman, illustrates such a limit, a limit noted in subsequent Codes of Ethics\textsuperscript{30}. Protecting a person’s life may mean that such a hitherto inviolate principle of medical ethics may be modified in certain circumstances.

Even in the most libertarian of states there are limits to personal liberty to protect citizens from harm\textsuperscript{31}. Personal autonomy or a parent’s autonomy in making decisions for their child cannot be endorsed as an absolute, particularly when it harms others. The choice not to be HIV-tested, even at the risk to one’s own life, may be an acceptable option, but to allow transmission to one’s infant, we submit, exceeds the bounds of autonomy. In exercising autonomy one is here potentially imposing one’s sickness on someone without their being able to consent to take the risk. Moreover, a mother may avoid an HIV diagnosis, as she feels unable to cope with it, but, in practice, she expects her child

to deal with it, should that child become infected. Proponents of personal responsibility would argue that it isn’t fair to subject another human to disease. Autonomy in this case violates justice and the principle of not doing harm. A similar rationale underlies regulations on exposure to second-hand tobacco smoke and seat belt use. Fathers too have an interest in having a healthy child.

Potential adverse consequences of testing all newborns for exposure to HIV need to be considered. Where the HIV epidemic is concentrated in certain populations, it has been argued that mandatory testing would represent an ‘affront to the dignity and rights of minority women’. Opponents of mandatory testing of newborns also argue that it singles out women, placing them in a special category, distinct from testing of men. Women and girls are more likely to face stigma, violence and abuse when their HIV-positive status becomes known by boyfriends, spouses or community members. With a burden of intimate partner violence and continued subordination of women, women’s privacy is a priority and further efforts are needed to reduce gender biases in stigma and to create a supportive policy and legal environment. Further, in an era of increasing patient autonomy there is likely to be resistance to medical approaches which appear paternalistic. It has been argued that mandatory testing may alter the communities’ perceptions of health systems and deter women from accessing health services. These

concerns have been cited as the main objection to mandatory testing of newborns. If this were to occur on a substantial scale, gains from identifying HIV-exposed infants would be offset by complications from a decrease in hospital births. There is an alternative hypothesis: the devastating HIV epidemic erodes confidence in the health services and more robust methods of tackling the disease would be welcomed, improving perceptions of service quality which are a key determinant of health seeking behaviour.

There is no evidence indicating that inclusion of opt-out HIV testing for adults has decreased numbers of people attending services. By contrast, the acceptability of such an approach has been high in several reports. Similarly, evidence indicates that concerns that mandatory name-based notification of HIV infection would deter people accessing HIV testing were overstated. While these findings are reassuring, their ability to predict outcomes of mandatory testing of newborns is limited. More relevant are the experiences in the US states which have implemented mandatory testing for newborns. With this policy and opt-out testing for pregnant women, HIV testing coverage is near universal. Introduction of mandatory testing was associated with increases in testing in


these states – following implementation of laws that included mandatory newborn testing in Connecticut, testing increased from 22% to 87%43. Despite speculation about likely effects of such policies on health-seeking behaviour, to our knowledge, there have been no reports of decreased attendance at health facilities.

CHILD’S BEST INTERESTS: DUTY OF CHILD HEALTH PROFESSIONALS

For women who opt out of HIV testing around childbirth, safeguarding the wellbeing of the child needs to be balanced with protecting the woman’s autonomy. The UN Convention on Rights of the Child (CRC) provides one framework for analysing this apparent clash of rights44. The overarching principle of the convention is that:

In all actions concerning children, whether undertaken by public or private social welfare institutions, courts of law administrative authorities or legislative bodies, the best interests of the child shall be a primary consideration.

One hundred and forty countries are signatories of the Convention and 136 have ratified it within their legislation, making it legally binding. The articles of the CRC also provide important guidance on the state’s responsibility to safeguard child’s health:

states parties shall ensure to the maximum extent possible the survival and development of the child [and] develop preventive health care.

Woman’s autonomy has also been viewed as a primary consideration. UNAIDS guidelines have long emphasized the importance of avoiding HIV prevention programmes that contain coercive measures, stating that such programmes are likely to

reduce participation of those living with HIV. We would argue that while the context of stigma is significant, the long-term goal – a healthy child – and the principle of protecting the best interests of child, trumps autonomy and privacy in these circumstances. We do not deny that such a decision is highly problematic. All we suggest is that it seems more fitting to serve the best interests of the child, all factors considered.

The state is obliged to assume ultimate responsibility for protecting the health and wellbeing of children, and to intervene when circumstances occur which are contrary to the child’s best interests. It is therefore worth considering several legal scenarios, using the hypothetical case report as illustration. The paediatrician caring for the newborn whose mother has refused HIV testing could launch an urgent court application to test the newborn for HIV exposure. The judiciary would have to rule based on legislation and legal precedent in some countries. In cases where doctors have approached the courts to overrule parental autonomy in favour of a child’s health, the courts have usually ruled in favour of the doctor, especially where there is a good prospect of favourable clinical outcomes for the child. Similarly, courts in both Holland and the United Kingdom have ordered HIV testing of source patients involved in occupational injuries, one judge ruling that the violation of the patient’s right was ‘relatively minor’ as confidentiality could be maintained and the benefits to the doctor could involve ‘reasonable and fair’ limits to rights.


46 K. Leask. The Role of the Courts in Clinical Decision-making. *Archives of Disease in Childhood* 2005; 90:1256-1258; Hay v B and others 2003 (3) SA 492 (W) Urgent court authorisation for transfusing an infant, opposed by parents on religious grounds. The judge ruled: ‘a child’s best interests were of paramount importance in every matter concerning the child and was the single most important factor to be considered when balancing or weighing competing rights and interests concerning children. The duty to afford children protection fell on law enforcement agencies, all right-thinking people and ultimately the Court, which was the upper guardian of all children’.

47 Sheldon T. Patients can be made to have HIV test to protect doctor; *BMJ*. Feb 7 2004;328:304
The paediatrician in the case presented here could decide to test the newborn for HIV antibodies, contravening prevailing policies. In doing so, she may be acting in a sincere manner, and from an informed conscience and interpretation of her duties. There are many previous examples where individuals have acted from their conscience, even when such actions were contrary to policy. In several of these examples, the action of a few individuals focused the spotlight on an issue, fomenting change and radical shifts in policy, and sometimes in historical trajectories. Such examples, from the medical field include the distribution of contraceptives for multiparous women when contraceptives were considered illegal. The recent importing of generic medication by the Treatment Action Campaign in South Africa, similarly was an act of conscience, though against laws at the time.

As an alternative, children with HIV infection (or their guardians) could legally argue that, by not testing them for HIV exposure at birth, health providers neglected to protect them from HIV infection and did not act in their best interests, as obliged under international and domestic law in many countries. Similarly, with the state as defendant, HIV-infected children could argue that health policies were inconsistent with the law and that the HIV transmission which occurred was, at least in part, due to the state not acting in their best interests. Conscience-based or legal action may be the most direct route to policy change.

Other options could be considered. Arguments have previously been made for mandatory HIV testing for pregnant women who decide to carry a fetus to term.\(^{48}\) Potentially, that strategy and giving ARV prophylaxis during pregnancy, labour and to infants would be more effective than infant-only prophylaxis. In many countries it is a

---

legal right for a woman to seek an abortion, at least until a certain point in a pregnancy. Should she waive that right it seems logical that she accepts moral responsibility for bringing the infant to birth\textsuperscript{49}, though this assertion is contested\textsuperscript{50}. Arguments for mandatory testing of pregnant women are built on the premise that a woman who chooses to carry a fetus to term and chooses not to reduce its chances of acquiring HIV is causing harm to others. Mandatory testing of pregnant women, however, would be harder to institute than infant testing. It is also a larger infringement on a woman’s autonomy, as it requires collection of a biological sample from the woman and for her to take drugs, possibly causing her harm by inducing viral resistance. Moreover, a competent adult cannot be forced to submit to treatment for the benefit of a third person, even if that third person is her child\textsuperscript{51}. Making this case among pregnant women also introduces complex conflicts of maternal-fetal rights. However, once born, the rights of the child are clearer, enshrined in international and domestic laws, and inaction is harder to defend.

It may be possible to test infants for HIV exposure, administer sd-NVP to exposed infants and not to inform women of their HIV status. This avoids undermining women’s personal autonomy (though not her parental autonomy). As a further alternative, all infants could receive sd-NVP, analogous to universal tetracycline eye ointment routinely given to newborns to prevent Ophthalmia neonatorum, caused by the sexually-transmitted infections \textit{Chlamydia trachomatis} or gonorrhoea. Both these strategies are potentially advantageous over the existing approach. However, a single dose of NVP for


infants is less effective than giving the infant single-dose NVP and one-week zidovudine, and without informing a woman of her HIV status, the infant would not benefit from infant feeding counselling and support. In the option presented in this paper, a woman would be informed of the test result, enabling provision of interventions to benefit her health and modify her infant feeding practices.

Several conditions may increase the likelihood of benefits from testing newborns for HIV exposure and minimise the negative consequences of undermining women’s autonomy. These conditions include assured access for women to high-quality HIV treatment and care, and structures which safeguard women’s wellbeing. Antidiscrimination laws and services are needed to protect women from harm, and to ensure they have recourse to justice when required. In particular, services for women who have experienced violence are needed, as women may have high risk of violence following disclosure of HIV status, or a breach in confidentiality by health workers. We also consider it essential that women obtain direct benefit from an HIV diagnosis, thus aiming to avoid instrumentalising women and treating them as conduits for healthy babies. Further, providing high-quality HIV testing and PMTCT services for pregnant women would mean that a low proportion of infants would be born with unknown HIV status. Raising the quality of antenatal testing is a less harmful means of achieving the desired goal, but mandatory testing may remain necessary for newborns of women who declined such testing.


RESEARCH NEEDS: ACTION FOR CHILDREN’S RIGHTS

Additional action and systematic assessment are needed. Current policies are not based on evidence. As commonly occurs, these policies were formulated by experts, often a hemisphere away from those living with the consequences of such policies. Despite a lack of evidence, international bodies contend that mandatory testing is ineffective for public health purposes. Actually, the only available evidence is that mandatory testing of newborns is an effective strategy. Policy development could benefit from increased use of insights from those with lived experience, such as the views of HIV-infected children and their parents. Input is needed from women who elected not to test for HIV during pregnancy and around childbirth, and now care for, (or lost) an HIV-infected child.

It is important to determine whether, with hindsight, they would have preferred the state to prioritize protection of their child’s interests.

Given the poor effectiveness of current PMTCT strategies, it may be worthwhile to implement pilot studies investigating the effects of mandatory testing of newborns. The almost decade-long experience with this strategy in several parts of the US could be used as ‘proof of concept’ for this research. The lack of evidence of harmful effects of this strategy in the US also serves to justify its further investigation. In particular, it would be important to closely monitor effects of mandatory newborn testing on health-seeking patterns. It would likely be prudent to initially investigate this strategy in settings which have pre-existing high levels of hospital delivery and safeguards to maintain confidentiality of these results. Also, establishing pilot sites in settings with a generalised

HIV epidemic would avoid potential targeting of minority groups and improve cost-effectiveness of the intervention. This would also increase the number of HIV-exposed newborns identified compared with the number of women’s privacy invaded, though attempting to determine this optimal ratio is precarious\textsuperscript{57}.

**CONCLUSION**

We have presented an abstract ethical case that the best interests of the infant and the infant’s right to preventive health care\textsuperscript{58} supersede the woman’s right to self-determination and not to know her HIV status. Moreover, we concur with the argument that choosing not to act to prevent harm when one could have acted without unreasonably high costs to oneself is comparable to similarly deliberate actions that produce the same amount of harm\textsuperscript{59}. Women or health workers who choose deliberately not to act – which can be directly linked with negative outcomes – should be asked to justify their inaction. Moreover, mandatory testing of newborns may stimulate increased coverage and quality of PMTCT programmes.

From birth, the child has an inherent right to life and deferred autonomy to their parents, which the state has a responsibility in monitoring and ensuring is used in the interests of the child. Though seemingly similar to the much-criticised notion of physician paternalism, persons with expert knowledge – like paediatricians – are best placed to objectively serve the best interests of the child in certain conditions. Indeed, paediatricians primarily have a duty to protect and preserve the health and wellbeing of the child. It is surprising, therefore, that child health workers have not been more vociferous advocates for mandatory testing of newborns. Resorting to legal action –


whether an urgent injunction to test a newborn, or an HIV-infected child contending the state did not act in their interests – offers an important means to influence policy.

Empirically, the right not to know is temporary for those infected with HIV. Within an enabling policy environment, the role of health workers is to make a timely diagnosis of early HIV disease and to ensure benefits from knowing one’s status for the infected individual, and their susceptible sexual partners and children. The degree and nature of benefits from an early HIV diagnosis differ markedly from benefits of a late diagnosis made with the inevitable severe diseases that occur in those infected with HIV. Perhaps for too long health workers have protected people from facing an inevitable diagnosis, rather than protecting people’s health and that of their children. Nowhere is such testing more urgent and benefits more apparent than for newborn infants.
Article 5: HIV-testing and antiretroviral prophylaxis for a newborn without its mother's consent: case report
HIV-testing and ARV prophylaxis for a newborn without its mother's consent
Matthew Chersich. MBBCh, MSc(Public Health), DCH, DObst,
International Centre for Reproductive Health, Kenya
Marlise Richter BA (Hons), MA, LLM, School of Public Health, University of the Witwatersrand
Article Submitted for the Southern African Journal of HIV Medicine, 23 August 2007
This article is based on a case study discussed on the “HIV Policy & Ethics Discussion Forum”.
http://groups.google.com/group/policy-ethics

Case Study
A paediatrician is called to the nursery ward of a government hospital to see a male infant born eight hours ago. The infant's mother is 33 years, wasted and has oral thrush. This is her second child, the first died in infancy after a short illness, which has a history typical of pneumonia.

The mother was not offered an HIV test during pregnancy as the clinic she attended does not have such services. A nurse had called the paediatrician as her offer of HIV testing to the mother had been declined. She requests the paediatrician to convince the woman to test, given the benefits such knowledge gives the woman, as well as to enable the provision of post-exposure prophylaxis for the newborn and of infant feeding counselling. The paediatrician examines the newborn, who is vigorous, fully grown for age and has no signs of HIV infection. She then carefully counsels the patient explaining the potential harms of testing, and benefits for the woman and her infant. Still the woman declines testing.

The paediatrician is aware of the efficacy of antiretroviral (ARV) prophylaxis given to HIV-exposed newborns whose mothers did not receive ARVs.1 2 3 Her informed conscience and medical duty to act in the best interests of her patient (the child), has to be balanced with hospital, and international policies which infer that newborns cannot be tested for HIV exposure and be given prophylaxis without their mothers’ consent. She thinks of many others - such as the previous medical superintendent for the East London Hospital Complex - who in similar situations acted from their conscience, even if such actions were contrary to prevailing policies and protocol. The paediatrician examines the newborn, whose antibody rapid tests show is HIV-exposed. The doctor provides ARV prophylaxis to the infant, counsels the woman about her own HIV status and enrols her in an HIV clinic which provides ART.

Questions for discussion
1.) Was the paediatrician correct to test the infant without the mother's consent? What is the optimum balance between a woman's right to autonomy and choice, and the infant's access to health care services?
2.) Was the paediatrician correct to provide ARV prophylaxis to the infant without consulting the woman? Should the paediatrician inform the woman that she had given the infant ARV prophylaxis?

Discussion
An Ethical and Rights-based approach
A woman's constitutional rights to privacy, reproductive choice and bodily autonomy are all too often violated and require adequate legal protection. Also, in common practice, it is a woman's right (and legal obligation) to make choices for her child. However, HIV infection in infants and its concomitant costs and suffering are essentially preventable. In such circumstances, rights are competing and need to be carefully weighed. Dedicated efforts, which are culturally-appropriate and ideally communicated in the woman's first-language, are needed to explore and address the underlying reasons the woman declined HIV testing. Increasingly in South Africa, ART is becoming available and systems are in place to safeguard confidentiality. In these settings, it is difficult to construct a reason for not testing the infant when the woman refuses, that is
more compelling than an HIV-free child. That does not discount the fear of knowing one is HIV infected, nor does it ignore the potential risks for violence following disclosure of HIV status to one’s partner.

Mandatory testing of newborns could signify the beginning of a slippery slope, potentially eroding the right to refuse testing in situations such as during pregnancy, post-rape, pre-marriage, post-occupational injury, even perhaps in the general population. By itself, a desire not to engage in a slippery slope argument is an inadequate rationale for not choosing between the child’s best interests (identifying exposure and receiving antiretroviral post-exposure prophylaxis) and a woman’s (potential?) interests in not knowing her own HIV status. Although legislation, policy, and guidelines emphasise informed consent, the Constitution trumps these. Section 28 (2) of the Constitution states that: "A child’s best interests are of paramount importance in every matter concerning the child.” This has been used to assert children’s best interests, such as where Jehovah Witnesses tried to decline a blood transfusion for their child.

Where current practice conflicts with the child’s interests, can health care workers act from their conscience, or is this the sole domain of the courts? Where policy and legislation are out-dated and lagging behind medical progress, bringing a test case to court could catalyse change. For example, in circumstances where a woman refuses HIV testing after birth, a health care worker could launch an urgent court application to test the infant and provide prophylaxis without the woman's consent. The authors feel that a paediatrician launching such a case is long over-due. It could be argued that each day paediatricians make active decisions not to test newborns for HIV exposure, even though this may be in the best interests of those they serve.

Several US states have successfully implemented mandatory testing of newborns for almost a decade and have, provided proof of concept and encouraging safety data, and this in itself should justify further investigation in a South African context. The state must assume ultimate responsibility for protecting the child's health and wellbeing, and should intervene when these are undermined. It should also be noted that a child who has contracted HIV could also argue that, by not testing her for HIV exposure at birth, the health providers who cared for her after childbirth neglected to protect her from HIV infection and did not act in her best interests.

**Legal Implications**

In the above scenario, it is doubtful that the woman would institute a legal course of action against the paediatrician. But, if so, the legal ramifications for this Case Study are essentially three-fold:

a.) Any invasive medical treatment or test without the patient’s consent (and in this instance that of the legal guardian of the infant - her mother) constitutes an assault under South African common law as well as an invasion of personality rights.

b.) It therefore follows that the mother could lay a charge of assault on behalf of her child against the doctor who tested the infant and provided medical treatment to the infant without the mother's consent.

c.) The mother will also be in a position to report the paediatrician to the Health Professions Council of South Africa (HPCSA) for unethical conduct.

However, it is unlikely that the course of action described above would succeed in court. In her defence, the paediatrician would be able to argue that the court is under a constitutional obligation to develop the common law so as to "promote the spirit, purport and objects of the Bill of Rights" (section 39(2) of the Constitution) and in line with the paramount place given to the interests of the child (section 28(2) of the Constitution).

Evidence is overwhelming that it is not in the best interests of the child to acquire HIV from the mother, and that providing HIV testing and post-exposure prophylaxis would reduce the risk of the child contracting a chronic and life-threatening illness. Also, medical evidence shows that administering a single dose of ARVs to the child does not harm the infant.

The paediatrician could therefore argue that the courts are constitutionally obliged to develop the common law of assault to exclude instances of beneficent intervention in the interests of a minor. On this approach it
is likely that the doctor would be acquitted of a charge of assault, while the Health Professions Council would probably make a similar finding.

Conclusion

Overall, a test case may effect policy change, though must never negate or minimize the real difficulties women face in this epidemic, and their needs for care and support. Ideally, women would be strongly encouraged to test and be referred to appropriate programmes during or prior, to pregnancy. In lieu of this, the infant’s interests in not contracting HIV are paramount.

Perhaps the epidemic could be reversed with more vigorous interventions, though carefully considered and with specific efforts to minimise any human rights infringements. Where access to HIV treatment and confidentiality are assured, the degree and range of benefits of an early HIV diagnosis differ markedly from those of a late diagnosis when HIV inevitably declares itself with severe diseases. Perhaps, for too long health workers have protected people from facing an inevitable diagnosis, rather than protecting people’s health and that of their children. We can never turn back the clock, but we can change the speed of its ticking.

References

9. Venter Z. Doctors go to court to get blood for baby. IOL 2005 October 25.
11. Stoffberg v Elliott 1923 CPD 128
12. Castell v De Greef 1994 (4) SA 408 (C)
3.3 Identifying HIV infection in women attending child health clinics

Article 6: HIV testing and counselling for women attending child health clinics; an opportunity for entry to PMTCT and HIV treatment
Full title: HIV testing and counselling for women attending child health clinics; an opportunity for entry to PMTCT and HIV treatment

Short title: HIV testing in child health clinics; PMTCT entry

Authors: MF Chersich¹,² MBBCh MSc; SMF Luchters¹,² MD MSc; MJ Othigo³ MD PhD; E Yard¹ MSc; K Mandaliya³ MBChB FRCPATH M Temmerman¹,² MD PhD

Affiliation:
¹ International Centre for Reproductive Health, Mombasa, Kenya,
² Ghent University, Department of Obstetrics and Gynaecology, Ghent University
³ Coast Provincial General Hospital, Mombasa, Kenya.

Institution where work carried out:
International Centre for Reproductive Health, Mombasa, Kenya,

Corresponding author: Matthew Chersich, Tudor Four Estate, Tom Mboya Avenue, P.O.Box 91109, Mombasa, Kenya. Email: matthewf.chersich@icrhk.org
Tel: +254 412494866; Fax: +254 412495025

Key words: Kenya; patient acceptance of health care; HIV infections; female; vertical prevention and control

Summary
The study assessed the potential for HIV testing at child health clinics to increase knowledge of HIV status, and entry to infant feeding counselling and HIV treatment. At a provincial hospital in Mombasa Kenya, HIV testing and counselling was offered to women bringing their child for immunization or acute care services. Most women said HIV testing should be offered in these clinics (472/493, 95.7%), with many citing the benefits of regular testing and entry to PMTCT. Of 500 women, 416 (83.4%) received test results, 97.6% the same day. After 50 participants, point-of-care testing replaced laboratory-based rapid testing. Uptake increased 2.6 times with point-of-care testing (95%CI=1.4-5.1; P=0.003). Of 124 women who had not accessed HIV testing during pregnancy, 98 tested in the study (79.0%). Measured by uptake and attitudes, HIV testing in child health clinics is acceptable. This could optimise entry into HIV treatment, infant feeding counselling and family planning services.
Introduction
HIV testing and counselling strategies have changed as the benefits of knowing one’s HIV status accumulate. Routine HIV testing during patient-provider encounters in clinical settings (“opt out testing”) is increasingly being promoted as a pivotal part of HIV prevention and treatment strategies.\textsuperscript{1,2} Previously, testing was either client initiated (voluntary counselling and testing (VCT)), or confined to a limited category of patients, such as pregnant women or people with advanced HIV disease. Testing has now been introduced during labour or shortly after childbirth,\textsuperscript{3,4} in family planning\textsuperscript{5} and other services such as abortion clinics.\textsuperscript{6} This aims to markedly increase the number of individuals who can benefit from knowing their HIV status. Accumulating evidence indicates that provider-initiated testing in these diverse clinical settings is acceptable\textsuperscript{7,8}.

Much effort has been made to integrate HIV testing and interventions to prevent mother-to-child transmission (PMTCT) within antenatal care and childbirth services (mostly focused around short-course antiretroviral prophylaxis). However, even where PMTCT programmes have been established, many women do not access HIV testing during pregnancy or around childbirth.\textsuperscript{9,10} Additional efforts to identify HIV-infected women in the postpartum period may assist in increasing effectiveness of PMTCT programmes as breastfeeding accounts for a third to half of HIV infections in infants\textsuperscript{11}. These women and their infants could benefit from entry to HIV care and treatment, infant feeding counselling and support, and provision of family planning counselling. This study assessed uptake of provider-initiated HIV testing among women attending child health clinics, and explored women’s attitudes towards testing.

Methods
At Coast Provincial General Hospital in Mombasa, Kenya, 500 women participated in a cross-sectional study to determine the health status and needs of postpartum women. From March to August 2006, women bringing their infant for immunization and well child services, or for acute paediatric care were invited to participate. Eligible participants were older than 16 years, biological mothers of
the child, and less than one year postpartum. The study protocol was approved by the Kenyatta National Hospital Ethics and Research Committee. Women gave written informed consent for study procedures. Information on demographics, sexual behaviour, HIV-related knowledge, attitudes to HIV testing, infant feeding practices and postpartum health was collected using a structured questionnaire administered in Swahili.

A lay counsellor offered all women HIV testing and counselling. Women who had tested HIV negative during pregnancy were informed that retesting can identify recent infection and retesting was recommended. Those women who had previously tested HIV positive were told that further testing was unnecessary but that they could confirm their results if they wished. Women were explicitly told they could opt out of testing and counselling procedures. Verbal consent was obtained from those wishing to receive their results. A serial rapid test algorithm was used for HIV diagnosis; tests reactive with Determine™ HIV-1/2 (Abbott Laboratories, Minato-Ku, Tokyo, Japan), were confirmed with Uni-Gold™ HIV (Trinity Biotech, Bray, Ireland).

HIV results were available the same day. For the first 50 participants, rapid HIV testing took place in the hospital laboratory using a blood specimen collected during other study procedures. Though efforts were made to minimize delays in obtaining test results, women cited a lack of time and lengthy delays as the main reason for declining testing. Therefore, for the remainder of the study, point-of-care testing took place, with the lay counsellor performing finger pricks.

**Data management and analysis**

Data were double entered by separate clerks. The postpartum period was categorised as early (four weeks to two months after childbirth) and late (two months to one year). Unmet need for contraception was measured as preventing unintended pregnancies is a key component of PMTCT strategies. Sexually-active women not using contraceptive methods were defined as having an unmet need for contraception. Lactational amenorrhea (exclusive breastfeeding and amenorrhea) was classified as a contraceptive method. Intercooled Stata 8.0
(Stata Corporation, College Station, Texas, USA) was used for statistical analysis. To detect associations between exposure variables and uptake of HIV testing, we compared women who did or did not receive test results. For analysis of binary variables, a Mantel-Haenszel odds ratio was calculated and for ordered categorical variables, a chi-square test for trend.

Attitudes to HIV testing in child health clinics were assessed by asking all women whether HIV testing and counselling should be offered in child health clinics and to explain their opinion. Women’s responses to these open-ended questions were coded. Code labels were developed as themes emerged. Text was grouped according to common themes for presentation in a frequency distribution. Representative quotations are used to illustrate main themes.

**Results**

Five hundred of 776 women (64.4%) eligible for the study agreed to participate. Reasons for declining participation in the study included: lack of time (120), need for partner approval before participation (54), and having a child requiring urgent care (48). No-one said the HIV testing and counselling procedures was the reason they declined study participation.

Study participants were on average 25.5 years of age (standard deviation=4.5 years) and a median 3.3 months postpartum (inter-quartile range=1.9-6.1 months) (Table 1). The majority of women were married or cohabiting (86.2%; 431/500), with the remaining women having never married (11.6%; 58/500) or were divorced, separated, or widowed (2.2%; 11/500). Less than half of the women reported that their recent pregnancies was planned (46.2; 231/500) and 39.4% (187/475) of women currently had an unmet need for contraception. Most study participants (81.6%, 395/484) had attended services for well children, such as immunization. Nearly all women reported attending antenatal care at least once (480/500; 96%), though fewer (77.8%; 389/500) delivered with a skilled birth attendant. Three-quarters of women (75.0%, 372/496) had accessed HIV testing during pregnancy or around childbirth. Mixed feeding predominated, even among women early in the postpartum (84.6%, 110/130).
Uptake of postpartum HIV testing and counselling (proportion of study participants who received test results) was 83.2% (416/500). The majority of those who received their results, chose same-day resulting (97.6%; 406/416). Of the women who had not accessed HIV testing during pregnancy, test uptake was 79% (98/124). HIV prevalence among study participants was 10.9% (54/496). No discordant results occurred during HIV testing.

The commonest reason given for opting out of testing was being afraid of a positive test result (26/84). Only 11 women gave “having previously tested” as the reason for declining testing. Other reasons reported included desire to consult with their partner before testing, fear for partner, preference for couple counselling and more time needed to decide. Thirteen of 15 women who declined laboratory-based testing cited lack of time as the reason for declining, while this reason was given by fewer women who declined point-of-care testing (7/67; \( P < 0.001 \)).

The analysis to detect an association between test uptake and demographic and other factors, showed women were more likely to decline testing if they had a higher household income or were more than two months postpartum (Table 2). Women who had resumed sexual activity were also more likely to decline testing, though controlling for the length of time postpartum reduced this association (adjusted odds ratio=0.54; 95%CI=-.28-1.1; \( P = 0.066 \)). No association was detected between test uptake and level of HIV and MTCT knowledge, or education. Women were 2.6 times (95%CI=1.4-5.1; \( P = 0.003 \)) more likely to accept point-of-care testing than laboratory-based rapid testing.

**Attitudes to testing: “One has to keep on being tested and be in a position to protect the baby”**

Most participants believed women should be offered HIV testing in child health services (472/493, 95.7%), though even more said HIV testing should be provided during antenatal care (488/492, 99.2%, \( P = 0.001 \)). The commonest reason women gave for testing in child health services, was that it is good to frequently check one’s HIV or health status (165/472; Table 3). One woman
described this as “a routine HIV check-up”, others remarked that confirming their status can lead to “a peaceful mind” and inform them of “the direction of your health”.

In the opinion of 21 women, those who had not accessed testing during pregnancy were most likely to benefit from testing at child health clinics. However, Fifty women specifically mentioned that retesting in the postpartum can detect infections which occur during pregnancy or after childbirth. Many related this to doubts about partner unfaithfulness at that time. For example: “men cannot be trusted during and after pregnancy” and another woman: “you do not know what your partner is doing with himself [during pregnancy] about sex”. Similarly, an additional 21 women felt that HIV testing was a way of checking if their partner had been faithful, as one woman surmised: “if one is still negative it’s a sign that the partner is still faithful”. Interestingly, nine women appeared concerned about acquiring HIV during healthcare procedures around childbirth.

Thirty-three women said testing would benefit both themselves and their child, with one woman summing their views that knowing one’s status “can save the baby and helps mother take care of herself”. A larger number (110) spoke only of the role of HIV testing in preventing HIV infection in their child. Sixty four of these 110 women said that knowing they were HIV positive would allow them to protect their child by stopping breastfeeding. One woman mentioned that if positive she could exclusively breastfeed, thereby preventing HIV transmission. Only one said identifying HIV infection would enable her to protect her husband from HIV.

Of the 21 women who believed testing should not be offered in child health clinics, nine said retesting was unnecessary while three cited the inconvenience of testing. Two women thought testing should rather be done at VCT sites, when women had planned for it, one saying: “this is the place for vaccines, not for testing” and the other “if a mother wants to know her HIV status she should go to VCT".
Discussion

Uptake of testing among women bringing their child for health care in Mombasa, Kenya was comparable to that seen during pregnancy or labour in other settings. As measured by uptake and women’s attitudes, the study suggests provider-initiated HIV testing among women attending child health clinics is acceptable in this setting. This supports current initiatives to implement HIV testing within all clinical services where individuals are likely to benefit from knowing their status. HIV testing during the postpartum period appears to complement antenatal testing. This may be particularly important for women who were not offered HIV testing during pregnancy, but also for those who had previously declined testing and have reconsidered their decision or form better rapport with the health worker who offers testing. In this population, one in four women had not accessed testing during pregnancy. HIV testing in child health clinics reduced the number of women with unknown status to one in twenty.

Though improving coverage and effectiveness of antenatal PMTCT interventions is the overarching priority, postpartum testing and support for safer infant feeding may be an important measure while this occurs. Currently at this hospital, pregnant women are offered HIV testing and counselling, and HIV-infected women are given single-dose (maternal and infant) nevirapine.

Women are particularly vulnerable to HIV acquisition during pregnancy and postpartum. This may be due to biological susceptibility or behavioural risks, such as low levels of condom use as seen in this population. Qualitative data presented here indicates many women are aware of this elevated risk. During acute HIV infection, risk of transmission to breastfeeding children and sexual partners is high. Modelling cost-effectiveness of retesting women late in pregnancy indicates such a strategy may be useful, even in low-level HIV epidemics. However, field experience with this strategy is discouraging. Given the longer time period between antenatal and postpartum testing, retesting of women in the postpartum may identify more incident cases and be more cost-effective than late in pregnancy.
While antiretroviral prophylaxis during pregnancy and around the time of childbirth has been shown to reduce MTCT, trials are evaluating the efficacy of antiretroviral drugs in reducing transmission during breastfeeding. This strategy could enable infants to benefit from breastmilk while minimizing their risk of HIV acquisition. Identifying HIV infection in women during the postpartum would optimise entry to such interventions. Women with HIV infection are particularly vulnerable to complications in the postpartum and it is important to ensure they receive care. Further, encounters with HIV-infected women during the postpartum are an opportunity to link them with family planning services, an important component of PMTCT strategies. Many women in this study previously had an unplanned pregnancy and currently have an unmet need for family planning.

Optimizing patient convenience appears important for increasing acceptability of testing. This was reflected by the proportion choosing same-day resulting, the higher uptake of point-of-care testing and women’s attitudes. Point-of-care testing minimises delays in obtaining results. However, as point-of-care testing was introduced after laboratory-based testing in this study, the increased uptake with point-of-care testing may have been partly due to improvements which occur as services become established. In addition, implications of point-of-care testing for patient flow must be considered. Attention is needed to avoid HIV testing and counselling becoming a bottleneck for patient flow. This would increase waiting times for patients, most of whom attended health services for reasons unrelated to HIV.

This study did not assess perspectives of health workers towards testing. Examining these perspectives is important for a comprehensive assessment of the acceptability of HIV testing at child health clinics. Selection bias may also limit ability to draw conclusions as a third of eligible women declined to participate.

Currently, few resources for maternal health are apportioned to postpartum care. PMTCT programmes mirror these trends. Previously, encounters with women accompanying their children for health visits have been used to deliver
interventions to improve women’s health, such as family planning. Further extending use of these encounters to reach women and offer entry to HIV prevention and treatment services warrants consideration.

Acknowledgements
Postpartum study team: Caroline Njeru, Jacinta Mutegi, Mary Kiambi, Moka Kilonza, Dr Nicole Kley and the study nurses, as well as women who participated in the study. The staff of Coast Provincial General Hospital, especially Dr K. Shikely, Matron V. Kapune and Dr G. Ogweno made a marked contribution to this study. The study was nested within the Uzazi Bora project which is funded by the European Union (grant number KE/AIDCO/2001/460).

Conflict of interest
The authors do not have a conflict of interest to declare.

Authorship statement
The study was conceived and designed by MF Chersich, SMF Luchters and E Yard. Study conduct was overseen by E.Yard, MJ Othigo and K Mandaliya. M Temmerman provided overall supervision of the project, and gave input during all phases of the study. MF Chersich analysed study data and developed the first draft. All authors made substantial contribution to revision of the paper.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Test uptake % (n/N)</th>
<th>Odds ratio* (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal age (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16-20</td>
<td>89.4% (59/66)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>21-24</td>
<td>77.9% (120/154)</td>
<td>0.42 (0.17-1.0)</td>
<td></td>
</tr>
<tr>
<td>25-29</td>
<td>84.0% (158/188)</td>
<td>0.62 (0.26-1.5)</td>
<td></td>
</tr>
<tr>
<td>30-45</td>
<td>85.9% (79/92)</td>
<td>0.72 (0.27-1.9)</td>
<td>0.44#</td>
</tr>
<tr>
<td><strong>Education level</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never attended school</td>
<td>76.5% (13/17)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>82.7% (206/249)</td>
<td>1.5 (0.46-4.8)</td>
<td></td>
</tr>
<tr>
<td>Secondary school</td>
<td>83.8% (160/191)</td>
<td>1.6 (0.48-5.2)</td>
<td></td>
</tr>
<tr>
<td>Tertiary level</td>
<td>86.1% (37/43)</td>
<td>1.9 (0.45-8.0)</td>
<td>0.43#</td>
</tr>
<tr>
<td><strong>Household income (€/month)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-33</td>
<td>92.8% (64/69)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>33-110</td>
<td>82.6% (199/241)</td>
<td>0.37 (0.14-0.98)</td>
<td></td>
</tr>
<tr>
<td>&gt;110</td>
<td>77% (77/100)</td>
<td>0.26 (0.09-0.75)</td>
<td>0.009#</td>
</tr>
<tr>
<td><strong>Attended antenatal care at least once</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>83.1% (399/480)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>85.0% (17/20)</td>
<td>1.2 (0.33-4.0)</td>
<td>0.82~</td>
</tr>
<tr>
<td><strong>Birth attended by a skilled health professional</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>84.6% (329/389)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>78.4% (87/111)</td>
<td>0.67 (0.39-1.1)</td>
<td>0.12~</td>
</tr>
<tr>
<td><strong>Reason for attending child health clinic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunization and well child care</td>
<td>81.8% (333/407)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Acute paediatric care</td>
<td>80.5% (62/77)</td>
<td>0.92 (0.49-1.7)</td>
<td>0.79~</td>
</tr>
<tr>
<td><strong>Length of time postpartum</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early postpartum</td>
<td>88.6% (116/131)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Late postpartum</td>
<td>81.3% (300/369)</td>
<td>0.56 (0.31-1.0)</td>
<td>0.057~</td>
</tr>
<tr>
<td><strong>Postpartum abstinence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>90.0% (108/120)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>81.1% (308/380)</td>
<td>0.48 (0.25-0.91)</td>
<td>0.02~</td>
</tr>
<tr>
<td><strong>Identified ≥8 correct statements about HIV</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>84.9% (124/146)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>82.5% (292/354)</td>
<td>0.84 (0.49-1.4)</td>
<td>0.51~</td>
</tr>
<tr>
<td><strong>Knows HIV can be transmitted from mother to child</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>84.0% (399/475)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>68.7% (11/16)</td>
<td>0.42 (0.14-1.2)</td>
<td>0.11~</td>
</tr>
<tr>
<td><strong>Identified ≥5 correct statements about MTCT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>84.9% (180/212)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>81.9% (238/288)</td>
<td>0.81 (0.50-1.3)</td>
<td>0.38~</td>
</tr>
<tr>
<td><strong>Testing strategy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Point-of-care testing</td>
<td>84.9% (382/450)</td>
<td>2.6 (1.4-5.1)</td>
<td>0.003~</td>
</tr>
<tr>
<td>Laboratory-based testing</td>
<td>68.0% (34/50)</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

*Odds of test uptake= no. receiving results/no. not receiving results; Exchange rate of 1€= 90 Kenya Shillings; ~ Mantel-Haenszel odds ratio, # chi-square test for trend; CI confidence interval
References


3.4 Effects of HIV on disease patterns and health needs in the first year after childbirth

Article 7: Morbidity in the first year postpartum among HIV-infected women in Kenya
Morbidity in the first year postpartum among HIV-infected women in Kenya

M.F. Chersich a,b,⁎, S.M. Luchters a,b, E. Yard a, J.M. Othigo c, N. Kley d, M. Temmerman a,b

a International Center for Reproductive Health, Mombasa, Kenya
b Department of Obstetrics and Gynecology, Ghent University, Belgium
c Coast Provincial General Hospital, Mombasa, Kenya
d Department of Obstetrics and Gynecology, Klinikum Fuert, Germany

Received 24 May 2007; received in revised form 11 June 2007; accepted 15 June 2007

Abstract

Objective: To assess the effects of HIV infection on morbidity and the needs of infected women for services in the first year postpartum. Methods: A cross-sectional study with 500 women attending a child-health clinic in Mombasa, Kenya. Results: Postpartum duration was a median of 3.3 months (interquartile range, 1.9–6.1 months). The 54 HIV-infected women had a lower income and less financial support than the uninfected women, and they were more likely to experience fever, dyspnea, and dysuria, and to have genital warts (odds ratio [OR], 9.6; 95% confidence interval [CI], 2.6–35.6; P<0.001), candidiasis (OR, 2.9; 95% CI, 1.2–6.8; P=0.012), and bacterial vaginosis (OR, 1.8; 95% CI, 0.95–3.3; P=0.066). Six (nearly 15%) of the HIV-infected women had low- or high-grade squamous intraepithelial lesions, and 21 (42%) had an unmet need for contraception. More than half of all women were anemic, and normocytic anemia was predominant among the HIV-infected. Conclusion: Compared with uninfected women, morbidity was increased for HIV-infected women during the year following delivery. This period could be used to offer these, and all-women, family planning services, cervical cancer screening, and treatment for anemia and reproductive tract infections.

© 2007 International Federation of Gynecology and Obstetrics. Published by Elsevier Ireland Ltd.

KEYWORDS
HIV-infected women; Kenya; Maternal morbidity; Postpartum

1. Introduction

In recent years, attention has been focused on the provision of adequate antenatal services [1,2] and on the training of birth attendants to effectively manage intrapartum complications [3]. In contrast, what postpartum services should...
consist of has not been determined and few resources are allocated to such services.

Yet, in areas heavily affected by HIV infection, the postpartum could be an opportune period for linking women with services and for providing safer infant feeding [4,5]. Women are particularly vulnerable to HIV acquisition during pregnancy and the postpartum, maybe because of a biologic susceptibility [6] or because of behavioral risks, such as low condom use during pregnancy and the postpartum. An active follow-up beyond the traditional 6-week postpartum period would improve the access of HIV-infected women and their children to medical care and antiretroviral treatment (ART). Infectious postpartum complications may be more common among women infected with HIV [7]. Moreover, malaria, anemia, and HIV coexist in many parts of sub-Saharan Africa. Each of these diseases exacerbates the effects of the other diseases and childbearing affects them all [8].

Several reports indicate that postpartum counseling for contraception and family planning is not integrated within programs for the prevention of mother-to-child transmission (PMTCT), and that many women have an unmet need for contraception following delivery [9,10]. Although HIV infection is associated with a reduction in fertility [11,12], women with HIV may be at higher risk for pregnancy in the postpartum period if they choose to stop breastfeeding early or not to breastfeed at all, thereby shortening the duration of lactational amenorrhea.

Like other obstetric services, PMTCT programs have largely focused on providing interventions during pregnancy and childbirth, with insufficient attention given to long-term follow-up and care of the woman and child. The present study assessed the effects of HIV infection on disease patterns in the postpartum period. Identifying the needs of HIV-infected women in the year following childbirth would inform the selection of interventions aimed at securing their sexual and reproductive health during this period.

2. Materials and methods

From March to August 2006, 500 women attending an immunization and acute care pediatric clinic at a provincial hospital in Mombasa, Coast Province, Kenya, participated in a cross-sectional study carried out to determine the health status and needs of women during the postpartum. The study was part of the Better Parenthood Project (http://icrh.dotnet39.hostbasket.com/kenya/projectdetails.aspx?id=126). This program initially focused on improving antenatal and childbirth services in 2 districts of Coast Province, but in the later stages aimed to strengthen postpartum care. Study activities were approved by the Kenyatta National Hospital Ethics and Research Committee and all participants gave written informed consent.

2.1. Participants and tests

The participants were older than 16 years and had given birth to the child seen at the clinic 4 weeks to 1 year previously. They were invited to participate after their child's health visit was completed. Information was gathered on demographic characteristics, access to sexual and reproductive health services, family planning needs, and sexual health using a pretested structured questionnaire administered in Swahili. To determine the participants' psychosocial status, it was determined whether they engaged in substance abuse, experienced postpartum depression, or were subjected to domestic violence. The World Health Organization (WHO) Alcohol Use Disorders Identification Test (AUDIT) identified women with hazardous or harmful patterns of alcohol consumption, and the ICD-10 Depression Inventory was used to screen for mild and major depression.

All participants received a breast and gynecologic examination from study nurses blinded to their HIV status. Blood, urine, and endocervical smear samples were collected. Serum hemoglobin concentration was measured with a Coulter Counter Act B (Coulter International Corp., Miami, Florida, USA). A concentration less than 11 g/L in conjunction with a mean corpuscular volume (MCV) less than 81 fL was considered diagnostic of microcytic anemia. Normocytic anemia was diagnosed when hemoglobin concentration was less than 11 g/L and MCV was 81 fL or greater [13]. Finger prick blood samples were obtained for microscopic diagnosis of malaria. A rapid plasma reagin test (Human GmbH, Wiesbaden, Germany) was used for syphilis detection. Using a serial rapid test algorithm, Determine HIV 1/2 test (Abbott Japan Co. Ltd, Tokyo, Japan) was used to detect antibodies to HIV, and the results were confirmed by Uni-Gold HIV; Trinity Biotech PLC, Bray, Ireland. Nitrites and leucocytes were detected using a urine dipstick (Human GmbH). Infection with Trichomonas vaginalis and Candida sp. was determined using a wet mount, and the Nugent criteria were used for diagnosing bacterial vaginosis. Participants were advised to return for test results and, if required, received treatment according to local guidelines. For conditions such as syphilis or malaria, the women with positive results were contacted and asked to return immediately. All participants were offered same-day HIV testing and counseling. Those identified as HIV positive were taken to an on-site clinic and entered into long-term HIV care services, which include ART.

2.2. Sample size and data analysis

A sample size of 500 women was chosen for population estimates to be sufficiently precise to inform local policy decisions. Because it was estimated that most of the diseases concerning the study would be found in 10% of the population sample, with 500 participants it was possible to infer with 95% certainty that the true level in the population was between 7.4% and 12.6%. The investigators considered this interval sufficiently narrow to inform policy.

Data collected during interviews and from laboratory studies were double entered by separate data entry clerks. The software Intercooled Stata 8.0 (StataCorp LP, College Station, Texas, USA) was used for statistical analysis. Sexually active women not using contraceptive methods were defined as having an unmet need for contraception. Lactational amenorrhea, defined as exclusive breastfeeding with amenorrhea, was classified as a contraceptive method. Statistical tests determined whether HIV was associated with psychosocial characteristics, access to services, indicators of postpartum health, and other variables. Binary variables were analyzed by the uncorrected $\chi^2$ test and Mantel–Haenszel odds ratios were calculated. For continuous variables, normal and non-normal distributions were compared by the unpaired $t$ test and the Wilcoxon rank-sum test, respectively. All tests were 2-tailed.

3. Results

Of 776 eligible women, 500 (64.4%) agreed to participate. Reasons given for declining participation included lack of time (n=120), need for partner approval before participation (n=54), and having a child requiring added care (n=48).

The mean ±SD age of the participants was 25.5 ±4.5 years (Table 1). Most participants (395 of 484 [81.6%] giving a usable response) had attended well-child services such as immunization services. Most were married or in a cohabiting relationship and only one half had received secondary or higher education. Of 496 participants with results, 54 were HIV infected, for a prevalence of 10.9%. The median time since delivery was 3.3 months (interquartile range [IQR], 1.9–6.1 months), with no difference between HIV-infected (median, 3.4 months; IQR, 1.9–6.4 months) and uninfected women (median 3.2 months, IQR, 1.9–6.1 months) (P=0.77).

Of the 54 HIV-infected women, 5 (9.3%) reported breastfeeding exclusively and 9 (16.7%) used replacement feeding, but mixed feeding predominated. Even among the 36 women whose HIV infection was determined during pregnancy, 24 (66.7%) were using mixed feeding (data not shown). The newborns of 214 (48.4%) of 442 uninfected participants and of 23 (42.6%) of the 54 HIV-infected participants were introduced to food and liquid supplements in the 2 weeks following their birth (P=0.42).

3.1. Underlying psychosocial vulnerability

Compared with the women without HIV infection, the HIV-infected women had a lower income, 29.6% of them earning less than $41 per month. They were also less likely to have received or be receiving financial support from the child’s father (45 of 54 [83.3%] vs 411 of 439 [93.6%]; P=0.007).

### Table 1

Demographic and psychosocial characteristics of 500 women in the postpartum period attending a child-health clinic in Kenya

<table>
<thead>
<tr>
<th>Variable</th>
<th>All women</th>
<th>HIV-negative women</th>
<th>HIV-positive women</th>
<th>P value[^b^]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, year</td>
<td>25.5 (4.5)</td>
<td>25.5 (4.4)</td>
<td>26.3 (5.1)</td>
<td>0.22[^c^]</td>
</tr>
<tr>
<td>Religion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Christian</td>
<td>425/499 (85.2)</td>
<td>379/441 (85.9)</td>
<td>43/54 (79.6)</td>
<td>0.32</td>
</tr>
<tr>
<td>Muslim</td>
<td>71/499 (14.2)</td>
<td>59/441 (13.4)</td>
<td>11/54 (20.4)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3/499 (0.6)</td>
<td>3/441 (0.7)</td>
<td>0/54</td>
<td></td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>17/500 (3.4)</td>
<td>16/442 (3.6)</td>
<td>0/54</td>
<td>0.15</td>
</tr>
<tr>
<td>Primary</td>
<td>249/500 (49.8)</td>
<td>213/442 (48.2)</td>
<td>34/54 (63.0)</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>191/500 (38.2)</td>
<td>174/442 (39.4)</td>
<td>16/54 (29.6)</td>
<td></td>
</tr>
<tr>
<td>Higher</td>
<td>43/500 (8.6)</td>
<td>39/442 (8.8)</td>
<td>4/54 (7.4)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never married</td>
<td>58/500 (11.6)</td>
<td>51/442 (11.5)</td>
<td>6/54 (1.1)</td>
<td>0.21</td>
</tr>
<tr>
<td>Married/cohabitating</td>
<td>431/500 (86.2)</td>
<td>383/442 (86.7)</td>
<td>45/54 (83.3)</td>
<td></td>
</tr>
<tr>
<td>Separated/divorced/widowed</td>
<td>11/500 (2.2)</td>
<td>8/442 (1.8)</td>
<td>3/54 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Source of drinking water</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piped water in house</td>
<td>77/500 (15.4)</td>
<td>71/441 (16.1)</td>
<td>4/54 (7.4)</td>
<td>0.086</td>
</tr>
<tr>
<td>Public tap</td>
<td>398/500 (79.8)</td>
<td>351/442 (79.6)</td>
<td>45/54 (83.3)</td>
<td></td>
</tr>
<tr>
<td>Well/borehole/surface water</td>
<td>24/500 (4.8)</td>
<td>19/441 (4.3)</td>
<td>5/54 (9.3)</td>
<td></td>
</tr>
<tr>
<td>Household income, $/mo[^d^]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 41</td>
<td>9/500 (13.8)</td>
<td>5/442 (12.0)</td>
<td>4/54 (29.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>41–135</td>
<td>241/500 (48.2)</td>
<td>218/442 (49.3)</td>
<td>21/54 (38.8)</td>
<td></td>
</tr>
<tr>
<td>&gt; 135</td>
<td>100/500 (20.0)</td>
<td>93/442 (21.0)</td>
<td>7/54 (13.0)</td>
<td></td>
</tr>
<tr>
<td>Does not know</td>
<td>90/500 (18.0)</td>
<td>78/442 (17.7)</td>
<td>10/54 (18.5)</td>
<td></td>
</tr>
<tr>
<td>Received financial support from husband/partner since childbirth</td>
<td>460/497 (92.6)</td>
<td>411/439 (93.6)</td>
<td>45/54 (83.3)</td>
<td>0.007</td>
</tr>
<tr>
<td>Ever pushed/hit by intimate partner</td>
<td>95/499 (19.0)</td>
<td>83/442 (18.8)</td>
<td>10/54 (18.5)</td>
<td>0.96</td>
</tr>
<tr>
<td>Ever physically forced to have sex</td>
<td>40/494 (8.1)</td>
<td>35/437 (8.0)</td>
<td>5/53 (9.4)</td>
<td>0.72</td>
</tr>
<tr>
<td>Drank alcohol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>148/477 (31.0)</td>
<td>123/424 (29.0)</td>
<td>24/49 (49.0)</td>
<td>0.004</td>
</tr>
<tr>
<td>Hazardous or harmful use</td>
<td>11/477 (2.3)</td>
<td>10/424 (2.4)</td>
<td>1/49 (2.0)</td>
<td>0.89</td>
</tr>
<tr>
<td>While pregnant/breastfeeding</td>
<td>38/477 (8.0)</td>
<td>30/424 (7.1)</td>
<td>7/49 (14.3)</td>
<td>0.075</td>
</tr>
<tr>
<td>Minor depression</td>
<td>18/499 (3.6)</td>
<td>13/441 (3.0)</td>
<td>5/54 (9)</td>
<td>0.019</td>
</tr>
<tr>
<td>Major depression</td>
<td>8/499 (1.6)</td>
<td>6/441 (1.4)</td>
<td>2/54 (4)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

[^a^] Values are given as number/number of usable responses (percentage) unless otherwise indicated. The HIV status of 4 women was unknown.

[^b^] By the χ² test unless otherwise indicated.

[^c^] By the t test.

[^d^] The exchange rate was 1 US dollar for 74 Kenyan shillings.
Rates of sexual and physical violence were high for all women and did not vary with HIV status. Women with HIV infection were 2.3 times more likely to have consumed alcohol in their lives than uninfected women (95% confidence interval [CI], 1.3–4.3; \(P = 0.004\)). Based on total AUDIT scores, few women had hazardous or harmful drinking patterns, although about 15% of those in the HIV-infected group had drunk alcohol after becoming aware that they were pregnant or even though they were breastfeeding. Women with HIV infection were 3.4 times more likely to experience mild depression than those without infection (95% CI, 1.1–9.9; \(P = 0.02\)).

### 3.2. Access to sexual and reproductive health services

Although 480 (96.0%) of the 500 participants attended the antenatal clinic at least once, the first consultation was later in pregnancy for those with HIV infection (Table 2). Other differences in health-seeking behavior were noted. Infected women were 2.1 times less likely to be delivered by a skilled birth attendant (95% CI, 1.1–3.8; \(P = 0.015\)).

<table>
<thead>
<tr>
<th>Variable</th>
<th>HIV-negative women</th>
<th>HIV-positive women</th>
<th>(P) value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimester first attended antenatal clinic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>40/424 (9.4)</td>
<td>2/52 (3.8)</td>
<td>0.05</td>
</tr>
<tr>
<td>Second</td>
<td>211/424 (49.8)</td>
<td>20/52 (38.5)</td>
<td></td>
</tr>
<tr>
<td>Third</td>
<td>173/424 (40.8)</td>
<td>30/52 (57.7)</td>
<td></td>
</tr>
<tr>
<td>Childbirth with skilled birth attendant</td>
<td>351/442 (79.4)</td>
<td>35/54 (64.8)</td>
<td>0.015</td>
</tr>
<tr>
<td>Received family planning information since childbirth</td>
<td>286/441 (64.9)</td>
<td>26/54 (48.1)</td>
<td>0.016</td>
</tr>
<tr>
<td>Ever had cervical screening</td>
<td>26/432 (6.0)</td>
<td>1/51 (2.0)</td>
<td>0.23</td>
</tr>
<tr>
<td>Gravity median (IQR) (n=490)</td>
<td>2 (10–3)</td>
<td>3 (10–4)</td>
<td>0.034*</td>
</tr>
<tr>
<td>Mode of delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>383/435 (88.1)</td>
<td>47/54 (87.0)</td>
<td>0.83</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>52/435 (12.0)</td>
<td>7/54 (13.0)</td>
<td></td>
</tr>
<tr>
<td>Birth weight median (IQR), kg (n=414)</td>
<td>3.3 (3.0–3.6)</td>
<td>3.0 (2.7–3.5)</td>
<td>0.037*</td>
</tr>
<tr>
<td>Planning of most recent pregnancy</td>
<td>207/442 (46.8)</td>
<td>23/54 (42.6)</td>
<td></td>
</tr>
<tr>
<td>Planned</td>
<td>235/442 (53.2)</td>
<td>31/54 (57.4)</td>
<td>0.56</td>
</tr>
<tr>
<td>Unintended</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fertility plans</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wants more children within 2 years</td>
<td>13/441 (3.0)</td>
<td>0/54</td>
<td>0.002</td>
</tr>
<tr>
<td>Wants more child after 2 years</td>
<td>245/441 (55.6)</td>
<td>19/54 (35.2)</td>
<td></td>
</tr>
<tr>
<td>Wants no more children</td>
<td>161/441 (36.5)</td>
<td>34/54 (63.0)</td>
<td></td>
</tr>
<tr>
<td>Unsure</td>
<td>22/441 (5.0)</td>
<td>1/54 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Current contraception</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unmet need</td>
<td>164/421 (39.0)</td>
<td>21/50 (42.0)</td>
<td>0.59</td>
</tr>
<tr>
<td>Modern or traditional</td>
<td>148/421 (35.2)</td>
<td>14/50 (28.0)</td>
<td></td>
</tr>
<tr>
<td>Postpartum abstinence</td>
<td>109/421 (25.9)</td>
<td>15/50 (30.0)</td>
<td></td>
</tr>
<tr>
<td>Condom use since childbirth among sexually active women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every time or almost</td>
<td>15/310 (4.8)</td>
<td>6/36 (16.7)</td>
<td>0.011</td>
</tr>
<tr>
<td>Sometimes</td>
<td>22/310 (7.1)</td>
<td>4/36 (11.1)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>273/310 (88.1)</td>
<td>26/36 (72.2)</td>
<td></td>
</tr>
<tr>
<td>Condom use at last sexual intercourse</td>
<td>26/435 (6.0)</td>
<td>9/54 (16.7)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Abbreviation: IQR, interquartile range.

* Values are given as number/number of usable responses (percentage) unless otherwise indicated. The HIV status of 4 women was unknown.

* By the \(\chi^2\) test unless otherwise indicated.

* By the Wilcoxon rank-sum test.


4 M.F. Chersich et al.
3.4. Postpartum morbidity

A substantial proportion of HIV-infected women reported symptoms of fever, dyspnea, and dysuria, and complaints were less common in the uninfected group (Table 3). Compared with uninfected women, HIV-infected women had a lower body mass index (calculated as weight in kilograms divided by the square of height in meters), but only 7 of 53 were underweight, with an index less than 18.5. More than half the study population was anemic, although patterns varied with HIV status. Infected women were more likely to have normocytic than microcytic anemia. Few women had malaria parasitemia, which was consistent with the reported levels of bed net use as about two-thirds of the participants (339 of 497 [68.2%]) reported sleeping under a net the previous night.

Painful, swollen, hot or red breasts was reported by 5.1% of HIV-uninfected and 11.5% of HIV-infected women ($P = 0.06$). Many participants (141 of 447) had bacterial vaginosis, for a prevalence of 31.5%, but syphilis was rare and on examination few women had genital ulcers. Compared with uninfected participants, those with HIV had similar odds of having trichomoniasis (OR, 1.13; 95% CI, 0.38–3.3; $P = 0.83$) but were more likely to have candidiasis (OR, 2.9; 95% CI, 1.2–6.8; $P = 0.012$), bacterial vaginosis (OR, 1.8; 95% CI, 0.95–3.3; $P = 0.066$), and genital warts (OR, 9.6; 95% CI, 2.6–35.6; $P < 0.001$). Cervical smears identified a high prevalence of low-grade (3 of 41 [7%]) and high-grade (3 of 41 [7%]).

Table 3 Postpartum morbidity: current symptoms, examination and laboratory investigations in 500 women in the postpartum period attending a child-health clinic in Kenya*

<table>
<thead>
<tr>
<th>Variable</th>
<th>HIV-negative women</th>
<th>HIV-positive women</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile symptoms</td>
<td>39/432 (9.0)</td>
<td>11/52 (21.2)</td>
<td>0.007</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>19/431 (4.4)</td>
<td>6/52 (11.5)</td>
<td>0.028</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>83/432 (19.3)</td>
<td>14/52 (26.9)</td>
<td>0.19</td>
</tr>
<tr>
<td>BMI, median (IQR)</td>
<td>23.2 (21.3–26.0)</td>
<td>21.3 (20.0–25.2)</td>
<td>0.013</td>
</tr>
<tr>
<td>Hemoglobin level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>205/433 (47.1)</td>
<td>18/53 (34.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Normocytic anemia</td>
<td>76/433 (17.5)</td>
<td>20/53 (37.7)</td>
<td></td>
</tr>
<tr>
<td>Microcytic anemia</td>
<td>152/433 (35.4)</td>
<td>15/53 (28.3)</td>
<td></td>
</tr>
<tr>
<td>Malaria</td>
<td>10/435 (2.3)</td>
<td>1/53 (1.9)</td>
<td>0.85</td>
</tr>
<tr>
<td>Painful, swollen, hot or red breasts symptoms</td>
<td>22/432 (5.1)</td>
<td>6/52 (11.5)</td>
<td>0.06</td>
</tr>
<tr>
<td>Nipple sores or bloody discharge symptoms</td>
<td>10/432 (2.3)</td>
<td>2/52 (3.8)</td>
<td>0.50</td>
</tr>
<tr>
<td>Breast examination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal breasts</td>
<td>396/413 (5.9)</td>
<td>41/44 (93.2)</td>
<td></td>
</tr>
<tr>
<td>Mastitis or abscess</td>
<td>6/413 (1.5)</td>
<td>2/44 (4.5)</td>
<td>0.49</td>
</tr>
<tr>
<td>Cracked nipples</td>
<td>9/413 (2.2)</td>
<td>1/44 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Lump</td>
<td>2/413 (0.5)</td>
<td>0/44</td>
<td></td>
</tr>
<tr>
<td>Pain or burning on micturition</td>
<td>39/432 (9.0)</td>
<td>9/52 (17.3)</td>
<td>0.059</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>4/432 (0.9)</td>
<td>2/52 (3.8)</td>
<td>0.072</td>
</tr>
<tr>
<td>Dipstick reading of urine leukocytes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>273/404 (67.6)</td>
<td>23/40 (57.5)</td>
<td>0.16</td>
</tr>
<tr>
<td>1+</td>
<td>75/404 (18.6)</td>
<td>7/40 (17.5)</td>
<td></td>
</tr>
<tr>
<td>2+ or 3+</td>
<td>56/404 (13.9)</td>
<td>10/40 (25.0)</td>
<td></td>
</tr>
<tr>
<td>Presence of urine nitrates</td>
<td>18/418 (4.3)</td>
<td>0/44</td>
<td>0.16</td>
</tr>
<tr>
<td>Foul-smelling vaginal discharge</td>
<td>56/432 (13.0)</td>
<td>8/52 (15.4)</td>
<td>0.63</td>
</tr>
<tr>
<td>Bacterial vaginosis</td>
<td>121/401 (30.2)</td>
<td>20/46 (43.5)</td>
<td>0.066</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>27/406 (6.7)</td>
<td>44/47 (8.5)</td>
<td>0.072</td>
</tr>
<tr>
<td>Trichomoniasis</td>
<td>31/406 (7.6)</td>
<td>44/47 (98.5)</td>
<td>0.83</td>
</tr>
<tr>
<td>Genital ulcer</td>
<td>5/400 (1.3)</td>
<td>2/46 (4.3)</td>
<td>0.11</td>
</tr>
<tr>
<td>Syphilis</td>
<td>5/441 (1.1)</td>
<td>0/53</td>
<td>0.44</td>
</tr>
<tr>
<td>Genital warts</td>
<td>5/400 (1.3)</td>
<td>5/46 (10.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cervical cytologic result</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>318/353 (90.1)</td>
<td>35/41 (85.4)</td>
<td>0.019</td>
</tr>
<tr>
<td>ASCUS</td>
<td>18/353 (5.1)</td>
<td>0/41</td>
<td></td>
</tr>
<tr>
<td>Low-grade SIL</td>
<td>12/353 (3.4)</td>
<td>3/41 (7.3)</td>
<td></td>
</tr>
<tr>
<td>High-grade SIL</td>
<td>5/353 (1.4)</td>
<td>3/41 (7.3)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); IQR, interquartile range; MTCT, mother-to-child transmission; ASCUS, atypical squamous cells of undetermined significance; SIL, squamous intraepithelial lesion.

* Values are given as number/number of usable responses (percentage) unless otherwise indicated. The HIV status of 4 women was unknown.

** By the $\chi^2$ test unless otherwise indicated.

*** By the Wilcoxon rank-sum test.

** There were 42 unusable cervical smear slides.
Reproductive and sexual morbidity was highly prevalent among both HIV-infected and uninfected participants in the year following childbirth, and all required access to comprehensive postpartum services. The prevalence of anemia was particularly high and there was substantial unmet need for contraception. Many of the women had experienced domestic violence, an important determinant of poor health and well-being.

However, the HIV-infected women had poorer health-seeking behaviors than the uninfected women; disease patterns also differed among the 2 groups; and infected women had a greater burden of disease. A lower household income and the likelihood of less financial support from their husbands or partners may have further increased their vulnerability.

Family planning and adequate birth spacing confer many benefits to women and their children. The WHO recommends that women wait at least 2 to 3 years between pregnancies [14]. Although preventing unintended pregnancies among HIV-infected women is a key component of global PMTCT [14], more than half of the recent pregnancies among this group in this study were unplanned. This finding is consistent with other reports [15]. Prevention in the periconception period remains a challenge whenever women breastfeed, for whatever reason. The lower household income and lesser financial support from husbands/partners in the HIV-infected group in this study reinforce the evidence of the need for additional support for women to safely carry out their infant-feeding choice.

While factors such as cesarean delivery rate [22] and HIV prevalence [23] were similar for the study population and the East African region, it is difficult to generalize the study's findings to rural areas, or lower levels of the health system like primary health facilities. In addition, women who do not attend child-health clinics or whose child has died are likely to be different from the study population.

In conclusion, a substantial proportion of HIV-infected women bringing their children for health services have unmet reproductive health needs, and these women require sexual and reproductive health services. They also need to be entered into an HIV prevention and/or treatment program. Infected women who received no treatment prior to delivery require continued HIV-related care and support in the postpartum period, as well as regular clinical and immunologic assessment to evaluate their eligibility for ART. Their socio-economic status also makes them more vulnerable and makes their access to services more difficult. Approaching women in child-health clinics facilitates their entry to services such as family planning and other forms of counseling; offers them cervical cytologic evaluation as well as detection and treatment of reproductive tract infections; and provides them with condom and iron supplements. Additional needs identified for HIV-infected women are infant-feeding counseling and support, breast care, and screening for alcohol use and depression. High-quality postpartum care, tailored to the women's needs, could form a bridge between PMTCT, pregnancy, and childbirth services—on the one hand—and family planning and other sexual and reproductive health services—on the other hand—thus ensuring continuity of care and entry into services that improve a woman's health and well-being.

Acknowledgements

This study was funded by European Union grant KE/AIDCO/2001/460 as part of the Uzazi Bora project.
References


Chapter 4. Discussion and conclusions

4.1. Summary of key findings

The studies presented here investigated ways of improving the coverage and effectiveness of PMTCT services, aiming to directly benefit women and their children. In particular, the studies assessed the role of interventions shortly after childbirth and in the first year postpartum. The results of this research has been summarized and placed in the context of other available evidence in two review articles (Annex 2 and 3).

The continued burden of HIV infection in children, due to poor coverage of PMTCT programmes and suboptimal quality of current interventions, strongly suggests there is a need to review existing strategies and to consider alternative options. Moreover, levels of maternal morbidity and mortality among HIV-infected women show that current PMTCT programmes are not adequately addressing their needs. In both Kenya and South Africa, maternal and child health services need to take additional steps to achieve their ultimate aim, a healthy mother and healthy child. This is the timeless mission statement of obstetrics. To assist in realising this mission, PMTCT programmes need to be designed and implemented based on these interlinked goals and to be integrated within antenatal, childbirth and child health services. In particular, there may be much benefit to situating PMTCT programmes within broader efforts to improve women’s health and wellbeing. Increased resources available for HIV services can, with carefully planning, strengthen the provision of sexual and reproductive health services and help to raise the capacity of the entire health system. Collaboration between services for HIV and those for sexual and reproductive health is necessary for a range of health system reasons. People may use different “entry points” or specific types of services, but they should be offered a full range of sexual and reproductive health, and HIV services to meet their needs. PMTCT programmes that are configured only to benefit the infant overlook the needs of the woman and risk treating her as a disease vector or instrumentalising a woman as a conduit for healthy babies.

Patterns of antenatal coverage and facility birth markedly limit effectiveness of PMTCT programmes. The effects of these patterns are most pronounced in Kenya. Though most women attend ANC at least once, only half return for a second visit in the rural district next to Mombasa (Kwale district), and only two thirds in Mombasa. With prophylaxis...
initiation at second ANC visits and infant NVP only given with facility birth then a maximum of about 40% and 20% of pregnant women in Mombasa and Kwale would benefit from PMTCT services respectively [82]. This clearly demonstrates that additional consideration is needed of the effects of current health seeking patterns when planning PMTCT service delivery. This finding also alludes to the importance of making optimal use of each patient-provider encounter during pregnancy, childbirth and in the postpartum period. For example, it may be necessary to dispense the full course of ARV prophylaxis for women and infants at the first ANC visit, regardless of gestation.

4.1.1 Securing maternal health is essential for improving child survival

Antenatal, childbirth and child health services provide a vital opportunity to reach women and provide them with HIV-related services: primary prevention for women not infected with HIV, and for women with HIV, treatment, care, and support as well as interventions to prevent MTCT. ARV treatment improves overall maternal survival and provides a highly effective PMTCT intervention for women with the highest risk of transmission. PMTCT programmes that focus only on a woman’s biological role in transmitting HIV to their infants may fail to attract many participants and will reinforce the widely-held perception that the primary objective of identifying HIV infection in pregnant women is to prevent transmission to infants rather than to benefit women. PMTCT programmes, by identifying women with HIV, have a clear ethical obligation to provide the full range of HIV services or to have explicit mechanisms of referral for such services. It is possible that women and children may be better served by centring interventions on the health of HIV-infected women, rather than their children. Addressing pregnant women’s health and wellbeing may thus be the optimum entry point to effectively preventing HIV in infants. Currently, this subset of women has disproportionately low access to ARV treatment in most settings, and additional effort and resources are required to operationalize links between PMTCT and ARV treatment towards the goal of achieving universal access to treatment for pregnant women living with HIV.

Prioritization of women within PMTCT is acknowledged in recent WHO guidelines, which stratify HIV-infected pregnant women into those requiring ARV treatment and those not. This adds two additional steps (a maternal CD4 cell count and a decision about ARV treatment eligibility) which are critical for ensuring that benefits of PMTCT programmes accrue to both women and infants. It will be important to achieve an optimal balance.
between expanding coverage of basic PMTCT services while also increasing the complexity of existing PMTCT programmes, which is necessary for improving their effectiveness. Issues of equity are also central to reaching this balance, so that services are designed to maximise access for those who need the services most. Given wide variation in resource constraints (human, structural and financial), the optimal balance between increasing coverage and service complexity may be setting specific. For the most part, health services in the eastern and southern Africa have marked systematic weaknesses, hampering the ability to provide high-quality services on a widespread scale. Quite possibly, the addition of two additional steps to an already poorly-functioning cascade of PMTCT interventions will further complicate these programmes. More so, this addition does create a chance to re-define the focus of PMTCT services, maximising opportunities for improving women’s health during encounters at antenatal, childbirth and child health clinics. This paradigm shift may encourage more women to access full HIV services and retain those diagnosed within treatment systems; allowing health workers to secure this highly vulnerable group within care and support structures.

Strong leadership and additional resources are needed to ensure this opportunity to re-define PMTCT is taken, rather than further overwhelming already failing services. In particular, attention is needed to optimise service delivery methods and to ensure woman-centred care and support, taking into account the social context in which they live. Optimising the effectiveness and safety of ARV drug regimens is also an important consideration in the provision of ARV treatment for women. Much of the debate in this regard concerns the use of efaviranz (EFV) in women who may become pregnant. Some of these considerations are discussed here, but article 11 and 12 provide a more comprehensive discussion of this topic (Annex 4 and 5).

EFV is widely considered a preferred drug for first-line ARV treatment regimens in many countries, as it is less hepatotoxic than NVP and has fewer drug interactions [120-122]. However, for women of reproductive potential these advantages need to be balanced with concerns that EFV increases risk for birth defects. Concerns about EFV-induced fetal effects arose following a trial with monkeys which showed increased risk for central nervous system defects after monkey fetal exposure to EFV [123]. However, the predictive value of animal studies for humans is unknown and there are limited human data available on the risks of EFV exposure during pregnancy. In fact, available human data indicates that the risk for birth defects is likely to be low [124]. Similarly, available
data indicates that in utero exposure to AZT does not increase risk for birth defects [10, 125, 126]. Findings of animal studies also raise concerns about fetal exposure to zalcitabine (ddC), while a report from a prospective ARV pregnancy registry suggest didanosine (ddI) may be a human teratogen [124].

Complex clinical situations may occur when women become pregnant while receiving ARV treatment regimens that contain drugs which are thought to cause fetal harm. A woman may consider temporarily suspending ARV treatment, changing their regimen or terminating an otherwise wanted pregnancy. These options need to be weighed carefully by the woman who requires adequate information and counselling. Full discussion of this and related scenarios is contained in articles 11 and 12.

4.1.2 Interventions in childbirth and child health clinics can complement antenatal PMTCT services

There is a need for tailoring PMTCT services to women, addressing their needs and streamlined with their actual attendance at these services. Increasing the focus on skilled birth attendants, and rationalising ANC and postpartum visits was important for optimising the delivery of essential obstetric services, and for tackling obstetric causes of maternal ill-health [127, 128]. However, during pregnancy and after childbirth, HIV-infected women currently fall between both maternal health and ARV treatment programmes. Above mentioned changes in delivery of maternal health services worsen this fit. The decreased number of ANC visits and poorly-functioning postpartum services limit encounters with HIV-infected women and opportunities to address their chronic needs. Pregnancy is transitory. Midwives and antenatal staff have little experience with chronic care. Maternal health structures are therefore poorly suited to the chronic care needs of HIV-infected pregnant women and their children.

Although PMTCT programmes must continue to increase accessibility, acceptability, and uptake of HIV testing during pregnancy, many women currently deliver without accessing HIV testing and could benefit from testing at this time. This may be as women have not accessed ANC services, or as testing services are unavailable, of poor quality, or because they declined the offer of HIV testing. HIV testing in childbirth and child health services may be an important measure while coverage of HIV testing and quality of counselling in antenatal clinics is being improved. Women who previously declined testing may accept a subsequent offer, as they have reconsidered their previous decision or form better rapport with the counsellor who offers testing. HIV testing and
counselling during labour or shortly thereafter, followed by ARV prophylaxis for the infant and infant feeding counselling has been shown to be feasible and effective in reducing MTCT, as discussed in article 3 and elsewhere [129-131]. Around the same time as the study reported in article 3 was being conducted; a randomized trial in Malawi assessed the effectiveness of dual ARV infant-only prophylaxis. This trial showed that a dual regimen (single-dose NVP and AZT) was more effective than single-dose NVP alone for HIV-exposed infants whose mother had not received ARV drugs [132]. It is possible that triple-ARV regimens are even more effective in reducing MTCT around childbirth, but evidence of this is not available.

WHO guidelines already recommend that HIV testing be included in essential care around childbirth for women of unknown HIV status [27]. This recommendation could be extended to women and children attending child health clinics. In the population of postpartum women studied in Kenya, one in four had not accessed testing during pregnancy. HIV testing in child health clinics reduced the number of women with unknown status to one in twenty (article 6) HIV testing in child health clinics was found to be acceptable in this setting, as measured by both uptake and attitudes. Uptake of testing among women bringing their child for health care in Mombasa Kenya was comparable to that seen during pregnancy or labour in other settings [80, 129, 133].

Each encounter with a woman in maternal and child health services could be considered an opportunity for the woman to benefit from knowing her HIV status and to prevent further transmission. Optimal selection of service delivery entry points in different settings will depend on the characteristics of the HIV epidemic (low-level, concentrated or generalized epidemics), and patterns of utilization of health services. The evidence presented here suggests that in both Kenya and South Africa, childbirth and child health clinics provide an important opportunity for entry to PMTCT services, complementing and enhancing the effectiveness of antenatal entry.

HIV infection will declare itself, commonly with a severe illness that has substantial morbidity and mortality. The earlier in HIV disease that people become aware they are infected, the greater the benefit of care and treatment interventions. From a public health standpoint, to prevent transmission of a communicable disease, infected individuals should be identified as soon as possible after acquisition. Timely diagnosis of HIV confers considerable benefits to the individual and the wider community by facilitating access to care and prevention interventions, and changes in behaviour that accompany
knowledge of status [134, 135]. Health workers have a key role to play in facilitating identification of early HIV disease and in maximising the benefits of knowing one’s status for the infected individual and for their susceptible sexual partners and children. In particular, within high-quality PMTCT services, women can gain marked benefits from an early HIV diagnosis, and their children benefit from identifying HIV exposure, and receiving ARV prophylaxis or safer infant feeding. After decades of over-mystifying HIV testing, the pendulum has slowly swung to principles of public health accompanied by attempts to simplify testing and counselling procedures [136, 137]. Increased provision of point-of-care HIV testing around childbirth and in child health clinics is consistent with these changes in HIV testing policies.

Women are particularly vulnerable to HIV acquisition during pregnancy and postpartum (for reasons of biology and behaviour, such as lower condom use). During acute HIV infection, risk of transmission to breastfeeding children and sexual partners is high [138, 139]. In settings with a high HIV incidence, retesting of women in child health clinics who tested negative during pregnancy may be important for identifying recent infection. Modelling cost-effectiveness of retesting women late in pregnancy indicates such a strategy may be useful, even in low-level HIV epidemics [140, 141]. However, field experience with this strategy is discouraging [142]. Given the longer time period between antenatal and postpartum testing, retesting of women in the postpartum may identify more incident cases and be more cost-effective than late in pregnancy.

As shown in article 7, both HIV infected and uninfected women had high levels of reproductive and sexual morbidity in the first year after childbirth, and require increased access to comprehensive postpartum services, as well as entry to HIV prevention, care and treatment. Many had experienced gender-based violence, an important determinant of poor health and well-being. Compared with those who were uninfected, HIV-infected women had poorer health seeking behaviours and different disease patterns. Lower household income and likelihood of financial support from their partners further increase their vulnerability.

Many women with HIV have an unmet need for family planning services during the postpartum period [143, 144]. Women in the cross-sectional survey in Kenya reported that more than half of recent pregnancies were unplanned and, despite a strong desire to postpone pregnancy, more than a third of these women had an unmet need for contraception. The postpartum is a period of substantial transition as women move from
pregnancy and childbirth back to fertility. Using encounters with HIV-infected women at child health clinics to prevent unintended pregnancies is potentially an important, intervention to reduce the proportion of children at risk for HIV. This remains a key, but as yet largely unrealised component of PMTCT strategies. Condom use was low, less than estimates for the general population in Kenya and the Coast Province, possibly as women perceive themselves at low risk for pregnancy in the postpartum.

Anaemia, often linked with poor nutrition, may worsen following pregnancy and childbirth. As in other studies [145, 146], anaemia was more common and more severe among women living with HIV than uninfected women. The aetiology of anaemia appears to differ, less likely to be solely due to iron deficiency. A substantial proportion of women are nevertheless likely to be iron deficient and require routine preventative or therapeutic iron supplementation in the postpartum, as recommended by WHO [147, 148]. Nearly one in six HIV-infected women had an abnormal Pap smear, about half of which were high-grade squamous intraepithelial lesions. Among HIV-infected women such lesions are known to progress more rapidly and with worse prognosis [26].

HIV-infected women, who have not initiated ARV treatment prior to childbirth, also require continued HIV-related care and support in the postpartum period, as well as regular clinical and immunological assessment to evaluate their eligibility for ARV treatment. Counselling for HIV-infected women should focus on equipping them to deal with a chronic infection. Encounters with women in child-health clinics offer an opportunity to provide or facilitate entry to services such as family planning, condom promotion and provision, iron supplements, cervical cytology, and detection and treatment of reproductive tract infections. Other needs identified for HIV-infected women were breast care, and screening for alcohol use and depression. High-quality postpartum care, tailored to women’s needs, could potentially form a bridge from PMTCT, pregnancy and childbirth services to family planning and other sexual and reproductive health services, ensuring continuity of care and entry into services that improve a woman’s health and wellbeing.

At any time during the breastfeeding period, identifying HIV infection in women or HIV exposure in infants enables them to benefit from infant feeding counselling and support for safer feeding options. Patient-provider encounters in child health and immunization clinics could therefore be considered an underutilized opportunity for reducing HIV infection in children. Supporting safer infant feeding could reduce transmission through
breastfeeding, which accounts for a third to half of HIV infections in infants and reduces the overall effectiveness of efforts to prevent MTCT [6]. The Kenyan study showed women with HIV infection have a lower household income and less financial support from fathers, again highlighting the particular need for supporting women to safely carry out their infant-feeding choice.

4.1.3 Improving quality of PMTCT services
Implementing effective PMTCT services is complex, more difficult than was anticipated in the initial period after the results of the HIVNET012 study, which was hailed as a simple feasible solution to the problem of MTCT [50]. Many countries have struggled to establish PMTCT programmes based on this supposedly simple regimen. It must be recognised that throughout the world, HIV policy makers and programme managers work under substantial pressures. New research findings emerge frequently and are often embroiled in complex controversies. Infant feeding debates and concerns about the effects of viral resistance following single-dose NVP are just two such examples. Difficulties for country-level staff in negotiating these controversies are compounded by disagreements among researchers and global leaders [149, 150]. The limited numbers of senior programmatic staff at a country level in resource-constrained settings have found themselves enmeshed in intricate debates rather than programme implementation, their forte.

To be effective, it is essential that governments, working with key stakeholders including the private sector and civil society, own and drive programme planning and implementation. This needs to be supported by adequate human and financial resources and guided by time-bound population-based targets to ensure accountability and sustainability.

Many countries initially established PMTCT pilot projects. Wider implementation together with repeat audit (or ongoing monitoring) may be a better approach than the strategy of developing best practice models and attempting to replicate such findings. In chapter 3.1, evidence is presented showing that repeat audit is able to detect problems and systematic weaknesses, allowing for tailoring of interventions to address problems at individual sites.

WHO has recently highlighted the need to move beyond pilot projects, with broad implementation at scale [27]. This will require strengthening of health systems, especially
high-quality maternal, newborn and child health and other sexual and reproductive health services. These services are predominately provided at primary care level, where the bulk of PMTCT services should also be provided. Well-functioning sexual and reproductive health services are essential for the effective delivery of PMTCT interventions and, in many countries, these services provide an opportunity – sometimes the only opportunity – for women to gain access to HIV prevention, treatment, care and support. As discussed in article 6, use of lay workers such as counsellors, may assist in overcoming the severe shortage of health care workers in most high-burden countries. Lay providers and shifting of tasks to less-specialised workers can alleviate the workload of health care providers and thereby achieve higher HIV testing rates and coverage of PMTCT programmes [151]. This cadre of worker also has an important role to play in expanding access to infant and young child feeding counselling.

Male involvement has long been recognized as a priority in PMTCT, as in other aspects of sexual and reproductive health [152]. Several attempts have been made to involve men through facilitating couple counselling in antenatal services and mutual disclosure [130, 153, 154]. In one study, couple counselling around childbirth was especially effective [130]. These efforts aim to benefit adherence, improve uptake of PMTCT and other HIV interventions, maintain continuation of family planning methods and facilitate provision of family-centred care and treatment. Male partners who are diagnosed as being HIV-positive would be able to access appropriate treatment and care. However, overall it appears that within PMTCT programmes, male involvement remains low and it is unknown which interventions would serve to alter such circumstances. While additional research and pilot projects address this issue, maximum use must be made of existing encounters with men in the health services they predominately attend, such as clinics for sexually-transmitted infections.

Practical aspects of developing well-functioning linkages between antenatal and ARV treatment services also warrant consideration. Detailed planning and careful treatment configuration is needed. Pregnancy and the progression to AIDS are exceedingly dynamic, necessitating time-limited decision making. To decrease MTCT risk it will often be necessary to accelerate initiation of ARV treatment for pregnant women. Difficulties with timely initiation of ARV treatment during pregnancy are compounded by health-seeking patterns, with many women in both Kenya and South Africa first attending antenatal care in the third trimester of pregnancy [101, 108]. Measuring CD4 cell counts
at the first antenatal visit appears particularly important for reducing delays. This provides evidence for the assertion that it is necessary to integrate ARV treatment provision within PMTCT, or at a minimum key components of ARV treatment services, like assessment for treatment eligibility. Strengthening linkages and integrating key components of ARV treatment within antenatal care reduced time-to-treatment initiation for pregnant women, to a median of 37 days in the study at Coronation Women and Children Hospital (chapter 3.1.2). Other lessons learnt during previous initiatives to integrate services like family planning and STD clinics could be used to inform integration of ARV treatment within maternal and child health services [155].

Without raising the quality of ARV regimens, unusual circumstances occur where women at high risk for MTCT who access ARV treatment have a lower risk of MTCT than women with high CD4 cell counts who receive single-dose NVP. In the study reported here which compared MTCT risk in women who initiated ARV treatment with those receiving single-dose NVP, risk for MTCT in women who initiated ARV treatment during pregnancy for their own health was lower than among women who do not have indications for ARV treatment and received single-dose NVP (article 2). This demonstrates the limitations of single-dose NVP – infants born to women with high CD4 cell counts had almost a threefold higher risk of HIV infection than infants born to women with advanced HIV disease (at substantially higher baseline risk of MTCT). This is potentially an important illustration of the shortcomings of simple interventions that have low effectiveness. It is necessary to balance the need for simple interventions suitable to settings with low infrastructure with the improved outcomes of more complex, higher quality interventions. This is summed up in the following quote from B Marstan and K De Cock [156]:

A fine balance is required between the search for “simple” and “appropriate” interventions and efforts to institute the effective measures that we in the industrialized world take for granted. “Cost-effective” should not be a polite term for cheap, nor should “simple” mean not very effective.

PMTCT may be able to build on lessons from ARV treatment and malaria programmes. Services for ARV treatment have made substantial progress with using regimens similar to those in high-income countries. Similarly, malaria control has been re-invigorated by adopting high-quality combination regimens. New treatment guidelines for malaria recommend the most effective antimalarial medicines be used, with the goal of reducing to a minimum the likelihood of malaria parasite resistance [157]. This approach has
transformed the chemotherapy of malaria in South-East Asia, and most African countries have begun using highly-effective artemisinin-based combination therapies.

The acceleration of PMTCT could be closer linked with the scaling up of ARV treatment. The challenge remains to translate increases in resources and quality of care within ARV treatment services into access to care and ARV treatment for women during and after pregnancy, tailored to their needs and specific drug safety considerations.

4.2. Contribution of this work to the field and research agenda at study sites

The studies in Mombasa Kenya, took place against a background of substantial previous research on maternal and child health at the study site [77, 85, 92, 158, 159]. Further, Mombasa is presently one of the sites in a WHO multi-country trial (Kesho Bora) assessing the efficacy of ARV drugs given to breastfeeding women to reduce the risk of MTCT.

Over the years, the Coronation Women and Child Hospital has been the site of many important studies and trials [160-163]. This continues today, with research addressing important public health issues. The studies reported in this thesis contribute to this legacy. After the study in 2002 (article 1), which assessed the effectiveness of the PMTCT programme using process indicators, a further study reported outcome indicators (risk of MTCT among woman-infant pairs receiving single-dose NVP at the hospital) [163]. When ARV treatment became available, process indicators and risk for MTCT were assessed again. The risk of MTCT among pregnant women who received ARV treatment at this hospital is lower than previously reported rates in South Africa [1, 164-166].

4.3. Limitations

The ability to generalize study findings to other settings may be limited, even across the two study sites. As shown in Table 1, there are substantial differences between the study sites, making it difficult to directly compare or generalise findings from each site. While factors like rate of caesarean section [167] and prevalence of HIV [5] in the cross-sectional study among women attending child health clinics are comparable to those in the East African region, it is difficult to generalize the study findings to rural areas, or lower-level health facilities. In addition, women who do not attend child-health clinics or whose child has died are likely to systematically differ from the study population.
The cross-sectional study design used in some of the studies also introduces several limitations. With measuring of exposures and outcomes at the same time, it is difficult to assess the reasons for associations that are detected. This study design is, however, well suited to assess the health care needs of populations, such as the needs of women in the first year after childbirth. While it is possible to draw conclusions about the uptake and attitudes of women in the study on HIV testing in child-health clinics, this study did not assess perspectives of health workers towards testing. Examining these perspectives is important for a comprehensive assessment of the acceptability of HIV testing at child health clinics. Selection bias may also limit ability to draw conclusions in this study as a third of eligible women declined to participate.

In both studies at Coronation Women and Children Hospital that assessed the effects of repeat audit and targeted interventions, several interventions occurred simultaneously. This makes it difficult to determine the relative importance of each intervention. Inherent limitations of comparing outcomes of service delivery before and after an intervention also restrict the ability to interpret and generalize study findings. It is possible that changes observed between the two time periods are attributable to improvements that occur naturally over time as new services mature and become established. Further, improvements noted in follow-up audits could be due to better documentation of interventions provided rather than actual improvements in care. Nevertheless, given the magnitude of improvements in service outcomes, this seems unlikely to be solely attributable to changes over time.

A further limitation affecting several of the studies reported here is the amount of unavailable data. Information in hospital records was recorded for other purposes, thus the studies that used such records were limited to data extraction with consequent missing information. In two of the studies (articles 2 and 3), a substantial proportion of infants have an unknown HIV status. Similar difficulties with infant follow-up have been reported from other settings [161, 168]. It is not possible to determine whether the infants with unknown status had higher or lower levels of HIV infection.

4.4. Priorities for future research

This thesis emphasises the need for a broadening of approach to PMTCT within health services, in particular for testing and other interventions around childbirth, and for women and children attending child health clinics. Additional strategies which further
broaden this approach warrant investigation, such as single-dose NVP for all infants in high-HIV prevalence areas.

Research is needed on the specific steps necessary to ensure implementation of ARV treatment also strengthens existing health systems, including services for HIV-related prevention and care. To ensure current levels of funding for ARV treatment is sustained in the long run, it is important to document the positive spin-offs (such as preventing HIV infection in infants) from these resources.

Safety of ARVs used during pregnancy also needs further investigation. About 4% of all children have a birth defect [169]. Therefore, birth defects among women on long-term ARV treatment are inevitable; these defects could be due to drug exposure or chance occurrence of a defect. It is often very difficult to make this distinction. Given the number of women of child-bearing potential who are receiving ARV treatment, birth defects, even of rare anomalies are inevitable. These could be cause considerable distress among health workers and women, unless more robust data are available to assist in interpreting such findings. With inadequate data, it is difficult to quantify the risks for birth defects. This may lead to unwarranted and exaggerated concerns about the level of risk, with women terminating otherwise wanted fetuses.

Recent WHO guidelines on provider-initiated testing [137] recommend similar strategies to those presented in article 6. Further evaluation of provider-initiated testing is required. Research and policies will have to balance the woman’s right to privacy and to decline HIV testing with the interests of infants in identifying HIV exposure and the public health benefits of HIV testing. Recent policies have shifted towards the later, but additional research and thinking is needed on this topic. Pilot projects assessing the effects of mandatory testing of newborns could provide useful information [170]. Test cases may be needed, where the legal system assesses the state’s responsibility to uphold the best interests of the child, or to defend a doctor who tests infants for exposure to HIV. The effects, if any, on health-seeking patterns of attempts to normalise HIV testing within health services warrants close monitoring. Moreover, the complex social and behavioural dimensions of HIV testing need further investigation and consideration within initiatives to expand knowledge of HIV status [171].

Much is known about the interventions necessary to reduce MTCT, what is needed is massive high-quality scale up of these interventions. Repeated audit and related operational research is needed to assess implementation of HIV interventions and
services for women within child health clinics. Additional research could highlight the differences in outcome between regimens used in South America, Caribbean, eastern and western Europe and North America, and those used in Africa. Already few pilot projects in African countries have investigated the role of triple-ARV regimens used solely for MTCT prophylaxis [172-175]. Further large-scale projects will be useful to inform countries decisions to replace single-dose NVP prophylaxis with regimens that have similar outcomes to those used in Brazil and other South American or Caribbean countries [9]. Science and ethics theory also has to develop a conceptual framework for understanding and explaining large equity and outcome gaps, and the use of simple interventions with relatively low efficacy among the poor. A potential option which warrants consideration is initiating triple-ARV regimens among all pregnant women identified as HIV-infected, while awaiting the maternal CD4 cell count result. Once the CD4 cell count result is available, those women with a high CD4 cell count who do not yet require ARV treatment for their own health could plan to stop their regimen after delivery. This strategy could avoid the delays caused by waiting for the maternal CD4 cell count result, which could be a considerable period of time in some settings.

Further efforts are needed to translate the comprehensive PMTCT approach into programmatic design and implementation, and to take on board the needs of women participating in these programmes. In particular, additional information will be needed on implementation of the new longer MTCT cascade of interventions. In sum, researchers would do well to prioritize investigation of methods of delivering high-quality regimens similar to those used in high-income countries and South America, and the reasons for falloff from the MTCT cascade of interventions, rather than additional studies of efficacy of ARV prophylaxis and consequent resistance.

4.5. Final remarks

While HIV infection in infants has virtually been eliminated in many settings, in Africa the potential for intervention at each service-delivery point is, so far, underutilised and of comparatively low quality. This inequitable mismatch between the burden of HIV in women and children, and the volume and quality of services provided, necessitates a critical review of current strategies.

PMTCT programmes are complex but could potentially play a major role in initiatives to counter the HIV epidemic. These programmes should focus not only on preventing transmission to infants but also on providing basic preventive care for mothers; access to
other sexual and reproductive health services, including family planning; and on facilitating access to ARV treatment for women.

Within child health clinics, postpartum PMTCT services could be built around HIV testing and counselling; infant feeding counselling and support; entry to HIV prevention, care and treatment services; as well as provision of family planning counselling and contraception. These interventions aim to complement and broaden the current antenatal focus of PMTCT programmes. HIV testing would thus be recommended for all women attending antenatal, childbirth and child health services in generalized epidemics.

Policy makers must balance the need for “simple” interventions in resource-constrained settings with the need for more complex highly-effective interventions which are used in relatively over-resourced settings. In achieving this balance, the true meaning of “simple interventions” must be made explicit. As attractive and important as simple interventions are and as massive as the shortage of basic public health infrastructure is, the need for highly-effective interventions in Africa is real and compelling [156].

Women are more than just mothers. Transmission to children may be best solved by meeting women’s needs. This would aim to improve the health and wellbeing of women and their children, strengthen access to high-quality care and stabilize family units.
Summary

HIV is a leading cause of death among women of reproductive age and their children, undermining previous gains in maternal and child survival. In addition to the inherent tragedy of any maternal death, a mother's death compromises the survival of her children. Addressing the interests of both women and children is therefore essential if PMTCT services are to be effective. Current PMTCT services provide insufficient direct benefits for women. Coverage and acceptability of these programmes is low. In contrast, high-income countries have virtually eradicated paediatric HIV, by focusing on women's health and using triple-combination regimens for pregnant women with or without indications for ARV treatment. There is a need for considering alternative PMTCT strategies, tailored to local epidemiological and socioeconomic contexts. Moreover, there may be much benefit to situating PMTCT programmes within broader efforts to improve women's health and wellbeing.

Research took place in Mombasa in the Coast Province of Kenya, and Johannesburg, South Africa. This aimed to investigate ways of increasing effectiveness of PMTCT services for both women and children. The feasibility of identifying HIV infection around childbirth and among women bringing their child for health care was also assessed. Women’s needs in the first year postpartum were evaluated. In South Africa, repeat audits of PMTCT services at a secondary-level hospital were used to identify programmatic weaknesses and to inform targeted actions. A randomized trial was also conducted in South Africa, assessing the efficacy of ARV regimens in reducing MTCT among newborns whose mothers had not received ARV drugs. The safety of ARV drugs for women who become pregnant while receiving ARV treatment is also explored. A case is reported of an infant with in utero exposure to ARV treatment who had a Dandy Walker birth defect. Approval was obtained from relevant ethical committees for all the studies presented here.

Taken together, the studies showed that each encounter with a woman in maternal and child health services provides an opportunity for a woman to benefit from knowing her HIV status and for preventing HIV transmission to infants. Childbirth and child health clinics can complement and enhance the effectiveness of antenatal PMTCT services. In the population of postpartum women studied in Kenya, one in four had not accessed testing during pregnancy. HIV testing in child health clinics reduced this number to one in twenty.
In the Kenyan study, women had high levels of avoidable reproductive and sexual morbidity in the first year after childbirth. More than half of recent pregnancies were unplanned, yet more than a third of postpartum women had an unmet need for contraception. Anaemia was more common and severe among women living with HIV than uninfected women. HIV-infected women also had poorer health seeking behaviours, and had lower household income and financial support from their partners.

Interventions tailored to systematic weaknesses identified in the audit of the PMTCT services increased programme effectiveness. Detailed planning and careful programme configuration is needed to develop well-functioning linkages between antenatal and ARV treatment services. Measuring CD4 cell counts at the first antenatal visit was particularly important for reducing delays in ARV treatment initiation. This shows the importance of integrating key components of ARV treatment within PMTCT services.

Women who access ARV treatment had a lower risk of MTCT than women who received single-dose NVP. This demonstrates the limitations of single-dose NVP and is potentially an important illustration of the shortcomings of simple interventions that actually have low effectiveness. It is necessary to balance the need for simple interventions suitable to settings with low infrastructure with the improved outcomes of more complex, higher-quality interventions.

There are substantial differences between the study sites, limiting the ability to generalise study findings to the other site. Further, the study design used in some of this research constrains the ability to interpret findings. In particular, there are inherent limitations in cross-sectional studies and in comparing outcomes of service delivery before and after an intervention.

The thesis highlights the need for a broadening of approach to PMTCT and tailoring of PMTCT services to women's needs, streamlined with their actual attendance at these services. PMTCT programmes are complex but could play a larger role in initiatives to counter the HIV epidemic. HIV testing should thus be recommended for all women attending antenatal, childbirth and postpartum services in generalized epidemics. The need for highly effective interventions for women and children in Africa is real and compelling. In particular, more vigorous efforts to address pregnant women's health and wellbeing may be the optimum entry point to effectively preventing HIV in infants.
Samenvatting
Humaan immunodeficiëntie virus (HIV) is een van de meest voorkomende doodsoorzaken van vrouwen en hun kinderen in ontwikkelingslanden. Na jaren van een toename in levensverwachting, is er nu een daling als gevolg van HIV. De dood van een moeder is op zichzelf al erg, maar het heeft ook verstrekende gevolgen voor de overlevingskansen van haar kind. Daarom is het belangrijk dat HIV interventies zich richten op moeder en kind: behandeling van de HIV-infectie van de moeder en het voorkomen van infectie bij het kind (PMTCT). De huidige PMTCT programma’s concentreren zich voornamelijk op het voorkomen van infectie van de baby en bieden onvoldoende directe voordelen voor de vrouw zelf. Daarnaast is momenteel de toegang tot behandeling van HIV als ook de preventie van overdracht naar het kind in veel ontwikkelingslanden beperkt.

Dit staat in scherp contrast met de zorg die vrouwen en kinderen in het Westen genieten. Door toegang tot effectieve antiretrovirale combinatietherapieën voor alle geïnfecteerde vrouwen worden er nauwelijks kinderen geboren met HIV.

In ontwikkelingslanden is het daarom belangrijk om lokaal toepasbare, alternatieve strategieën te ontwikkelen die meer effectief zijn voor moeder en kind. Door de aandacht te verschuiven richting de zorg voor de moeder kan er al veel gewonnen worden.

Dit onderzoek werd uitgevoerd in Mombasa aan de Keniaanse kust en in Johannesburg in Zuid Afrika. Het doel van dit onderzoek was om interventies te evalueren, die mogelijk meer effectief zijn voor de gezondheid van de geïnfecteerde moeders en hun kinderen.

Dit proefschrift beschrijft de mogelijkheid om meer vrouwen te testen op HIV rond de bevalling en gedurende de postnatale raadpleging (immunisatie). Door meer vrouwen te testen kan de gezondheid van de moeder, zowel in relatie met HIV als met andere ziekten, beter worden.

In een ziekenhuis in Zuid-Afrika hebben meerdere evaluaties van de PMTCT programma’s zwakheden in deze programma’s aangetoond. Dit heeft er weer voor gezorgd dat corrigerende acties ontwikkeld werden. Ook is er een gerandomiseerd onderzoek in Zuid-Afrika uitgevoerd om de effectiviteit van verschillende pediatrische antiretrovirale interventies te vergelijken bij kinderen waarvan de moeders geen antiretrovirale interventies hadden ontvangen. Bijwerkingen van sommige antiretrovirale middelen bij zwangere vrouwen zijn eveneens onderzocht. Zo is er een casus
beschreven van een kind met een aangeboren syndroom van Dandy Walker waarbij de moeder antiretrovirale middelen kreeg tijdens de zwangerschap.

Alle genoemde studies werden goedgekeurd door ethische comités in de betreffende landen en instituten.

Een eerste bevinding is dat elke ontmoeting van een vrouw met moeder-kind gezondheidsdiensten een kans biedt om de HIV status van de vrouw te kennen. Ze kan hier zelf voordeel uit halen en de kans op HIV transmissie verminderen. Materniteiten en pediathische diensten kunnen een aanvulling bieden op antenatale PMTCT voorzieningen en de effectiviteit vergroten. In de populatie van Keniaanse vrouwen in de postpartumraadpleging was 25% niet antenataal getest. Door het aanbieden van de HIV-test postpartum werd dit gereduceerd tot 1 op 20.

In de Keniaanse studie hadden veel vrouwen vermijdbare reproductieve en seksuele aandoeningen in het eerste jaar na de geboorte. Meer dan de helft van recente zwangerschappen was ongepland en één derde van de vrouwen in de postpartumperiode uiten de wens tot anticonceptie. Anemie was frequenter en erger in de HIV+ vrouwen dan in de HIV-. Geïnfecteerde vrouwen hadden ook meer moeite om de weg naar gezondheidsvoorzieningen te vinden, ze hebben een lager gezinsinkomen en minder financiële steun van hun partner.

Tijdens een evaluatie van PMTCT-diensten werden structurele zwakheden blootgelegd en wanneer die gebreken aangepakt werden, steeg de effectiviteit van de programma’s. Het vergt een degelijke planning en configuratie om de antenatale diensten samen te laten werken in de verstrekking van antiretrovirale therapie (ART). Daarnaast is het van cruciaal belang om bij het eerste antenatale contact over CD4-telling te kunnen beschikken, zodat het opstarten van ART niet vertraagd wordt. Hierbij is het essentieel dat sleutelcomponenten van ART-diensten in de PMTCT-diensten ingebouwd worden.

Immuungecompromiteerde vrouwen met ART hadden een lagere transmissie naar het kind dan immuuncompetente vrouwen die de klassieke eenmalige dosis van nevirapine (sd-NVP) kregen. Dit demonstreert de beperkingen van sd-NVP programma’s en dit is een illustratie van de tekortkomingen van eenvoudige interventies met lage effectiviteit. Het is nodig om een evenwicht te vinden tussen eenvoudige interventies, aangepast aan lokale situaties en weinig infrastructuur, en de betere resultaten van interventies die meer complexiteit en ook kwaliteit vertonen.
Het is moeilijk om de resultaten van de verschillende studies te transponeren omwille van de substantiële verschillen tussen de onderzoekssites. Bovendien is het moeilijk met de studie opzet van sommige van deze studies, om harde conclusies te trekken uit de bevindingen. Met name cross-sectionele studies hebben hun inherente beperkingen en het is moeilijk om de resultaten van de dienstverlening te vergelijken voor en na een interventie.

Acknowledgements

Reaching this stage is due, in large part, to a few exceptional people who each mentored and supported me, especially at major life points. Marleen, my supervisor and the head of ICRH, provided unfailing and timely assistance, as well as fine example. She never obstructs progress, always its facilitator. The friendship with Stanley JMF secured my public health entry at the beginning of this shared journey, with decades to come of papers, projects and cities – life really. Two Mikes also filled pivotal roles, teaching and signposting me: from initial lessons in epidemiology among piles of patient files at Coro and another, even earlier, Mike who showed that anything is possible with a principled approach and ‘eating at the desk’. My colleagues at ICRHK and Coro have been great friends and this work would never be without them, particularly the boundlessly affable Ashraf and Karin-Karl team, and the PPS group, Jeff- and Jerry-man, and all in Mombasa who made me welcome and part of the family there. Other essential ingredients were rich learning experiences with those super bright at PHRU, RHRU, WHO and FARR, who all gave me so much and put up with my rather unconventional working style. My family and friends have been just brilliant; my parents, sweet-sister Natalie, Martin with newborn niece, many Jesuit mentors, Adams JMF family, William and all.

There has never been a five-year plan, but now I understand its value. Thanks to you all.
Annexes

Annex 1: Vertical HIV transmission in South Africa: translating research into policy and practice (Article 8)
Vertical HIV transmission in South Africa: translating research into policy and practice

Vertical (mother-to-child) transmission of HIV in South Africa ranges from 19 to 36%, depending on whether the child is breastfed or not.1 In 2000, the prevalence of HIV infection in antenatal clinic attendees in public health services was 24.5%, and recent estimates suggest that about 75 000 infants were born with HIV-1 infection in infection status, which may prevent further sexual or vertical transmission. The argument that nevirapine can only be used if the mother is breastfeeding or formula feeding has been prevented if short-course antiretroviral treatment had been available.** The South African Government has claimed these interventions cannot be universally implemented due to cost, toxicity, drug resistance, breastfeeding, and the capacity of the health service to implement programmes. Antiretroviral drugs have become much cheaper over the past few years because of lobbying by activist groups, including those in South Africa. The manufacturers of nevirapine have offered the drug free over the next 5 years to countries in Africa to reduce vertical transmission. The costs to be incurred would therefore be the costs of providing establishing voluntary counselling and testing at antenatal clinics, including staff training and extra counsellors. Such costs may be considerable but need to be weighed against those of not providing this intervention (lives lost and treatment of HIV-infected children). Widespread counselling and testing would have additional benefits such as informing individuals about their infection status, which may prevent further sexual or perinatal transmissions. Counselling and testing is cost effective.9 Costing studies10 in South Africa have shown that antiretroviral therapy to prevent vertical transmission is cost effective. Short-course regimens used to prevent vertical transmission have been shown in several studies11,12 to be safe with minimum side-effects. Follow-up of mothers and children many years after receiving zidovudine showed an acceptable safety profile.13 A decision analysis model14 has shown that nevirapine is beneficial even if its toxicity was up to 42 times that observed in clinical trials, and concluded that implementation of nevirapine should not be delayed by toxicity concerns.

Drug-resistance mutations in some mothers after a single dose of nevirapine are usually variants present at low frequency before the use of antiretroviral drugs, which are then selected and expanded when nevirapine is introduced. However, resistance does not affect the efficacy of antiretroviral prophylaxis to prevent vertical transmission, since these variants are not transmitted to the child, and they wane over time with absence of drug pressure.14 Drug resistance is not unique to HIV. As with tuberculosis and other infectious diseases, there needs to be good surveillance and monitoring for drug resistance.

Breastfeeding is a route of HIV transmission, but several strategies can minimise this risk.15 One solution is to replace breastfeeding with formula feeding. However, in the settings where many HIV-infected women live, formula feeding is not a safe alternative and the risk of HIV transmission is exchanged for the risk of mortality from diarrhoea and pneumonia.16 Counsellors need to advise mothers to understand the risks and benefits of breastfeeding and formula feeding so that they can make an informed choice. Women who choose to breastfeed can be assisted to make breastfeeding safer.

The argument that nevirapine can only be used if women are not breastfeeding is not valid. Nevirapine used according to the HIVNET 012 regimen has its effect intrapartum and the reduction in transmission is obtained regardless of whether the mother is breastfeeding or formula feeding. The HIVNET 012 trial in Uganda showed that the acquisition of new infections due to breastfeeding at age 6 weeks to 12 months was not increased in the babies of mothers receiving nevirapine, the rate being similar to that in those of mothers who did not receive nevirapine.

The operational capacity to implement use of nevirapine already exists in several health-care facilities. It is ethically and morally unacceptable for government policy to preclude them from providing nevirapine in the best interests of their patients or instructing them to hold back until research at pilot sites is completed, since these pilot studies merely add to the substantial South African data already available on the experience of implementing antiretroviral prophylaxis to reduce vertical transmission.14,15 In settings with less capacity, less resource-intensive alternatives could be considered while resources and training are provided to address operational inadequacies. For example, although not universally accepted, the option of nevirapine for all pregnant women without HIV testing has been suggested, especially in high-prevalence settings.

Screening all pregnant women for anaemia, weight gain, syphilis, and rhesus factor is routine in the public health service. This capability serves as a foundation for a national programme to prevent HIV vertical transmission. Short-course antiretroviral therapies to prevent vertical transmission are being used successfully

Rights were not granted to include this image in electronic media. Please refer to the printed journal.
in the Western Cape.\textsuperscript{14} We applaud the provinces of KwaZulu-Natal and Gauteng for announcing that nevirapine will be widely available within the next few months.

In a developing country such as South Africa the few opportunities for controlling HIV spread need to be maximised. Over 5 million of the 42 million people living in South Africa are HIV-infected, and with more than half of these infections occurring in women, vertical transmission will continue to increase. There is a moral and public-health imperative to provide cost-effective interventions of known efficacy. The South African Government has an exemplary record by providing free immunisations against major childhood infections to children under the age of 6. The lack of a similar policy to prevent the single most common perinatally transmitted cause of mortality in children is of concern. In a recent court case the judge stated that “prohibiting the use of nevirapine outside the pilot sites in the public health sector is not reasonable and that it is an unjustifiable barrier to the progressive realization of the right to health care\textsuperscript{15}”. The court ordered the government to provide a comprehensive national roll-out plan against vertical transmission by March 31, 2002. The government is appealing against this judgment.

As scientists and clinicians, we share a deep commitment to our patients and the public health of our nation. We have conducted and/or supported research aimed at decreasing vertical transmission. We remain fully committed to the implementation, within the broader government programme for AIDS prevention and care, of a national programme against vertical transmission, and to do further research in support of this goal. There is strong evidence in support of the use of antiretrovirals to reduce vertical transmission. The challenge remains in translating these research findings into policy and practice in South Africa.

\textbf{COMMENTARY}

The health (and wealth) of nations

Violence, corruption, tyranny, starvation, and political misjudgment drive the world’s perceptions of Africa as a continent with few prospects for progress. This comforting blanket of pessimism wrapped itself around many of those attending what should have been one of the more important global gatherings this year—the International Conference on Financing for Development, held in Monterrey, Mexico, last week. The goal of Monterrey was to devise a strategy to eradicate poverty, strengthen economic growth, and promote sustainable development. Indeed, politicians proclaimed the 21st century as “the century for development”,\textsuperscript{14} the language of the Monterrey consensus was vigorous. Political leaders spoke of greater resolve, stronger partnerships, and renewed commitments. But the actions of those leaders, and in particular the actions of US President George Bush, displayed only cruel neglect.

The utter failure of Monterrey was made all the worse by the extraordinary hopes created by the Millennium Development Goals (panel) and the pledges made by G8 leaders at their Okinawa summit in 2000. At Okinawa, politicians were unusually specific: they wanted to cut cases of HIV/AIDS by 25%, tuberculosis transmission (MTCT) of HIV. 13th International AIDS Conference, Durban, South Africa, 2000; abstr TuO8B355.

4 Moodley D, Toob SI. The SAINT Trial: nevirapine (NNRT) versus zidovudine (ZDV) + lamivudine (3TC) in prevention of peripartum HIV transmission. 13th International AIDS Conference, Durban, South Africa, 2000; abstr Lb682.


Annex 2: Progress and emerging challenges in preventing mother-to-child transmission (Article 9)
Progress and Emerging Challenges in Preventing Mother-to-Child Transmission

Matthew F. Chersich, MBBCh, MSC, and Glenda E. Gray, MBBCh, FCPaed(SA) *

Address
*Perinatal HIV Research Unit, University of the Witwatersrand, Chris Hani Baragwanath Hospital, Old Postch Road, PO Bertram, Soweto 2013, South Africa.
E-mail: gray@pixie.co.za

Current Infectious Disease Reports 2005, 7:393–400
Current Science Inc. ISSN 1523-3847
Copyright © 2005 by Current Science Inc.

Introduction
Every day about 1700 children are newly infected with HIV; 90% of these infections occur in sub-Saharan Africa [1]. As access to antiretroviral (ARV) treatment—particularly for children—remains limited in most African settings, at least one quarter of these children die before the age of 1 year, up to 60% die before their second birth-

day, and most die before reaching 5 years of age [2]. Despite the magnitude of the problem, about 90% of women with HIV in sub-Saharan Africa do not have access to interventions to prevent mother-to-child transmission (MTCT) of HIV-1 [3]. They have a 15% to 45% risk of MTCT, varying with the length of breastfeeding. For a woman with HIV in these settings with access to a program to prevent MTCT (PMTCT), which includes single-dose maternal and infant nevirapine (NVP), the risk of transmitting HIV to her infant is about 13%, which is higher if she breastfeeds. In contrast, new HIV infections in children are increasingly rare in many other parts of the world. In Brazil, Europe, and the United States, long-course, triple ARV prophylaxis is provided to a woman with HIV during pregnancy and childbirth, and the risk of transmitting HIV to her infant is less than 2% [4–6]. Consequently, it is estimated that in 2004, less than 200 children were infected with HIV in North America and western Europe combined [7].

Antiretroviral Regimens for MTCT Prophylaxis: a Spectrum of Effectiveness and Resistance
Although similar regimens are used for ARV treatment in both resource-constrained settings and high-income countries, regimens used for MTCT prophylaxis differ markedly. Similarly, MTCT prevention trials using different durations of single, dual, or triple ARV prophylaxis vary considerably. In Europe and the United States, clinical trials of ARV prophylaxis to prevent MTCT have focused only on long-course regimens. The first such trial, which investigated the efficacy of zidovudine (ZDV), began in 1991 and enrolled women starting at 14 weeks of pregnancy [8]. By contrast, almost all studies in Africa have evaluated ARV prophylaxis initiated at 36 weeks of pregnancy or during childbirth. Overall, the results of MTCT prevention trials indicate that longer courses and a combination of two or three drugs are more effective than shorter courses and single-drug prophylaxis. Therefore, ARV regimens for PMTCT can be conceptualized as a spectrum of effectiveness, from highly effective, long courses of triple ARV prophylaxis to...
moderately effective, dual-drug, short courses and single-drug, single-dose NVP, the least effective regimen.

For pregnant women with indications for ARV treatment, PMTCT guidelines for high-income countries as well as for resource-constrained settings recommend starting ARV treatment during pregnancy [9–11,12••,13••]. Based on results from PMTCT trials, between 6% and 16% of pregnant women with HIV in Africa have a CD4 count of less than 200 cells/mm³ [14]. Triple-drug ARV treatment in these women benefits their health, is the most effective means of reducing MTCT, and, by improving maternal health, is likely to increase child survival [2]. However, triple combination ARV regimens are used in Brazil, Europe, and the United States for MTCT prevention, even for women with HIV who do not have indications for ARV treatment [9–11,12••]. In these settings, long-course, triple-drug prophylaxis is initiated during pregnancy and discontinued after childbirth for women who do not have indications for ARV treatment. By achieving undetectable plasma viral loads before delivery, the use of triple-drug ARV prophylaxis by most pregnant women with HIV has led to a dramatic reduction in MTCT rates in high-income countries and Brazil. Use of such prophylaxis has increased substantially over the last few years. In 2002, the European Collaborative Study reported that about 90% of pregnant women taking ARV drugs during pregnancy received triple-combination regimens (either as part of ARV treatment or solely for MTCT prophylaxis) [4]. Similarly, in the United States, only 10% of pregnant women with HIV were given single-drug MTCT prophylaxis in 2001 [15]. Changes over the years to the United States PMTCT guidelines reflect a shift towards triple-combination regimens for MTCT prophylaxis. The January 1998 guidelines recommended that such regimens be “offered” to all pregnant women [16]. In January 2001, the guidelines recommended that the combination of ZDV prophylaxis with additional ARV drugs be “strongly considered” for any woman with a plasma viral load above 1000 copies/mL, regardless of clinical or immunologic status [17]. In June 2004, reflecting accumulating evidence on the effectiveness of triple-combination regimens for preventing MTCT, “Standard combination antiretroviral regimens for treatment of HIV-1 infection should be discussed and offered to all pregnant women with HIV-1 infection regardless of viral load; they are recommended for all pregnant women with HIV-1 RNA levels greater than 1000 copies/mL” [12]. Current Brazilian, British, and European PMTCT guidelines similarly recommend the use of triple-combination regimens for MTCT prevention in women not requiring ARV treatment for their own health, albeit at different immunologic and/o virologic levels.

Triple ARV regimens have been associated with increased risk of premature birth, predominantly among women receiving regimens containing protease inhibitors in early pregnancy. However, it is unclear whether these infants are at higher risk of MTCT of HIV than term infants [18]. In addition, there are concerns of increased toxicity during pregnancy when using a NVP-containing regimen in women with higher CD4 counts. Symptomatic hepatotoxicity in women with higher CD4 counts is associated with use of NVP-based ARV regimens in pregnancy [19].

Use of single-dose NVP followed the Ugandan HIVNET 012 trial which reported in 1999 that single-dose (maternal and infant) NVP reduces the risk of MTCT by about 50%. These findings coincided with strong advocacy efforts and increased funding for PMTCT programs in sub-Saharan Africa. Demonstration of the feasibility of PMTCT programs based on single-dose NVP provided momentum and catalyzed action for the development of these programs. It remains the simplest regimen to deliver, is the preferred regimen in settings with limited capacity for delivering health services, and is an important option when HIV infection is identified late in pregnancy or during labor. However single-dose NVP, in addition to being less effective than other regimens in reducing the risk of MTCT, selects for viral resistance. Fully suppressive triple-drug prophylaxis is less likely to select for viral resistance. A regimen of ZDV from 28 weeks of pregnancy plus single-dose NVP is highly efficacious, reducing the risk of MTCT to about 2%, but also selects for viral resistance to NVP [20]. Limited evidence indicates that such resistance adversely affects a woman’s response to subsequent ARV treatment. In a Thai study, after 6 months of non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ARV treatment, women previously exposed to single-dose NVP were 2.6 times (95% CI: 1.2–5.5) less likely to achieve a plasma viral load less than 50 copies/mm³ than women who had not been exposed to single-dose NVP [21]. However, the study did not detect differences in weight gain (0.5 kg NVP-exposed group, 0.95 kg non–NVP-exposed group, P = 0.32) and in CD4 cell counts. The clinical implications of the finding that women previously exposed to single-dose NVP are less likely to achieve virologic suppression after 6 months of ARV treatment are uncertain [13••]. However, in an analysis of 13 prospective cohort studies, failure to achieve virologic suppression after 6 months of ARV treatment strongly predicted progression to a new AIDS-defining disease or death [22]. Resistance is of particular concern as first-line ARV treatment regimens are NNRTI-based, and second-line protease inhibitor regimens have high pill counts, significant metabolic abnormalities, high cost relative to NNRTI-based regimens, and limited availability in resource-constrained settings.

Although additional research is required, the findings of the Thai study are consistent with current concepts of virologic resistance—that drug pressure selects for resistant mutations, which become undetectable if drug pressure disappears but persist in viral reservoirs and reappear when drug pressure is reapplied. Resistance to NNRTI drugs (such as NVP) develops more rapidly than in other drug classes and can confer cross-resistance to other
progress and emerging challenges in preventing mother-to-child transmission • Chersich and Gray

Feasibility of Triple-drug, Long-course MTCT Prophylaxis in Resource-constrained Settings

Current arguments for providing different regimens for MTCT prophylaxis are similar to those used during the years in which ARV treatment in resource-constrained settings was considered unsafe, unlikely to be effective, and not cost effective. The above-mentioned WHO guidelines do not recommend the use of triple-combination regimens for MTCT prophylaxis, based on concerns that their safety and efficacy have not been assessed in resource-constrained settings. “Although triple-combination regimens are widely used in industrialized countries for preventing MTCT in women who do not yet require ARV treatment for their own health, their safety and effectiveness have not been assessed in resource-constrained settings” [13••]. It should be noted that high-income countries recommended triple-combination prophylaxis for preventing MTCT before their safety and effectiveness for this indication had been assessed. Furthermore, recent evidence has become available from a study in Mozambique of the safety and effectiveness of triple-combination prophylaxis in resource-constrained settings [30]. In the study, the risk of MTCT 1 month after delivery was 4.1% (the lowest thus far in Africa), and no serious adverse events were reported among the 515 woman-infant pairs.

Long-course MTCT prophylaxis aims to suppress viral replication and provide prophylaxis to the fetus and infant during and after exposure to HIV, which can occur during pregnancy or in childbirth. In the absence of MTCT prophylaxis, of 100 infants born to women with HIV, 5 to 10 are infected during pregnancy and 10 to 20 in childbirth [31]. An individual patient data meta-analysis found that the risk of HIV transmission through breastfeeding is 8.9 transmissions per 100 years of breastfeeding (95% CI, 7.8–10.2) [32]. Based on this data, it can be calculated that the risk of MTCT during pregnancy is equivalent to the risk of HIV transmission from 6.7 to 13.5 months of breastfeeding. Surprisingly, in resource-constrained settings, little attention has been given to decreasing MTCT during pregnancy even though the risk of MTCT during pregnancy is equivalent to the risk of MTCT from at least 6 months of exposure to breast milk. Relative to the challenges faced in resource-constrained settings in safely reducing HIV transmission through breastfeeding, starting ARV prophylaxis earlier in pregnancy (therefore targeting HIV transmission during pregnancy) may be more feasible and cost effective to implement.

Furthermore, the health infrastructure in resource-constrained settings frequently requires additional financial and technical inputs to provide PMTCT interventions [33]. Although NVP itself is inexpensive, the substantial investments in health system enhancements and HIV testing and counseling make PMTCT interventions more costly, and the low effectiveness of single-dose NVP makes the package less cost effective. In a study of the cost effectiveness of single-dose NVP, health system costs accounted for most of the program expenses, followed by HIV testing and counseling; an extremely small proportion of total costs were for ARV drugs for MTCT prophylaxis [34]. The authors of the study concluded that by using an ARV regimen that increases the efficacy of prophylaxis from 50% to 70%, one could spend up to $152 per client on ARV prophylaxis and have a program equivalently as cost effective as single-dose NVP programs.

The effectiveness of PMTCT regimens can also be compared by calculating the number needed to treat (NNT) for each regimen (ie, the number of women that need to receive ARV prophylaxis to prevent one infant from being infected with HIV). The NNT can be estimated using an MTCT risk of 13% with single-dose NVP, 2% with triple-drug, long-course prophylaxis, and 25% among women not receiving ARV prophylaxis. Using these risks, about eight woman-infant pairs need to receive single-dose NVP to prevent one infant HIV infection whereas only four woman-infant pairs need to receive triple-drug, long-course prophylaxis to avert one infant infection.
Although it is seemingly a simple regimen to implement, there have been several reports of difficulties in timing the administration of maternal single-drug NVP, suboptimal adherence, repeat doses due to false labor, missed NVP dosing of the newborn, and difficulties in ensuring continuity of care for the woman-infant pair postpartum [35–38]. Research is needed to determine whether a longer regimen with frequent visits, regular follow-up counseling, and more intensive care for women with HIV during pregnancy may reduce such problems.

There are concerns that long-course MTCT prophylaxis may not be feasible in sub-Saharan Africa due to low levels of health service coverage and utilization. However, an analysis by WHO and the United Nations Children’s Fund (UNICEF) on coverage and uptake of antenatal care in middle- and low-income countries reported that about 70% of women who access antenatal care in sub-Saharan Africa present for antenatal care before 28 weeks of pregnancy [39]. Thus, based on existing health-seeking patterns, it may be possible to initiate MTCT prophylaxis from the third trimester of pregnancy for most pregnant women in sub-Saharan Africa. As the risk of MTCT prior to the third trimester is negligible, it is not necessary to initiate prophylaxis before this time. Furthermore, in a study of women attending antenatal clinics in 13 countries in Africa, acceptance and return rates for HIV testing did not depend on the ARV regimen used in the different sites [40]. This suggests that the regimen used is not a major factor in determining acceptability and participation in PMTCT programs.

Guidelines in Brazil, Europe, the United Kingdom, and the United States recommend that a woman’s CD4 cell count and/or plasma viral load be taken into account when selecting an ARV regimen for MTCT prophylaxis. Initiatives to expand access to ARV treatment in resource-constrained settings have demonstrated that standardization of ARV regimens is a key factor in the provision of such treatment. Similarly in these settings, standardization of ARV prophylaxis will be necessary for implementing PMTCT programs based on triple-combination regimens. Standardization, by using the same ARV regimen for MTCT prophylaxis in pregnant women with HIV irrespective of their plasma viral load or CD4 cell count, has several advantages: the complexity of the program and of drug procurement is decreased; plasma viral load and CD4 cell count measurements are not available in many settings; and these tests increase the costs of the program, require an additional clinic visit for women to receive the results of such tests, and delay the initiation of MTCT prophylaxis. Moreover, using a standard triple-combination regimen for MTCT prophylaxis in all pregnant women with HIV is not contrary to guidelines in high-income countries [12**]. However, as side effects of these regimens may occur more frequently in pregnant than nonpregnant women, it will be necessary to ensure that adequate monitoring of pregnant women occurs.

Although the HIV plasma viral load correlates with the risk of MTCT, transmission of HIV has been observed across the entire range of plasma viral load levels, including in women with a plasma viral load below the limit of detection. Analysis from a collaborative registry of European and United States studies found that the risk of MTCT in women with a plasma viral load below 1000 copies/mL who did not receive MTCT prophylaxis was 9.8%, compared with a 1.0% risk in women with a plasma viral load below 1000 copies/mL who received ARV drugs [30]. Moreover, data from the United States showed that the risk of MTCT in women with a plasma viral load below 1000 copies/mL was significantly lower with use of dual or triple-combination regimens compared with single-drug prophylaxis [17]. Therefore, there are programmatic, logistic, and evidence-based reasons for adopting a standardized approach to triple-drug MTCT prophylaxis, regardless of plasma viral load or immunologic status.

Alternative Programmatic Approaches to MTCT Prevention

Given the continued low coverage of PMTCT programs, several alternatives to the current approach to MTCT prevention have been considered [41]. Currently, a targeted approach is used in which HIV testing is offered during pregnancy and ARV drugs and other interventions are provided only for women who test positive. In the universal approach, all women who do not have access to HIV testing are offered single-dose NVP. Using a combined approach, women who have declined HIV testing and women known to be HIV-positive are offered single-dose NVP. In the face of weak health systems, low uptake of HIV testing in many centers and a high probability that the benefit to the individual exceeds the probability of harm, these alternative approaches may provide a valuable temporary measure in some settings. However, there are several disadvantages to such approaches: current comprehensive strategies and the motivation to expand HIV testing may be undermined, confusion regarding infant feeding recommendations may occur, and adherence to universal single-dose NVP may be low [42]. Moreover, concerns of drug resistance need to be considered before adopting such a strategy; the benefits of universal NVP accrue to the infant and not the woman.

In areas with a high HIV prevalence, use of universal NVP in infants—analogous to the universal use of tetracycline eye ointment in newborns for preventing *Opithalmania neonatorum*—would avoid NVP resistance in women. Recent studies have demonstrated the substantial efficacy of post-exposure prophylaxis for the newborn [43,44]. Research on the effectiveness of universal NVP in infants is urgently needed.

Offering HIV testing and counseling around the time of labor or shortly thereafter is an important, though neglected, opportunity for entry into HIV-related services,
including interventions to prevent MTCT. Although PMTCT programs must continue to focus on increasing accessibility, acceptability, and uptake of HIV testing during pregnancy, many women currently deliver without accessing HIV testing and could benefit from testing at this time. HIV testing and counseling during labor or shortly thereafter, followed by ARV prophylaxis for the infant and infant feeding counseling has been shown to be feasible and effective in reducing MTCT [43–46]. Such a strategy could complement existing approaches and increase overall effectiveness of MTCT programs.

A Comprehensive Approach is Needed
Interventions during pregnancy, childbirth, and postpartum aim to improve maternal health, maternal well-being, and/or child survival. To achieve these objectives, PMTCT programs need to be designed and implemented based on these interlinked goals and integrated within broader efforts to improve child survival and the health and well-being of women with HIV. PMTCT programs are complex but could play a major role in initiatives to counter the HIV epidemic. Offering HIV testing and counseling to all pregnant women, as part of basic and routine essential care during pregnancy, has several beneficial outcomes. Reaching women who are not infected with HIV can assist in preventing HIV transmission among adolescents and adults through changes in behavior that can accompany awareness of HIV status and quality risk-reduction counseling. For women with HIV, knowledge of HIV status enables entry into treatment, care, support, and prevention—allowing for tailoring of reproductive health care and counseling according to HIV status—and assists women to make decisions about their sexuality and reproduction. Also, implementation of PMTCT programs is an opportunity to strengthen existing health systems. PMTCT programs, which seamlessly operate within a continuum of care and provide appropriate and accessible treatment, care, and support for the needs of women and their children, have tremendous potential to reduce maternal mortality, secure the health and sexual well-being of women with HIV, and improve child survival.

In heavily affected countries, HIV is a leading cause of maternal death [47]. In addition to the inherent tragedy of any maternal death, in many settings a mother’s death seriously compromises the survival of her children. Data from several African countries indicate that there is an increase in child mortality in the year before and after a mother’s death [2]. A pooled analysis of seven PMTCT trials in Africa showed that child mortality is associated with maternal deaths, regardless of whether the child is infected with HIV [48]. Among children not infected with HIV, mortality was five times higher among those whose mother had died compared with children whose mother was alive. This finding is consistent with a study in rural Uganda in which death or terminal illness of a mother was an independent predictor of mortality among children [49]. Improving child survival is inseparable from improving maternal health. Indeed, in the absence of a broad integrated approach with strengthening of existing health infrastructure, the provision of ARV prophylaxis alone is unlikely to have a marked impact on child survival.

For many years, PMTCT programs have been the focus of considerable attention and efforts. These programs, similar to other initiatives aimed at pregnant women and infants, easily captured widespread interest and funding. However in recent years, this momentum has dissipated, PMTCT has largely slipped off the agenda and expansion of access has faltered. The broader purposes of PMTCT programs have been poorly understood, and controversies surrounding single-dose NVP and infant feeding have contributed to programmatic confusion. Reflecting this confusion, many critics have targeted the name “PMTCT,” commenting that it ignores the role of males in HIV-transmission dynamics, and that PMTCT programs benefit only the infant, overlooking the needs of the woman, even treating her as a disease vector.

In many countries, antenatal, childbirth, and postpartum services form the backbone of primary health care and provide a vital opportunity to reach women and provide them with HIV-related services: primary prevention for women not infected with HIV, and for women with HIV, treatment, care, and support as well as interventions to prevent MTCT. Thus far, few PMTCT programs have used this opportunity effectively, and some have chosen to focus narrowly on women as bearers of children, and in most facilities, the opportunity is missed altogether. PMTCT programs that focus on women’s biologic role in transmitting HIV to their infants may fail to attract many participants and reinforce the widely-held perception that the primary objective of identifying HIV infection in pregnant women is to prevent transmission to infants rather than to benefit women. PMTCT programs, by identifying women with HIV, have a responsibility to provide the full range of HIV services or have explicit mechanisms of referral for such services.

The Role of PMTCT Programs during the Postpartum
With the current focus of PMTCT largely on pregnancy and childbirth, insufficient attention has been given to providing long-term follow-up services for women and their children who participate in these programs. Women living in areas heavily affected by HIV are highly vulnerable to reproductive and sexual ill-health during the postpartum [10,50] and require access to quality postpartum services. Such services consist of assessment of maternal healing after delivery; evaluation for postpartum complications, which are more common among women with HIV; access to HIV-related treatment, care, and support; malaria prevention and case management, where needed;
promotion and provision of condoms; family planning counseling and contraceptive methods; promotion of sexual health; and ongoing infant feeding counseling and support [51].

Many women with HIV have an unmet need for contraception during the postpartum period [52,53]. Although HIV infection is associated with a reduction in fertility [54,55], women with HIV may be at high risk for pregnancy in the postpartum if they choose not to breastfeed or stop breastfeeding early and, therefore, have a shorter duration of amenorrhea. Ovulation may occur as soon as 4 weeks after delivery in women who do not breastfeed.

Preventing unintended pregnancies among women with HIV is an important, though neglected, component of the United Nations strategic approach to preventing HIV infection in infants [56]. Insufficient attention has been given to the relative impact of each component of this approach and to their potential for synergistic contribution. A study using cost-effectiveness modeling, based on data from actual field implementation in eight African countries, demonstrated the importance of family planning services in reducing HIV infection in infants. It estimated that reducing unintended pregnancies among women with HIV by 16% would have the equivalent impact in averting HIV infection in infants as ARV prophylaxis using single-dose NVP [34].

Postpartum care includes ongoing infant feeding counseling and support for the woman’s infant feeding choice. HIV transmission during breastfeeding reduces the overall effectiveness of efforts to prevent MTCT. However, preventing transmission during this period remains a challenge for women who are not able to refrain from breastfeeding. The current United Nations recommendations on HIV and infant feeding are that women with HIV should avoid all breastfeeding when replacement feeding is acceptable, feasible, affordable, sustainable, and safe. Otherwise, exclusive breastfeeding is recommended for the first months of life and should be discontinued as soon as is feasible [57].

Conclusions
Variances in risk for MTCT starkly illustrate global inequities. Nine years after the introduction of triple-drug ARV treatment in high-income countries, a combination of community mobilization, widespread political commitment, reductions in the price of ARV drugs, and availability of generic, fixed-dose combinations resulted in unprecedented efforts to scale up access to ARV treatment in resource-constrained settings. ARV treatment programs in resource-constrained settings have achieved similar levels of effectiveness as high-income countries, in spite of adoption of standardized approaches to ARV treatment. However, for many years, it was believed that ARV treatment in resource-constrained settings was not feasible, or cost effective. It was not until the feasibility of ARV treatment had been demonstrated in places like Brazil, in South Africa (through the Khayelitsha program), and in Cange, Haiti that scaling up access to ARV treatment occurred. Although Brazil, Europe, the United Kingdom, and the United States introduced triple-combination regimens for MTCT prophylaxis several years ago, there are concerns about the safety and feasibility of such regimens in resource-constrained settings [13••]. Compared with PMTCT programs in Brazil, Europe, and the United States, PMTCT programs in most resource-constrained settings use ARV regimens with lower levels of effectiveness and which potentially compromise a woman’s response to future ARV treatment.

In resource-constrained settings with adequate infrastructure and programmatic capacity, use of standardized long-course triple-drug regimens for PMTCT may achieve similar levels of effectiveness as seen in Brazil, Europe, and the United States. However, additional data on the safety and effectiveness of these regimens in resource-constrained settings may be needed to convince policy makers. These policy makers must balance the need for “simple” interventions in resource-constrained settings with the need for more complex highly-effective interventions which are used in relatively over-resourced settings. In achieving this balance, “cost effective” should not be a polite term for cheap, nor should “simple” really mean not very effective. As attractive and important as simple interventions are and as massive as the shortage of basic public health infrastructure is, the need for highly effective interventions in Africa is real and compelling [58].

Acknowledgments
The authors would like to thank Sanja Gohre for providing editorial assistance.

References and Recommended Reading
Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance


13. World Health Organization: Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants. Guidelines on care, treatment and support for women living with HIV/AIDS and their children in resource-constrained settings. Geneva, Switzerland: World Health Organization; 2004. These are guidelines that have been developed for the management of HIV-infected pregnant women and provide a choice of options that are available in resource poor settings.


This is an important article that documents that by using new assays to detect NVP resistance following its use in MTCT, we underestimate NVP resistance. This article is important as it may affect, hopefully, future MTCT policy in resource-poor settings.


Annex 3: Increasing the scope and intensity of interventions to prevent HIV infection in infants: best interests of women and children (Article 10)
INCREASING THE SCOPE AND INTENSITY OF INTERVENTIONS TO PREVENT HIV INFECTION IN INFANTS: BEST INTERESTS OF WOMEN AND CHILDREN

M F Chersich, MB BCh, MSc (Public Health), DTM&H
S M F Luchters, MD, MSc (Public Health)
International Centre for Reproductive Health, Mombasa, Kenya
M Temmerman, MD, MPH, PhD
International Centre for Reproductive Health, University of Gent, Belgium

This year another 460,000 children were infected with HIV in sub-Saharan Africa, signalling an ongoing failure of programmes for PMTCT of HIV and the need to revise existing strategies. Despite initial energetic promotion, in recent years PMTCT has slipped down the policy agenda and coverage of these services remains below 10% in most African countries. Overall impact of current PMTCT programmes on HIV-free survival among infants at a population level is unknown but likely to be low. In contrast, in many other settings the risk of transmission is reduced to below 2%, with near-elimination of paediatric HIV. In this paper we critique PMTCT strategies used in Africa and argue they require urgent revision. Under-utilised opportunities to prevent HIV infection in infants around childbirth and during breastfeeding are also highlighted. Interventions during childbirth and postpartum would broaden the present antenatal focus of PMTCT programmes.

Key messages:
• There is a mismatch between the HIV prevention needs of children and the quality and scope of prevention of mother-to-child transmission (PMTCT) services.
• Although near-elimination of paediatric HIV has taken place in many settings, PMTCT programmes in Africa have little impact so far.
• Given that it is in the child’s best interests to detect exposure to HIV shortly after birth and to institute preventive interventions, routine HIV testing may be justified for all infants born to women of unknown HIV status.
• HIV testing for women at child health and immunisation clinics would enable more women to benefit from knowing their status and to receive infant feeding counselling and support.

BENEFITS OF EARLY KNOWLEDGE OF HIV STATUS

HIV infection will declare itself, commonly with a severe illness that has substantial morbidity and mortality. The earlier in HIV disease that people become aware they are infected, the greater the benefit of care and treatment interventions. To prevent transmission of a communicable disease, infected individuals should be identified as soon as possible after acquisition. Timely diagnosis of HIV confers considerable benefits to the individual and the wider community by facilitating access to care and prevention interventions, and changes in behaviour that accompany knowledge of status. Within an enabling policy environment, the role of health workers is to identify early HIV disease and to maximise the benefits of knowing one’s status for the infected individual and their susceptible sexual partners and children. Nowhere is this more clearly illustrated than in PMTCT programmes.

Each encounter with a woman in maternal and child health services is an opportunity for the woman to benefit from knowing her HIV status and to prevent further transmission. While the advantages for infants in being HIV-free are implicit, the benefits for women of having an uninfected child need to be highlighted. When giving pre-test information, health care workers should ensure that women are adequately informed of the benefits of PMTCT interventions, and of the emotional and financial consequences of having an HIV-infected child. However, many opportunities to benefit from knowing HIV status are missed with the current emphasis on the individual’s right to decline testing and the potential harms associated with testing. The epidemic-long adoption of this approach has, paradoxically, undermined the individual’s access to interventions to secure their right to health and that of their sexual partners and children. After decades of over-mystifying HIV testing, the pendulum has slowly swung to principles of public health accompanied by attempts to simplify testing and counselling procedures.
Additional efforts to ensure that women directly benefit from PMTCT programmes may increase their acceptability and uptake. Renaming and remarketing of these programmes may be necessary. The name PMTCT ignores men’s role in paediatric HIV infection, and fails to acknowledge that women are more than just mothers, and require maximum benefits from an HIV diagnosis, preferably made early in their HIV disease.

DUAL STANDARDS OF CARE: THE OUTCOME GAP

Initiating antiretroviral therapy (ART) for pregnant women helps ensure that benefits of PMTCT programmes accrue to both women and infants. Though given high priority by PMTCT guidelines, ART for pregnant women with indications for treatment has been inadequately operationalised. Guidance is needed on practical aspects of developing well-functioning linkages between antenatal and ART services. For pregnant women, accelerating initiation of ART is often necessary to decrease MTCT risk. Difficulties with timely initiation of ART during pregnancy are compounded by health-seeking patterns, with women often first attending for antenatal care late in pregnancy. Measuring CD4 cell counts at the first antenatal visit appears particularly important in reducing delays.11

So far, efforts to prevent HIV infection in children have focused on providing short-course ARV regimens for MTCT prophylaxis, most commonly single-dose NVP (sd-NVP). In several African countries, studies have recently investigated the role of triple-ARV regimens used solely for MTCT prophylaxis.14-17 These regimens are given to women without indications for ART, and are stopped after childbirth (or after weaning). Such interventions bridge the gap in outcomes between infants born to women with advanced HIV disease (at substantially higher baseline risk of MTCT).

A recent study in Johannesburg showed that risk for MTCT in women who initiate ART during pregnancy is lower than in women who do not have indications for ART and receive sd-NVP.17 This demonstrates the limitations of sd-NVP – infants born to women with high CD4 cell counts had almost a threefold higher risk of HIV infection than infants born to women with advanced HIV disease (at substantially higher baseline risk of MTCT).

Several studies are investigating whether ARV drugs, given either to breastfeeding women or infants, reduce MTCT during breastfeeding.21 This offers a promising alternative for a problem that causes tremendous difficulties wherever replacement feeding is not feasible. ARV drugs have been shown to reduce MTCT during pregnancy and childbirth in randomised trials, and in observational studies to reduce HIV acquisition after sexual or occupational exposure. Evidence from randomised trials that ARV drugs reduce postpartum transmission is expected in the next years – about 14 years after demonstration that ARV drugs reduce antenatal and intrapartum transmission.

PMTCT ENTRY: THE CHILD’S BEST INTERESTS

In addition to using more effective ARV prophylaxis, to improve impact of PMTCT programmes, several interventions around childbirth and during breastfeeding warrant consideration. These interventions aim to complement and broaden the current antenatal focus of PMTCT programmes. Shortly after childbirth, identifying HIV-exposed infants born to women who have not accessed PMTCT services (either because these services are unavailable or because they declined the offer of HIV testing) would enable HIV-exposed infants to benefit from interventions to reduce their risk of acquiring HIV. Rapid HIV tests, using whole-blood specimens from heel sticks, are especially suited to testing newborns for HIV exposure. Giving ARV post-exposure prophylaxis to infants born to women who did not receive ARV drugs during pregnancy or labour has been shown to reduce MTCT in a randomised trial in Malawi22 and in South Africa.23 If ARV prophylaxis is delayed more than 2 days, it is unlikely to have any benefit.24

HIV testing is considered part of essential care around childbirth for women of unknown HIV status.11 In women who decline HIV testing, safeguarding the wellbeing of the child needs to be balanced with protecting the woman’s right to privacy. The UN Convention on Rights of the Child (CRC) provides guidance on achieving this balance, stating: ‘In all actions concerning children, whether undertaken by public or private social welfare institutions, courts of law administrative authorities or legislative bodies, the best interests of the child shall be a primary consideration’.25

South Africa is a signatory of the Convention and in 1995 ratified it, making it legally binding.26 With evidence that post-exposure prophylaxis for infants is effective, and the high mortality associated with childhood HIV infection, we argue that in the best interests of the child HIV exposure should be detected, irrespective of the mother’s wishes. Using these arguments, consistent with the CRC, the overarching priority is to identify infants exposed to HIV and to deliver interventions to reduce risk of HIV acquisition. With adoption of this policy, all infants born to women of unknown HIV status would be routinely tested for HIV shortly after childbirth.

Disadvantages of routinely testing all newborn infants may include: infringing a woman’s right to privacy and deterring women from accessing labour and delivery services. Counselling women in these circumstances would be
challenging, though essential to enable the mother–infant pair to benefit from safer infant feeding. Concerns about deterring attendance at health facilities need to be addressed. So far, inclusion of opt-out HIV testing for adults has not decreased numbers of people attending services and acceptability of such testing has been shown to be high in several reports.27-31 While these findings are reassuring, they may not reflect outcomes of routine testing of newborns. Routine testing of newborns has occurred in several states in the USA since 1999. With this policy and opt-out testing for pregnant women, HIV testing coverage is near universal.32 To our knowledge, no reports of decreased attendance at health facilities have been published.33

Essentially, a case could be made that the best interests of the infant and the infant’s right to preventive health care (article 24 of CRC)26 supersedes the woman’s need for autonomy. Further ethical and legal consideration of this scenario is necessary. It is surprising that paediatricians have not been more vociferous advocates for routine testing of newborns, well within the best interests of those they serve. Similarly, children with AIDS could argue that by failing to test them for HIV exposure, the health providers who cared for them around childbirth neglected to protect them from HIV infection and did not act in their best interests, as legally obliged. That would make a fascinating, perhaps winnable, legal test. Schuklenk and Kleinsmith go further, arguing for mandatory HIV testing for women who decide to carry the fetus to term.24 They contend that women who choose to carry a fetus to term and choose not to reduce its chances of contracting HIV constitute harm to others. The authors write: ‘choosing deliberately not to act to prevent harm when one could have acted with unreasonably high costs to oneself is comparable to similarly deliberate actions that actively produce the same amount of harm.’

CONCLUSION

In sum, while HIV infection in infants has effectively been eliminated in many settings, in Africa the potential for intervention at each service delivery-point is, so far, underutilised and of low quality. There is an inequitable mismatch between the HIV prevention needs of children and the services provided, necessitating a critical review of prevailing strategies. Despite the level of funding and attention available for HIV interventions, by measures such as coverage, outcomes and equity, PMTCT programmes have performed worse than syphilis control or ART programmes. PMTCT has fallen off the HIV bandwagon and needs to climb back on. For that to occur, stronger bolder national and international leadership is needed, reenergising the current approach with innovative strategies based firmly on public-health principles.

REFERENCES


POSTPARTUM PMTCT SERVICES

Patient-provider encounters in child health and vaccination clinics could be used to reduce MTCT. For women who have not accessed HIV testing during pregnancy or around childbirth, identifying HIV infection and supporting safer infant feeding could reduce transmission through breastfeeding, which accounts for a third to half of HIV infections in infants. Postpartum testing may be an important measure while coverage of HIV testing in antenatal clinics is being improved. Also, women who previously declined testing may reconsider their decision or form better rapport with the health worker who offers testing. Women are particularly vulnerable to HIV acquisition during pregnancy and postpartum (for reasons of biology and behaviour, such as lower condom use) and retesting of women who tested negative during pregnancy may identify recent infection. During acute HIV infection, risk of transmission to breastfeeding children34 and sexual partners is high.

Within child health clinics, postpartum PMTCT services could be built around HIV testing and counselling; infant feeding counselling and support; entry to HIV prevention, care and treatment services; as well as provision of family planning counselling and contraception. Reducing unintended pregnancies among HIV-infected women has been promoted as a key component of PMTCT strategies. Many HIV-infected women have an unmet need for family planning services, especially with shortened lactational amenorrhea due to replacement feeding or early cessation of breastfeeding. At any time during the breastfeeding period, identifying HIV infection in women or HIV exposure in infants enables them to benefit from infant feeding counselling and support for safer feeding options.


Annex 4: Efavirenz use during pregnancy and for women of child-bearing potential (Article 11)
Efavirenz use during pregnancy and for women of child-bearing potential
Matthew F Chersich*1, Michael F Urban2, Francois WD Venter3, Tina Wessels4, Amanda Krause5, Glenda E Gray6, Stanley Luchters7 and Dennis L Viljoen8

Address: 1Epidemiologist and Statistician, International Centre for Reproductive Health, Mombasa, Kenya, 2Fellow in Medical Genetics, Department of Human Genetics, National Health Laboratory Service and University of Witwatersrand, Johannesburg, South Africa, 3Clinical Director, Esselen Street Project, Reproductive Health and HIV Research Unit, University of the Witwatersrand Johannesburg, South Africa, 4Genetic counselor, Genetic Counselling Clinic, National Health Laboratory Service & University of the Witwatersrand, Johannesburg, South Africa, 5Professor, Department of Human Genetics, National Health Laboratory Service and University of Witwatersrand, Johannesburg, South Africa, 6Director, Perinatal HIV Research Unit, University of Witwatersrand, Johannesburg, South Africa, 7Field Director, International Centre for Reproductive Health, Mombasa, Kenya and 8Professor and Head of Department of Human Genetics, National Health Laboratory Service and University of Witwatersrand, Johannesburg, South Africa

Email: Matthew F Chersich* - chersich@doctors.org.uk; Michael F Urban - mike.urban@nhls.ac.za; Francois WD Venter - f.venter@rhrujhb.co.za; Tina Wessels - tina.wessels@nhls.ac.za; Amanda Krause - amanda.krause@nhls.ac.za; Glenda E Gray - gray@pixie.co.za; Stanley Luchters - stanley.luchters@icrh.org; Dennis L Viljoen - lucy.mashigo@nhls.ac.za

* Corresponding author

Abstract

Background: Efavirenz is the preferred non-nucleoside reverse transcriptase inhibitor for first-line antiretroviral treatment in many countries. For women of childbearing potential, advantages of efavirenz are balanced by concerns that it is teratogenic. This paper reviews evidence of efavirenz teratogenicity and considers implications in common clinical scenarios.

Findings: Concerns of efavirenz-induced fetal effects stem from animal studies, although the predictive value of animal data for humans is unknown. Four retrospective cases of central nervous system birth defects in infants with first trimester exposure to efavirenz have been interpreted as being consistent with animal data. In a prospective pregnancy registry, which is subject to fewer potential biases, no increase was detected in overall risk of birth defects following exposure to efavirenz in the first-trimester.

Discussion: For women planning a pregnancy or not using contraception, efavirenz should be avoided if alternatives are available. According to WHO guidelines for resource-constrained settings, benefits of efavirenz are likely to outweigh risks for women using contraception. Women who become pregnant while receiving efavirenz often consider drug substitution or temporarily suspending treatment. Both options have substantial risks for maternal and fetal health which, we argue, appear unjustified after the critical period of organogenesis (3–8 weeks post-conception). Efavirenz-based triple regimens, initiated after the first trimester of pregnancy and discontinued after childbirth, are potentially an important alternative for reducing mother-to-child transmission in pregnant women who do not yet require antiretroviral treatment.

Conclusion: Current recommendations for care for women who become pregnant while receiving efavirenz may need to be re-considered, particularly in settings with limited alternative drugs and laboratory monitoring. With current data limitations, additional adequately powered prospective studies are needed.
Background

An increasing number of women worldwide are benefiting from expanding access to antiretroviral treatment, allaying initial concerns that women would have inequitable access to treatment. In sub-Saharan Africa nearly six out of ten adults receiving antiretroviral (ARV) treatment are women, an equitable distribution as more women are infected than men [1]. A substantial proportion of these women will plan to conceive or have unintended pregnancies [2]. This raises concerns of potential ARV-induced fetal effects. Such concerns often require women and their clinicians to make trade-offs between reproductive and treatment choices.

Efavirenz (EFV) is the preferred non-nucleoside reverse transcriptase inhibitor (NNRTI) in many countries [3-5] as it is less hepatotoxic than nevirapine (NVP), does not require dose adjustment and can be used concomitantly with tuberculosis treatment. However, for women of reproductive potential these advantages are balanced by concerns that EFV increases risk for birth defects.

This paper reviews evidence of EFV teratogenicity and considers implications for common clinical scenarios.

Evidence of efavirenz teratogenesis

Pregnant women are actively excluded from clinical trials during drug development. Assessment of drug safety in pregnancy is therefore based on less rigorous evidence, such as reproductive toxicology studies in small mammals and non-human primates, retrospective case reports and pregnancy registry data.

Concerns of EFV-induced fetal effects began after a trial with cynomolgus monkeys [6]. In the trial, monkeys were exposed to EFV throughout pregnancy at plasma drug concentrations similar to humans receiving 600 mg EFV per day. No major congenital malformations were observed in 20 control infant monkeys, but 3 of 20 EFV-exposed infants had significant abnormalities [6]. Anencephaly and unilateral anophthalmia were observed in one monkey infant, microphthalmia in another and cleft palate in a third. An increase in fetal resorptions was observed in rats given EFV, but no significant teratologic findings were reported in studies with pregnant rabbits treated with EFV [7]. Thus far in humans, four retrospective cases of central nervous system (CNS) defects in infants with first trimester exposure to EFV have been reported (three infants with meningomyelocele and one with a Dandy-Walker malformation) [7-9].

The predictive value of animal studies for humans is unknown; making it difficult for health workers to translate animal risks into an assessment of teratogenic risk in their patients. Many associations have ultimately been shown to be false positive in humans and in some instances drug testing in animals has been negative and the drug subsequently shown to be teratogenic in humans [10]. Of approximately 1 200 animal teratogens, only about 30 are known to be teratogenic in humans [11]. However, the EFV animal studies are particular concerning as abnormalities were observed in primates at drug levels comparable to therapeutic ranges in humans and positive findings were detected in more than one animal species.

The retrospective case reports in humans are difficult to interpret as neural tube defects are among the commonest birth defects (occurring in about 1 in 1000 pregnancies, with marked ethnic and geographic variation in prevalence [12]). A few case reports can establish a strong association if a drug is taken by a relatively small number of women, causes a characteristic or obvious pattern of abnormalities (as is the case with most teratogens, for example thalidomide, warfarin and retinoic acid), or results in a rare malformation [13]. However, reports of common defects may reflect either background occurrence of these malformations in the general population or an increased risk for drug-induced birth defects. Moreover, without knowing the denominator (the total number of infants exposed to EFV in the first trimester of pregnancy), the relative risk of exposure is unknown.

Studies with prospectively followed pregnancies are subject to fewer biases than retrospective case reports. Enrollment in these studies occurs before the outcome of pregnancy is known and prior to tests that could provide knowledge of pregnancy outcome, such as antenatal ultrasound or alpha-fetoprotein measurement. These studies have been used to support a change in the United States Federal Drug Administration (FDA) pregnancy risk category, for example acyclovir changed to category B: "Positive animal data but adequate and well-controlled studies in humans failed to show a fetal risk".

In an prospective antiretroviral pregnancy registry based in the United States, birth defects were observed in 5 of 228 (2.2%; 95% CI: 0.7%-5.1%) live-born infants following first-trimester exposure to EFV and in 1 of 14 live births with second- or third-trimester exposure [14]. This prevalence of birth defects is comparable to the United States general population (3.1%; 95% CI: 3.1%-3.2%) [15]. The European Collaborative Study also collects data on pregnancy outcomes following ARV exposure during pregnancy. Thus far, 19 women in this study have become pregnant while receiving EFV-containing regimens, no congenital abnormalities were reported (0%; 95% CI: 0%-17.6%) [16]. In contrast to findings of the United States registry and European Collaborative Study, in a French cohort three of ten infants born to women who became
pregnant while receiving EFV had birth anomalies [17]. None of the prospectively reported anomalies in the United States antiretroviral pregnancy registry or the French cohort were similar to those in the animal study or case reports.

A sufficient number of live births have been monitored in the United States antiretroviral pregnancy registry to detect a two-fold increase in overall risk for birth defects following first-trimester exposure to EFV; no such increase has been detected [14,18]. Several features of the registry limit the ability to draw definitive conclusions. Of eligible woman-infant pairs, only about 15% are enrolled [14]. It is unknown whether those not enrolled are at higher or lower risk of birth defects. Moreover, ascertainment of birth defects is not standardised, with varying use of diagnostic tests and level of expertise of reporting clinicians. Nevertheless, this evidence does provide some assurance that EFV is not a major human teratogen [19]. In sum, these findings indicate that any overall increase in risk for birth defects following exposure to EFV is likely to be low. However, larger studies are required to exclude an increased risk for specific congenital anomalies such as neural tube defects; current prospective studies have inadequate power to draw conclusions about the risk of neural tube defects [19].

Efavirenz use in women of childbearing potential

In the FDA classification EFV is a category D drug: "Positive evidence of human fetal risk. Nevertheless, potential benefits may outweigh the potential risks" [20]. This disclaimer is understandable from a medicolegal standpoint, but provides no practical information for deciding whether potential benefits to a woman outweigh risks to a fetus or how to respond to inadvertent fetal exposures [21]. Furthermore, several critics argue that drugs are commonly assigned high-risk FDA categories based on limited information [13,21].

Two commonly used ARV treatment guidelines, developed by WHO and the United States Public Health Service Task Force, both recommend that EFV be avoided among women trying to conceive or not using contraception [22,23]. However, they differ for women using contraception. WHO guidelines indicate that EFV is a viable option for women using effective contraception [23], whereas guidelines from the United States recommend alternatives to EFV should be strongly considered because of known failure rates of contraception [22]. These guidelines target different settings with considerable variation in availability of ARV treatment options, which may account for differing recommendations.

Based on advantages of EFV and that existing data indicates any increase in overall risk for birth defects is likely to be small, withholding EFV-based treatment from women using contraception in settings with limited ARV options is likely to cause more harm than its provision. Further, safety advantages of EFV are particularly important in many high HIV burden settings with limited capacity for clinical and laboratory monitoring.

Withholding such treatment is contrary to principles guiding use of other drugs essential for a woman’s health such as antiepileptic medication [24,25]. Much evidence indicates that carbamazepine and sodium valproate increase risk for neural tube defects [26,27], but in view of the need for effective control of seizures, recommendations are that in almost all cases, the optimum drug for controlling seizures should be used [24,25]. Principles guiding care for women with epilepsy share commonalities with those guiding ARV treatment decisions and could assist policy makers in selecting ARV regimens for women. This comparison applies particularly in settings with limited alternative drugs, while is less relevant to high-income countries with increased ARV options.

Analogous to antiepileptic medication, benefits of ARV treatment accrue both to the woman and to her fetus, and are likely to outweigh potential harm to the fetus. ARV treatment for women reduces mortality and morbidity, is the most effective method of preventing HIV transmission to the infant, and by securing the health of women, improves child survival [23,28]. On the basis of available evidence, several authors argue that decisions to initiate ARV treatment should be based primarily on a woman’s need for such treatment [23,29,30].

Risk of unintended pregnancy is low with correct and consistent use of contraception [31]. However, evidence that EFV increases bioavailability of steroid hormones in hormonal contraceptives must be considered when selecting a contraceptive method [32]. Increased bioavailability may increase risk for estrogen- or progestin-related side effects. Alternative contraceptive methods with low typical-use failure rates need to be considered [31].

Women receiving EFV-containing regimens may later plan to become pregnant or have an unintended pregnancy [33]. For women who plan conception, substitution with NVP or a PI needs to be considered, although risks and benefits of substitution should be taken into account (Box 1). Drug substitution is best undertaken prior to pregnancy.

Some studies suggest teratogenic activity of drugs that increase risk for neural tube defects is mediated by interference with folic acid metabolism and that folic acid supplementation protects against teratogenic effects of these drugs [34,35]. Although potential mechanisms of EFV-
induced fetal effects are unknown, folic acid supplementation is important for women receiving EFV as it is for other women of childbearing age.

**Use of efavirenz during pregnancy**

Pregnancy recognition often occurs after the critical period of organogenesis (3–8 weeks post-conception). Development and closure of the neural tube are normally complete by 28 days post-conception, approximately the same gestation when the first symptoms of pregnancy occur. Changes to EFV-based regimens after four weeks post-conception will not reduce the risk of neural tube defects and after eight weeks will have minimal effect on risk for other structural malformations. There are theoretical risks that exposure to EFV or other ARV drugs in the second and third trimester of pregnancy could affect neurodevelopment of infants. However, in the absence of evidence from neurobehavioral development studies, effects of exposure to any ARV drug after the period of organogenesis remain speculative.

Women who realise they are pregnant early in gestation can consider substituting EFV with NVP or a PI, or temporarily suspending treatment. Substituting EFV with another ARV drug is commonly considered, but is not without risk [23] (Box 1).

**Box 1. Factors to consider when substituting efavirenz in pregnant women:**

- Following substitution, women have to get used to a new ARV regimen, with different side-effects, pill counts and dosing times;
- Treatment-related increases in CD4 cell count may have occurred. Substituting EFV with NVP in women with treatment-related CD4 cell restoration to levels above 250 cells/mm³ could, in theory, place them at increased risk for NVP-associated hepatotoxicity;
- In many settings alternative ARV drugs are limited by availability, cost or co-existing conditions; and
- Substituting EFV with other drugs may limit the effectiveness of future regimens. Pharmacokinetic evidence suggests that when substituting EFV with NVP, women should commence on 200 mg twice a day, as dose escalation of NVP is associated with sub-therapeutic NVP levels in these individuals [36].

Temporarily suspending ARV treatment also has several risks. Suspending ARV treatment at recognition of pregnancy has been associated with significant viral rebound and CD4 cell count decline [37], potentially increasing risk for HIV transmission to the fetus and compromising a woman’s health. In addition, EFV has a longer half-life than nucleoside analogue reverse transcriptase inhibitor (NRTI) drugs resulting in functional monotherapy, which increases risk for viral resistance [38,39]. Many experts recommend continuing the NRTI backbone for a period of time after NNRTI discontinuation [5,22]. Although evidence is accumulating [40,41], the optimal interval between stopping NNRTI and other ARV drugs is unknown.

Women who become pregnant while receiving EFV require counselling and full information on potential risks to the fetus. High-quality counselling entails non-directive individualised discussion of options and support for a woman to make an autonomous decision about use of ARV drugs or termination of pregnancy, to the extent allowed by law [42]. It is important to note that an exaggerated perception of fetal risk can result in a woman terminating an otherwise wanted pregnancy [13]. Such decisions are complex and underpinned by biomedical as well as socio-cultural considerations.

Women who become pregnant while receiving EFV may benefit from screening for CNS abnormalities with a fetal anomaly ultrasound or maternal serum alpha-fetoprotein test [43]. These non-invasive tests are preferable as amniocentesis has been associated with increased risk for HIV infection in infants [44].

**Efavirenz for preventing HIV infection in infants**

Advocacy is mounting for prevention of mother-to-child transmission (MTCT) programmes in resource-constrained settings to introduce more effective ARV prophylaxis than single-dose (maternal and infant) NVP [45,46]. Evidence is accumulating of the feasibility of providing triple-ARV regimens for prophylaxis in resource-constrained settings [47,48]. In Brazil, Europe and the United States, for a woman without indications for ARV treatment, triple-ARV prophylaxis is provided during pregnancy and discontinued after childbirth [22,49,50], and the risk of transmitting HIV to her infant is less than 2% [51,52]. Triple-ARV prophylaxis is used for almost all pregnant women with HIV in these settings. For example, United States MTCT-prevention guidelines state: “Standard combination antiretroviral regimens for treatment of HIV-1 infection should be discussed and offered to all pregnant women with HIV-1 infection regardless of viral load; they are recommended for all pregnant women with HIV-1 RNA levels greater than 1000 copies/mL” [22].

MTCT-prophylaxis regimens are initiated after the first trimester of pregnancy, hence past the period of organogenesis. An EFV-containing triple ARV regimen could be a useful alternative for MTCT-prevention programmes that adopt similar strategies to Brazil, the United States and...
Europe. Based on WHO guidelines, EFV-based triple regimens are a viable option for MTCT prophylaxis [23]. Alternative triple regimens for pregnant women without indications for ARV treatment pose several difficulties: women with a high CD4 cell count have an increased risk for hepatotoxicity with NVP; and protease inhibitor containing regimens have a higher pill burden, more complex side-effect profile and higher cost.

Conclusion

Existing ARV treatment guidelines do not adequately address the complex clinical scenarios that women and clinicians increasingly face. This has compounded difficulties in making the inevitable trade-offs between reproductive and treatment choices. Based on existing evidence we have outlined general considerations in these scenarios. In particular, as described in current WHO guidelines for resource-constrained settings, the benefits of EFV are likely to outweigh risks for women using contraception. However, we argue that in women who become pregnant while receiving EFV, a decision to temporarily suspend treatment or to substitute EFV after the period of organogenesis is unavoidable, especially in settings with limited alternative drugs. Moreover, given limitations of existing data, additional evidence is needed to assist individual patients to balance risks and benefits.

Several research centres in Africa have the capacity to recruit an adequate number of exposed woman-infant pairs and to ensure high rates of cohort retention and accurate ascertainment of pregnancy outcomes. With the rapid increase in women receiving ARV treatment in Africa and as EFV is the preferred NNRTI in many settings, these centres are ideally situated to establish an adequately powered ARV registry. Additional scientifically valid data and estimates of relative risk would provide more detailed powered ARV registry. Additional scientifically valid data and estimates of relative risk would provide more detailed scientifically valid data and estimates of relative risk would provide more detailed scientifically valid data and estimates of relative risk.

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

MC conceived of the review and with MU drafted the manuscript. WW wrote sections of the review. TW, AK, GG, SL and DI made substantial contributions to content of the paper.

References


30. Mintsch H, Augenbraun M: 


34. Biale Y, Lewenthal H:


41. McIntyre J, Martinson N, Investigators for the Trial 1413: Addition to short course combivir (CBV) to single dose zidovudine (sdNVP) for prevention of mother-to-child transmission (MTCT) of HIV-1 can significantly decrease the subsequent development of maternal NNRTI-resistant virus. Abstract LoBr09: July 11-16; Bangkok, Thailand. 2004.


48. van der Merwe K, Coovadia A, Technau K, Malan E, Barry G: A model for providing efficient care of pregnant women requiring HAART. 7-10 June; Durban, South Africa.


Annex 5: Dandy-Walker variant in an infant exposed to antiretroviral medication (Article 12)
Nurses reported that they most valued the system when
the feedback they received was prompt and consistent, and
when volunteers worked regularly and were well known to the
nurses. It would seem to be important, therefore, to embed a
supervision, management and support system in a community-
based organisation in order to ensure that volunteers continue
to operate the system on a regular basis. This support could
be offered by professionals and community volunteer co-
ordinators working together.

It is now necessary to subject volunteer mental health
outreach systems that integrate community volunteer health
workers into mental health care systems to rigorous evaluation.
Such studies should include assessment of patients’ clinical
outcomes, long-term retention in services, costs, community
impact and the sustainable management of volunteer
programmes.

This project was supported by a grant from the British Council.
We would like to thank all the community volunteers who
participated in this project, especially Luvuyo Horatius Maqakaza
and Avonke Nikelo, who were responsible for co-ordinating the
community volunteer system.

References
zza/docs/rg/2004/sp0167.html (last accessed 20 October 2006).
schizophrenia one year after hospital discharge. (PM 1991, 10: 1022-1024.
4. Stark LL, Santos AR. Assertive Community Treatment for Persons with Severe Mental Illness. New
5. Tshabalala-Msimang M. Speech by the Minister of Health, Dr Manto Tshabalala-Msimang
zza/docs/rg/2004/sp0228.html (last accessed 20 October 2006).
6. Bradshaw T, Marks H, Richards N. Developing mental health education for health volunteers

Dandy-Walker variant in an infant prenatally exposed to
antiretroviral medication

To the Editor: We report a case of Dandy-Walker variant
(DWV) in the infant of a 35-year-old woman who received
treatment for human immunodeficiency virus type 1 (HIV)
and tuberculosis. She received stavudine (D4T), lamivudine
(3TC), nevirapine and cotrimoxazole throughout pregnancy,
and isoniazid, rifampicin, pyrazinamide and ethambutol from
before pregnancy until 29 weeks’ gestation, when DWV was
detected on antenatal ultrasound. She had no history of genetic
disorders, consanguinity, and alcohol or recreational drug use.
Ammnioncentesis revealed a normal male karyotype. Serology
for cytomegalovirus and toxoplasmosis did not indicate
recent infection. The infant was full-term and appropriate
for gestational age, with a normal head circumference, no
dysmorphism, and no clinical features of HIV infection.

Cranial ultrasound confirmed the presence of DWV and mild
ventriculomegaly.

DWV is part of a continuum of rare developmental
abnormalities of the posterior brain fossa. It includes cystic
dilatation of the fourth ventricle and partial agenesis of
the cerebellar vermis. Only in a minority of cases is there a
known cause, such as a chromosome abnormality or other
genetic syndrome, or teratogen – especially alcohol. The
developmental mechanism is unknown but relates to abnormal
hindbrain development at 7 - 8 weeks’ gestation. 1 Its prognosis
varies from normality to severe neurodevelopmental delay
with hydrocephalus. 2

The question arises as to whether the reported DWV
represents a teratogenic effect of one or more of the maternal
medications. We highlight deficiencies in the existing evidence.

The regulatory framework for assessing drug safety has not
promoted optimal collection of information on teratogenicity.
The most important authority regulating registration of new
drugs is the United States Food and Drug Administration
(FDA), from which other national registering agencies often
take a lead. The FDA provides for assessment of drugs prior
to approval for marketing and for post-marketing adverse
event reporting. As pregnant women are not included in
human clinical trials prior to FDA approval, assessment of
teratogenicity relies heavily on animal studies (that cannot give definitive information regarding risk in humans) and post-marketing surveillance. The post-marketing surveillance system was recently strongly criticised, particularly its over-reliance on passive surveillance and retrospective data, and poor enforcement.

Teratogenicity data for antiretrovirals (ARVs) is better than for most drugs because an Antiretroviral Pregnancy Registry aims to obtain prospective information. Although aiming to collect data worldwide, the registry suffers from substantial under-reporting, containing only 15% of US exposures and, so far, only about 50 ARV-exposed pregnancies in South Africa. Ascertainment of birth defects is also not standardised, with varying use of diagnostic tests and level of expertise of reporting clinicians. A further problem in assessing teratogenicity data is the complexity of collecting information on drug combinations. Whether combination therapy increases the risk of birth defects is unclear, but one study has raised this possibility for the combination of ARVs and cotrimoxazole.

Teratogenicity data collected elsewhere may not hold true for South Africans. An example of this is the unusually high rates of fetal alcohol syndrome in South Africa. This is not easily explained by alcohol consumption patterns, and aggravating factors related to poor socio-economic status have been implicated.

Regarding ARVs, most evidence for teratogenicity exists for efavirenz, which our patient did not receive. Efavirenz is an FDA category D drug, i.e. ‘Evidence of human fetal risk exists, but benefits may outweigh risks in certain situations’, owing to concerns that it may cause birth defects of the central nervous system, based on animal data and four retrospective case reports, including one infant with Dandy-Walker syndrome. The magnitude of risk with first-trimester exposure to efavirenz is unknown, and the four case reports may reflect background rates of birth defects. Prospective data, collected in the Antiretroviral Pregnancy Registry, indicates that the overall increased risk for birth defects among efavirenz-exposed infants is low: the rate of birth defects among infants with first-trimester efavirenz exposure was 2.4% (6 of 225 infants; 95% CI = 0.9 - 0.1%), compared with an expected rate of 3.1% (the background rate of congenital anomalies detectable at birth).

Our case of DWV is an infant prenatally exposed to a drug combination including ARVs, but not efavirenz. We highlight the limited nature of information available to support the fears regarding the teratogenicity of efavirenz, and the converse lack of concern regarding other combinations of ARVs and other drugs used in HIV-infected individuals. Although we support current guidelines to avoid efavirenz in reproductive-age women not using contraception, the evidence indicates a low risk to an inadvertently exposed fetus and does not justify pregnancy termination based on the possible risk of teratogenesis. A fetal anomaly ultrasound scan at 18 - 24 weeks’ gestation is recommended, and genetic counselling is advisable for women who are anxious or want further information. In view of the limited available information and the large numbers of reproductive-age women initiating highly active ARV therapy, there is an opportunity and a need to systematically collect local data.

References

References


Accessed: 15 September2007


programme in rural Malawi: scaling-up requires a different way of acting. 
*Trop Med Int Health* 2005,10:1242-1250.


114. Chersich MF, Rose I, Urban M, Gray G. Nevirapine: should it be self-administered or administered by hospital staff? Oral presentation- 21st conference Priorities in Perinatal Care in Southern Africa Fish River Sun, Eastern Cape, South Africa, 5-8 March 2002


164. Coetzee D, Hilderbrand K, Boulle A, Draper B, Abdullah F, Goemaere E. Effectiveness of the first district-wide programme for the prevention of


