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Preventing mother-to-child transmission of HIV

An evaluation of PMTCT and follow-up infant HIV testing in KwaZulu-Natal, South Africa

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by
Juliana Chen
2010

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ABSTRACT

AN EVALUATION OF PMTCT AND FOLLOW-UP INFANT HIV TESTING IN KWAZULU-NATAL, SOUTH AFRICA. Juliana Chen. Edendale Hospital, Pietermaritzburg, KwaZulu-Natal, South Africa. (Sponsored by Brian Forsyth, Department of Pediatrics, Yale University School of Medicine).

Background: The primary cause of pediatric HIV infection is mother-to-child transmission, which can be reduced significantly by interventions that include highly active antiretroviral therapy (HAART) and antiretroviral (ARV) prophylaxis. Prevention of mother-to-child transmission (PMTCT) programs serve as critical entry points for the provision of HIV testing and treatment, though often remain poorly implemented and underutilized. Such programs are especially critical in resource-limited settings that have a heavy burden of HIV infection.

Methods: Data were collected via retrospective medical record review of pregnant women who accessed antenatal services at a public sector PMTCT program from December 2006 to June 2007. A supplementary review of pregnant women with no prior history of HIV testing was conducted to evaluate HIV testing at delivery. Finally, an analysis of infant PCR testing was conducted to assess rates of follow-up testing among HIV-exposed infants.

Results: High rates of testing reveal that half of women presenting for antenatal care were HIV positive. Rates of repeat testing during pregnancy and testing at delivery were low. There were high rates of ARV prophylaxis among mothers and infants, though less than two-thirds of eligible mothers initiated HAART. At most, only half of HIV-exposed infants returned for HIV testing by twelve weeks of age. Of those tested, over 16% were found to be HIV positive.

Discussion: Despite significant enrollment in PMTCT and high acceptance of HIV testing in pregnancy, gaps in service delivery and/or failures in documentation result in multiple missed opportunities. An inability to link mother-infant pairs, poor follow-up of HIV-exposed infants, and a lack of coordination of services further limit overall PMTCT program effectiveness. More effective regimens will have limited success without fundamental improvements in service delivery. Improved training and protocols for care, as well as the development of uniform data collection tools, are critical to overall PMTCT program effectiveness.

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INTRODUCTION

Background

Worldwide, there are an estimated 33.4 million adults and 2.1 million children living with HIV. Africa remains the global epicenter of this pandemic, where the burden of HIV is borne disproportionately in sub-Saharan Africa. [1] An estimated 67% of the world's HIV-infected individuals live in sub-Saharan Africa, with an estimated 5.7 million persons infected in South Africa alone. [2] Globally, half of all people living with HIV are women, and in sub-Saharan Africa, HIV/AIDS is the leading cause of mortality among women of reproductive age. [1] In South Africa, young women are four times more likely to be HIV-infected than young men, and among pregnant women, the prevalence remains highest in the province of KwaZulu-Natal (KZN). [3]

The primary cause of pediatric HIV infections is mother-to-child transmission (MTCT). More than 1.5 million HIV-positive women become pregnant each year. [1] In 2008, an estimated 430,000 children worldwide were newly infected with HIV, [1] and an estimated 900 children die each day from AIDS-related illnesses. [2] Pediatric HIV infection occurs almost exclusively through MTCT, with an estimated 90% of these infections occurring in sub-Saharan Africa. [1-2] The mortality risk in HIV-infected children in South Africa is twelve times that of uninfected children, [4] and this increased mortality has reversed decades of improvement in child survival rates. [5] Without antiretroviral (ARV) treatment, it is estimated that one in five children vertically infected with HIV will progress to AIDS or death within the first year of life. [6-7]

Prevention of mother-to-child transmission (PMTCT) initiatives are critical in the fight against pediatric HIV infection. [8] As defined by UNAIDS, the strategic approach to preventing pediatric HIV infection involves four components: 1) primary prevention of HIV infection; 2) prevention of unintended pregnancies among women living with HIV; 3) prevention

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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. [2] While all of these components are critical, current PMTCT interventions target especially the prevention of mother-to-child transmission of HIV. Despite international focus on such efforts, coverage remains low in most resource-limited settings. In Africa, PMTCT programs in 13 countries reach less than 3% of HIV-infected women, and an estimated 35-59% of HIV-infected children will die by their second birthday. [9] In 2001, the UN General Assembly set a global target of reducing the proportion of infants infected with HIV by 20% by 2005 and 50% by 2010, [10] though to date, progress has been slow and these targets are far from being reached. [2, 11]

Preventing MTCT

Mother-to-child transmission of HIV can occur during pregnancy, labor and delivery, or through breastfeeding. [12-13] In the absence of any intervention, the risk of MTCT has been estimated to be between 15-25% in non-breastfeeding populations and as high as 25-48% in breastfeeding populations. [14] This risk can be reduced significantly by interventions that include highly active antiretroviral therapy (HAART) and ARV prophylaxis given to women during pregnancy and labor and to the infant in the first weeks of life. Delivery by caesarean section (prior to the onset of labor) and complete avoidance of breastfeeding have also been found to be successful in reducing vertical transmission. [15-18] Using these interventions, in resource-rich settings, mother-to-child HIV transmission rates have been decreased to as low as 1-2%. [13, 19-20]

Given limitations of caesarean delivery and avoidance of breastfeeding, global efforts to reduce mother-to-child transmission of HIV have relied on the use of ARV drugs. In many resource-limited settings, elective caesarean delivery is seldom feasible because of limited availability, cost and the risk of complications. [21] In addition, though breastfeeding is an important contributing factor to mother-to-child HIV transmission, it is often neither acceptable

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nor safe for mothers to refrain from breastfeeding; [22] in resource-limited settings, the use of formula feeding has further been shown to increase the risk of morbidity and mortality in children from other causes. [23] Early mixed feeding and breastfeeding beyond six months have similarly been shown to increase the risk of MTCT. [24] Various studies have demonstrated the relative safety of exclusive breastfeeding and its ability to improve child survival. [25-27] As a result, the World Health Organization (WHO) recommends exclusive replacement (formula) feeding only when it is "safe, feasible, acceptable, accessible and sustainable;" otherwise, exclusive breastfeeding should be promoted. [28-29] In resource-limited settings such as KZN, where HIV prevalence is extremely high, a policy of exclusive breastfeeding for the first six months, irrespective of maternal HIV status, is promoted.

It is widely known that HAART regimens and ARV prophylaxis have the capacity to significantly reduce HIV transmission rates. [30] In 1994, the landmark Pediatric AIDS Clinical Trials group (PACTG) protocol 076 demonstrated that long-course zidovudine (AZT) prophylaxis given early in pregnancy and during delivery to the mother and for six weeks to the infant reduced the risk of MTCT from 25% to 8%. [31] Subsequent trials in Thailand [32] and West Africa [33-34] demonstrated that short-course AZT regimens started later in pregnancy could also be effective at reducing vertical transmission. Since that time, there have been numerous trials evaluating various combination regimens [35-38] and regimens based on single-dose nevirapine (NVP). Notably, the HIVNET 012 trial demonstrated that a single-dose of NVP given to the mother at the onset of labor and to the baby after delivery lowered the risk of MTCT by nearly 50%. [36, 39] The combination–the addition of a maternal and infant NVP dose to short-course antenatal AZT–can further reduce vertical transmission rates to approximately 5%, a lower rate that that achieved by either AZT or single-dose NVP alone. [40-42] Even beginning as late as the third trimester of pregnancy, the use of HAART can reduce the risk of MTCT to 2-4%. [16-17] Given their effectiveness, HAART-based regimens have been adopted in resource-rich settings, as well as in many resource-limited settings with a heavy burden of HIV. [43-44]

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In resource-limited settings, HAART is recommended in HIV-positive pregnant women who need treatment for their own health. According to the WHO, all HIV-positive adults, including pregnant women, should be initiated on lifelong HAART. Per guidelines current at the time of the study, pregnant women who met HAART eligibility criteria included: 1) all pregnant women in clinical stage 4 irrespective of CD4 count; 2) pregnant women in clinical stage 3, with CD4 < 350 cells/mm3 count, or if CD4 count is not available, all pregnant women in stage 3; and 3) pregnant women in clinical stage 1 or 2 with CD4 < 200 cells/mm3. [8] Treating eligible pregnant women with HAART reduces maternal mortality and morbidity, but also dramatically decreases the risk of vertical transmission. HIV-positive pregnant women who do not meet clinical and immunologic eligibility criteria for HAART should receive short-course ARV prophylaxis to prevent MTCT. [8] In most resource limited settings worldwide, including South Africa, the most commonly used ARV prophylaxis is single-dose NVP. [45]

Despite the efficacy of HAART and concerns over viral resistance, single-dose NVP has been widely used as ARV prophylaxis around the world. It is well established that given its long half-life, the use of single-dose NVP can lead to viral resistance mutations in mothers and infants. [46-47] It has been estimated that NVP resistance may develop in up to 20% of mothers, [48] and resistance has been found in some mothers and infants following only one dose of NVP. [49] Resistance is of particular concern as HAART regimens based on NVP are recommended as first-line antiretroviral therapy in resource-limited settings by the WHO. [8, 50] Due to such concerns, WHO guidelines at the time of this study stipulated that single-dose NVP should be used at a minimum, while programs work towards the capacity to deliver more effective treatment regimens. [8] However, in resource-limited settings including South Africa, NVP-based regimens have remained popular given their efficacy, low cost and ease of use. Though not as effective as HAART, NVP has demonstrated success at preventing perinatal transmission of HIV, with transmission rates of 10-15%. [39, 51-52]

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The Need for Early Intervention

Increased childhood mortality rates due to HIV have reversed previous global gains in child survival. [2, 53] An estimated 15-20% of HIV-infected infants will rapidly progress to AIDS or death in the first year of life, [6-7] and without antiretroviral treatment, most HIV-infected children will die before their fifth birthday. [54-55] Various studies examining the extent of the impact of HIV on childhood mortality rates have found a profound effect. Some studies report that HIV-infected children are three to four times more likely to die than children born to HIV-negative mothers, and this increased mortality risk has been observed to continue throughout the childhood years. [4, 56-59] Little et al. found that vertically-infected infants have a four-fold increase in mortality by the age of two. [60] Newell et al. used data from seven major clinical trials conducted in sub-Saharan Africa to perform a combined analysis of mortality data in infants born to HIV-infected mothers. Mortality in these children was approximately nine times greater than that of uninfected children. Approximately one-third of infants had died by age one and more than half had died by age two, compared with 5% and 7% of uninfected children. [4]

Identification and treatment of HIV-infected women during pregnancy is crucial. Though the relative contribution of each mode of MTCT–namely, during pregnancy, during delivery and through breastfeeding–has been difficult to quantify, it is generally accepted that most MTCT occurs in late pregnancy and during delivery. A study by Zijenah et al. found that over half of transmission events in the first six months of life occurred in the intrapartum period, and over 75% of transmission events occurred either in utero or in the intrapartum period. [61] Kourtis et al. found that half of MTCT occurs in the days prior to delivery and one third occurs during delivery; early in utero transmission events were infrequent. [62] A study by Newell et al. further found that infants who were infected in utero or during delivery were at higher risk of death within 12 or 24 months than infants who acquired infection through breastfeeding. [4]

Maternal treatment in pregnancy decreases the risk of MTCT associated with advanced maternal HIV disease. Worldwide, an estimated 15-25% of HIV-positive pregnant

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women have sufficiently advanced disease that would qualify them for HAART. [63] The benefits of HAART are well established. Effective drug treatment can result in a rapid decrease in viral load and a gradual increase in CD4 count, with partial correction of many other HIV-related immune dysfunctions. If initiated, HAART treatment will lead not only to improved maternal health, but will also reduce the risk of MTCT. [64] However, most women eligible for HAART are not being identified and treated. This is concerning for a pregnant woman's own health status, but additionally concerning given the higher rates of perinatal transmission among infants born to HIV-infected mothers with advanced disease. [65] Even among HIV-infected pregnant women without advanced disease, various studies have demonstrated the higher risk of perinatal transmission associated with high maternal viral load. [12, 65-67] In a study by Dickover et al., HIV-positive mothers who transmitted HIV infection to their infants were more likely to have plasma HIV RNA levels > 50,000 copies/mL at delivery than non-transmitting mothers. [66] In a study by Thea et al., HIV-positive mothers with measurable viral load were found to be six times more likely to transmit HIV to their infants than HIV-positive mothers with undetectable viral load. [67] Similarly, other studies have demonstrated a higher risk of MTCT with low maternal CD4 count. [12, 61, 68-69]

Early identification of HIV-infected infants at risk for rapid disease progression is critical. HIV-infected infants born to HIV-positive mothers with advanced disease are at increased risk for rapid disease progression. [7, 54, 70-71] Blanche et al. found increased risk of opportunistic infections or encephalopathy in the first 18 months of life among HIV-infected infants of mothers with advanced disease. [70] Abrams et al. demonstrated that HIV-positive infants whose mothers have a high viral load, low CD4 count and/or advanced HIV during pregnancy are more likely to develop AIDS or die by 24 months of age when compared to infants born to HIV-positive mothers without advanced disease, and high HIV RNA levels were the strongest predictor of disease progression. [7, 72-73] A ten-year long study based in Europe found that children who were initiated earlier on ARV therapy were significantly less likely to

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progress in their disease. [6] Obimbo et al. reported multiple factors associated with a higher risk of early mortality in HIV-infected infants. These predictors include advanced maternal HIV disease, maternal anemia, delivery complications, early growth faltering, formula-feeding and low infant CD4 count. [74]

HIV-infected children with slower disease progression remain at significant risk and require close follow-up. The bimodal disease course of pediatric HIV infection is well documented. [75] While a portion of HIV-infected infants will experience rapid disease progression, a larger portion of vertically-infected children less frequently have serious signs or symptoms of HIV disease. [6, 75] In resource-limited settings, while an estimated 35–54% of antiretroviral-naive children will die by two years of age, [75-78] children who survive beyond two years of age experience slower progression of their disease, with a 5-year mortality rate of approximately 62%. [75-76] Identification of these children is complicated by their slower disease course, but early diagnosis and treatment are necessary to prevent long-term morbidity and mortality.

Maternal HIV disease also impacts the uninfected infants of HIV-positive mothers. Various studies have shown that HIV-uninfected infants born to HIV-positive mothers are at increased risk of adverse perinatal outcome, including prematurity, IUGR, low birth weight and death. A study in Malawi comparing infants born to HIV-positive mothers with those born to HIV-negative mothers found a higher incidence of prematurity and IUGR among HIV-exposed infants (12.7% versus 3.8% and 7.7% versus 4.4%, respectively). [79] An analysis of over 11,000 U.S. infants born to HIV-infected women found a higher incidence of low birth weight and preterm birth. The rates of both declined among infants born to women receiving antiretroviral therapies. [80] A study in Zambia investigating HIV-uninfected infants of HIV-positive mothers found that infants were at increased risk of morbidity and mortality through at least the first four months of life. Infants of mothers with low CD4 counts (< 350 cells/microL) were more than twice as likely to die and more than twice as likely to be hospitalized, even after adjusting for

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such factors as maternal death, separation due to maternal hospitalization and low infant birth weight. [81] More recently, a study conducted in Malawi, Zambia and Tanzania demonstrated that among infants born to HIV-positive mothers, maternal morbidity and mortality, maternal CD4 count and maternal viral load were all predictors of infant mortality, regardless of an infant's HIV status. [82]

Deficiencies in PMTCT

PMTCT programs can help to reduce mother-to-child transmission rates of HIV but remain underutilized. PMTCT programs serve as a critical entry point for pregnant women to access the services they need to improve their own health and prevent transmission of HIV to their infants. [8, 21] However, while programs have been shown to be both feasible and effective, [83-85] they have not been implemented widely in resource-limited settings. [83, 86-88] A study involving 48 countries in sub-Saharan Africa found that an estimated 31,474 infant HIV infections and/or deaths by six to eight weeks of age were prevented due to ARV prophylaxis in 2004 and 2005. [89] Despite these advances, in 2005, only 9% of pregnant women living with HIV in low- and middle-income countries were receiving ARV therapy to prevent HIV transmission, [90] and in most PEPFAR (U.S. President's Emergency Plan for AIDS Relief) countries, only a very small percentage of women are benefiting from PMTCT services. It is estimated that PMTCT programs are reaching less than 10% of HIV-infected pregnant women in most countries. [91-93]

Program gaps are common and occur at all steps along the PMTCT continuum of care. A study of ten public sector delivery centers in Zambia found significant gaps in service and loss of follow-up at each step of the PMTCT pathway. [94] Studies of PMTCT programs in South Africa and other resource-limited settings have similarly revealed various program gaps, as demonstrated by women not being offered voluntary counseling and HIV testing (VCT), women who are tested but do not receive their results, women who do not have their CD4 counts

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measured, women who do not receive NVP, women who do not adhere to ARV prophylaxis, women with advanced disease who are not initiated on HAART, infants who do not receive NVP, and infants who do not return for follow-up testing. [95-97] Various operational and cultural barriers–including long waiting times, transportation costs, staff burnout, stigma, fear of discrimination, lack of knowledge, and lack of support–contribute to high rates of loss to follow-up across the PMTCT continuum. [98-100] The cumulative effect of such program gaps and loss to follow-up on coverage and overall PMTCT program effectiveness can be substantial. A recent study of a district hospital in Malawi found that while over 90% of antenatal clinic attendees accepted VCT, over 75% of the cohort of HIV-positive mothers and infants had been lost to follow-up by the six-month postnatal visit. [101] As described by Stringer et al., successful PMTCT therefore requires that each mother-infant pair negotiate a "cascade of events" that begins with testing and continues through adherence to the long-term care of HIV-infected mothers and their children. [94]

HIV testing in pregnancy is the primary point of access to PMTCT but uptake is incomplete. HIV testing is an integral component of essential care in pregnancy, and for most women, the first encounter with PMTCT programs. Per WHO guidelines, VCT should be routinely offered to all pregnant women who access antenatal care. [8] Despite these recommendations, a range of HIV testing rates–between 40-100%–in over 42,000 pregnant women from 11 different countries has been reported. [102] Other studies have similarly found an overall low uptake rate of PMTCT testing in sub-Saharan Africa. [9, 103-104] Multiple factors which contribute to low rates of testing are cited in the literature. An evaluation of PMTCT in Botswana found that older, less-educated and rural women were less likely to be offered counseling and HIV testing. [104] In a study in Uganda, the three most commonly cited reasons for maternal test refusal were lack of access to ARV therapy, a need for partner approval, and fear of a partner's reaction. [105] Other factors associated with a low uptake of HIV testing include the use of "opt-in" versus routine ("opt-out") testing, low levels of maternal education, lack of prior

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knowledge of PMTCT, lack of testing supplies, unavailability or poor quality of counseling, fear of a positive diagnosis, and stigma. [97, 105-109]

Failures in pre- and post-test counseling equate to missed opportunities to educate mothers and increase uptake of PMTCT services. Studies in Kenya and Côte d'Ivoire found that despite a high uptake of HIV testing, as much as one-third of pregnant women did not receive pre-test counseling. [110-111] Among those who were tested, between 20-30% did not return to receive their test results. This low rate of return was especially pronounced among HIV-positive women. [111-112] In areas where rapid testing is not available, delays in obtaining test results are also common. [113] When counseling does occur, the quality and effectiveness of the counseling can vary substantially. [114-115] A study evaluating PMTCT in a KZN district hospital found that almost 11% of pregnant women who consented to HIV testing were not counseled on the meaning of their test results. Among women who consented to testing and were found to be HIV positive, 9% reported not having knowledge about medicines that could be taken to reduce the risk of MTCT. [97] A survey of HIV-positive pregnant women who did not return for additional counseling after learning their HIV status revealed that most had had negative experiences while interacting with program staff. While some women reported disbelief of their test results and "personal factors" as reasons for not returning for PMTCT services, the most commonly cited reason was "staff with limited time and sympathy." [116]

Failures in infant feeding counseling increase the risk of post-natal HIV transmission. Though most transmission events occur in the late uterine and intrapartum periods, there is also a risk of mother-to-child HIV transmission during breastfeeding, particularly with mixed feeding or early weaning. [22, 26, 117-118] This risk has to be balanced against the risk of formula feeding, which itself is associated with increased child morbidity and mortality. [23, 119-120] In settings where breastfeeding is the safest and most feasible option, the best strategy to prevent MTCT and increase child survival is to promote exclusive breastfeeding for at least six months for all infants of HIV-positive mothers. [24-25] Breastfeeding for any shorter period of time has been associated

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with a six-fold increased risk of mortality in infants. [121-122] Infant feeding counseling is therefore an important intervention to prevent new pediatric HIV infection. Despite this, as with HIV test counseling, the prevalence and quality of counseling can vary considerably. A survey in South Africa found substantial knowledge gaps among midwife infant feeding counselors, such that expectant HIV-positive mothers could not make an informed decision about infant feeding method. [123] In evaluating a PMTCT program at a South African district hospital, it was found that 17% of HIV-positive pregnant women did not receive any form of infant feeding counseling. Among those mothers who were counseled, almost half reported that the advice they received from the feeding counselor was the most influential factor in their choice of feeding method. [97] A recent study conducted in Cambodia, Côte d'Ivoire, Burkina Faso, Cameroon and Kenya revealed that the duration and timing of infant feeding counseling, the information provided, and the ranking of feeding options can vary significantly by counselor. Notably, in all five countries, counseling sessions were found to be shorter and less detailed when women indicated their plan to breastfeed exclusively. [124] Though there is widespread knowledge among mothers that HIV can be transmitted via breast milk, there seems to be less understanding that transmission is a risk, not a certainty, [125] and early mixed feeding still remains the norm in much of southern Africa. [126]

Repeat testing in pregnancy could allow for identification and treatment of HIV-positive women with recently acquired infection. Acute HIV infection is characterized by an initial period of rapid viral replication, during which time HIV-specific antibodies are undetectable. [127-128] In most individuals, antibodies generally appear within three months after infection. [129-130] As a result, women who have tested HIV-negative in pregnancy are still at risk for acute HIV infection. This is particularly concerning given the extreme infectiousness of this period and the associated increased risk for MTCT. [65, 131] While there is some evidence to suggest higher rates of seroconversion among pregnant women when compared to non-pregnant women, [132-133] making repeating testing even more critical, this finding has not been

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supported in other studies. [134] HIV rescreening late in pregnancy in high-prevalence, resource-limited settings has been shown to be a cost-effective strategy for reducing MTCT. [135-136] However, despite its obvious benefit, there are limited data regarding the extent to which repeat testing occurs in pregnancy.

Testing at delivery could allow for identification and treatment of HIV-positive women with undiagnosed infection. In resource-limited settings, the proportion of pregnant women who have never received HIV testing can also be substantial. A study evaluating five PMTCT clinics in South Africa found that 42% of antenatal clinic attendees had unknown HIV status. [125] In studies conducted at two large urban referral hospitals in Kenya, the number of women presenting for delivery with unknown status was as high as 70-90%. While some of the women had no prior history of antenatal care, most had received antenatal care but had never received HIV testing. [110, 137] The implementation of intrapartum testing has also been shown to be feasible in resource-limited settings. In a busy hospital in India, the implementation of round-the-clock rapid HIV testing, including prepartum and extended postpartum counseling, led to HIV testing of over 80% of women with unknown HIV status and PMTCT interventions for those women newly found to be HIV positive. [138] For HIV-positive women who are identified through intrapartum testing, it has been demonstrated that starting antiretroviral therapy in labor or soon after birth can still decrease the risk of perinatal HIV transmission. [139-141] This can be particularly critical given the higher prevalence of HIV infection found in pregnant women with unknown status. [142-144]

Despite recent improvements, ARV coverage of both mothers and infants remains low. The percentage of HIV-positive pregnant women receiving ARV therapy increased more than three-fold between 2004 and 2007. [2] However, despite recent progress in expanding treatment access, coverage rates for both mothers and infants have remained unsatisfactory. In 2008, only one-third of HIV-positive pregnant women worldwide were assessed for HAART eligibility. [1] In a study combining 2005 data from 71 countries, Luo et al. estimated that fewer

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than 50% of women who tested HIV positive during pregnancy received some form of ARV treatment for PMTCT. Among those women who did receive medication, one-quarter of HIV-exposed infants failed to receive ARV prophylaxis at birth. [145] A study by Ginsburg et al. combining 2006 data from 18 resource-limited countries, including South Africa, found better NVP coverage rates of 80% in mothers and 51% in infants, [146] though these rates are still well below goal. Similarly low rates have been reported in South Africa alone. In 2006, despite antenatal clinic coverage rates of over 90% [147], NVP coverage for HIV-positive women was only 50%. [148] For the same time period, infant NVP coverage rates of more than 90% were reported in 31 districts in South Africa; however, the validity of these data is unclear given that some districts reported uptake rates of over 100%. [148] Low ARV coverage of mothers and infants can be secondary to issues related to capacity and access, [149] though health system failures also contribute. A recent year-long study in Zambia including 60 PMTCT programs throughout the country found major "bottlenecks" to HAART initiation. Notably, over 80% of HIV-positive women did not have their CD4 count measured, a third of CD4 results were never reported back to the primary clinic, and 27% of eligible women never initiated HAART. [150]

PMTCT programs are substantially hindered by the lack of infant follow-up care. High loss-to-follow-up rates prevent the testing of HIV-exposed infants and the early identification and management of HIV-infected children. As a result, large numbers of children continue to present to public health facilities in South Africa, often with advanced disease. [151-153] In a year-long study evaluating a South African PMTCT program, more than one-third of infants never returned for follow-up and more than 70% were lost to follow-up by four months of age. [83] In a study evaluating a PMTCT program in the Gauteng province of South Africa, only ten percent of HIV-exposed infants were tested for HIV. [154] This lack of follow-up can be devastating for children in need of ARV therapy, in light of the risk for rapid disease progression and the high mortality risk for infected infants. [4, 152] Poor post-natal follow-up also means there are limited data on the extent to which PMTCT programs have reduced the number of HIV

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infections and deaths in children. Even with improvements in HIV testing and treatment, without proper infant follow-up, the ability to prevent pediatric HIV infection and to treat HIV-positive children most in need will be severely limited.

Barriers to treatment access further contribute to reduced PMTCT program effectiveness. HIV-positive pregnant women have limited access to PMTCT and ARV programs, and as a result, many HIV-infected infants are also not identified for HIV treatment as part of PMTCT follow-up. [83] The reasons for limited access are multi-factorial, including but not limited to lack of capacity, limited knowledge of HIV by health care providers, limited knowledge of national guidelines amongst individuals implementing the PMTCT and ARV programs, incorrect provider perceptions, and lack of ownership. [155] Lack of coordination may also result in missed opportunities for HIV diagnosis and management and overall sub-optimal delivery of care for both mothers and infants. [107] Among pregnant women, lack of education, lack of transportation, stigma, and fear also contribute towards reduced program effectiveness. [156] These barriers to treatment, in addition to gaps in service and the significant dropout that can occur at each point in the process of receiving antenatal care and PMTCT services, significantly undermine the fight against pediatric HIV infection.

Evaluating PMTCT Effectiveness

PMTCT program evaluation is an integral component to increasing coverage and improving program effectiveness. PMTCT programs are composed of a continuum of services, including counseling, testing, ARV prophylaxis and treatment. Routine monitoring of each of these components is essential to understand overall program functioning. [157] As a result, various health facility indicators (e.g., number of health facilities providing PMTCT services, number of practicing trained health care workers) and patient indicators (e.g., number of pregnant women tested for HIV, percentage of HIV-infected children born to HIV-infected mothers) have been used to measure PMTCT program effectiveness. If there is low coverage at any point in the

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PMTCT continuum, the overall effectiveness of a program is compromised. [158] On-going audit and intervention are therefore critical steps to identify program deficiencies and obstacles to care and to develop strategies for program improvement. [83, 157, 159] Accurate record keeping is also necessary to facilitate routine program monitoring. [83]

Despite their critical role in reducing pediatric HIV infection, in South Africa there are limited data on the full performance of PMTCT programs in clinical sites. [160] The South Africa PMTCT Program was first established in 18 pilot sites around the county in 2001. Since the program's national expansion in 2002, there has been limited site-based research evaluating the full coverage and efficacy of individual South African PMTCT programs. Notably, there were also limited data on mother-infant pairs and specifically, the effect of local PMTCT interventions on HIV transmission rates and infant outcome. [83, 161] Worldwide, HIV-positive pregnant women and their children are cited as priorities, with a need to increase the percentage of women and children receiving treatment for HIV. [2] However, accurate program statistics are often unavailable, particularly at large government facilities with a heavy burden of infection. Achieving success in this area will be difficult without site-specific information to guide local efforts for program improvement.

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PURPOSE

The goal of this study is to report on the uptake and performance of a public-sector PMTCT program. The hope is that study findings will result in recommendations that will lead to improved delivery of HIV care as measured by the uptake of PMTCT and HAART services, with the long-term goal of decreasing the rate of mother-to-child transmission of HIV. Achieving success in this setting may serve as a model for other resource-limited sites in KZN and throughout South Africa.

Hypotheses

1. The incomplete identification and treatment of HIV-positive women during pregnancy result in higher rates of pediatric HIV infection.
2. Program gaps and health system failures interfere with the delivery of PMTCT services.
3. Follow-up of HIV-exposed infants is poor, significantly increasing the risk of childhood morbidity and mortality.

Specific Aims

1. To determine the proportion of pregnant women receiving care as per South Africa's national PMTCT protocol.
2. To identify gaps in service that could potentially contribute to reduced PMTCT program effectiveness.
3. To document the follow-up of HIV-exposed infants and the detection of HIV disease among children.

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METHODS

Study Setting

This study was based at Edendale Hospital (EDH), a 900-bed teaching hospital in Pietermaritzburg, KZN, South Africa. EDH is the second largest government hospital in the province; it serves as a government ARV rollout site, PEPFAR Broadreach treatment site, and tuberculosis (TB) treatment center. As the referral hospital for a population of over one million, EDH serves a primarily Zulu population spread over a vast geographic area of both periurban and rural settings. Poverty is the norm among this patient population, and high rates of both HIV and TB infection are typical of the province. Hospital wards are overfilled with patients in end-stage AIDS, and patients, most living in extreme poverty, must travel significant distances to receive care. [162]

The EDH PMTCT program was implemented as part of the national expansion of the South Africa PMTCT program to the public sector. [163-164] At the time of this study, the EDH PMTCT program was run in collaboration between the EDH Antenatal Clinic (ANC) and Gynecology Outpatient Department (GOPD). In accordance with national protocol at the time of this study, the EDH PMTCT package of care included (a) routine VCT, (b) infant feeding counseling (with encouragement for six months of exclusive breastfeeding), (c) CD4 count measurement and evaluation of HIV-positive pregnant women for HAART eligibility, (d) single-dose NVP to women in labor and NVP syrup to infants within 72 hours of delivery, (f) infant PCR testing of all HIV-exposed infants at six weeks of age, and (g) free formula milk for a period of six months for mothers choosing not to breastfeed. [163]

At the time of this study, the EDH PMTCT program involved a continuum of services provided by multiple sites within the hospital. This continuum is depicted in Figure 1. Pregnant women received routine VCT, infant feeding counseling, and CD4 count measurement through the ANC. Women with eligible CD4 counts initiated on HAART were referred to the GOPD.

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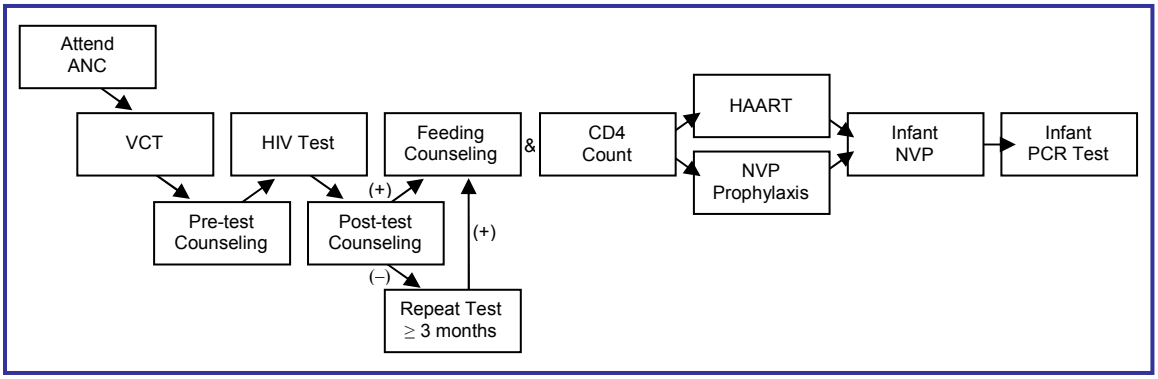
Intrapartum HIV testing and NVP administration were managed in the Labor and Delivery Wards, and HIV-exposed infants received PCR testing and all follow-up care in the Family Clinic, the hospital's pediatric HIV clinic.

FIGURE 1: EDH PMTCT Continuum of Services



Though established in 2001, the EDH PMTCT program has never been evaluated prior to this study in terms of its coverage, provision of services, and overall program effectiveness. Additional program aspects specific to EDH are worth noting. While national guidelines dictated HAART referral for all pregnant women with CD4 counts < 200 cells/mm^3, at the time of this study, EDH had adopted a higher threshold for eligibility, referring all pregnant women with CD4 counts < 250 cells/mm^3. Single-dose NVP was provided to all HIV-positive pregnant women at 28 weeks' gestation to be taken during labor. All HIV-exposed infants were administered a single dose of NVP syrup at birth. Infants whose mothers did not take NVP prior to delivery were administered a double dose of NVP syrup. All follow-up infant PCR testing was performed in the EDH Family Clinic, the hospital's pediatric HIV clinic. Initial PCR testing at six weeks of age coincided with national pediatric immunization guidelines, which call for immunizations at both six and ten weeks of age. National PMTCT guidelines called for repeat PCR testing at six weeks after termination of breastfeeding, and a confirmatory ELISA HIV antibody test on all HIV-exposed infants at 18 months of age.

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At the time of this study, at EDH, the provision of PMTCT services during pregnancy was documented in the antenatal card. In South Africa, antenatal cards include a complete medical and obstetric history, and they are carried by all women receiving antenatal care. Expectant mothers are expected to bring the card to each ANC visit and to the hospital when in labor. Upon admission to the Labor Ward, expectant mothers were registered in monthly log books kept on the Labor Ward and completed by nursing staff. Delivery registers included general patient information, including date of admission, patient name, medical record number, antenatal clinic where care was received (if any), and HIV status (positive, negative or unknown). The provision of intrapartum PMTCT services was documented in the delivery record, which included a woman's complete labor and delivery history. Upon hospital discharge, both antenatal cards and delivery records are stored in the hospital medical records department. In South Africa, all infants are discharged home with infant health cards known as Road-to-Health cards, which function as family-held infant medical records. As with the antenatal card, families are expected to bring the Road-to-Health card to each health facility visit. Finally, infant PCR testing was documented in Family Clinic PCR testing registers, which included general patient information, including date of test, patient name, date of birth, and PCR test result.

Study Design

Data for this study were collected via two separate retrospective medical record reviews. The primary retrospective review included all pregnant women documented to have accessed antenatal services at EDH and delivered at EDH between December 2006 and June 2007 (n = 240). Due to the high rate of HIV testing during pregnancy in this cohort, in order to evaluate the extent to which pregnant women were tested at the time of delivery if they had not been tested earlier in pregnancy, a secondary retrospective review was conducted. This review included a randomized sample of pregnant women who had not accessed antenatal services at EDH and who presented to EDH for delivery with no documented history of prior HIV testing. These women

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either did not receive antenatal care or received antenatal care outside of EDH and delivered at EDH between December 2006 and June 2007 (n = 105). The women included in this review comprised approximately 12.7% of the total number of women who presented for delivery with no prior history of HIV testing during the review period. The exact proportion is approximate given the absence of an electronic database and the exclusive reliance on paper medical records and handwritten department registers.

For the retrospective review of pregnant women who accessed ANC services and were offered HIV testing during pregnancy, information was collected regarding: (i) HIV testing; (ii) HIV retesting for those women who tested HIV negative more than three months prior to delivery; (iii) documentation of HIV status; (iv) documentation of CD4 testing for HIV-positive women; (v) initiation of HAART treatment for eligible HIV-positive women; (vi) ANC visits; (vii) NVP administration for HIV-positive women; and (viii) NVP administration for HIV-exposed infants. For the retrospective review of pregnant women with no prior history of HIV testing prior to delivery, information was collected regarding: (i) documentation of unknown HIV status; (ii) intrapartum HIV testing; (iii) NVP administration for HIV-positive women; and (iv) NVP administration for HIV-exposed infants.

In order to assess PMTCT infant follow-up care, the initial study design included a retrospective medical record review of those infants born to those women identified as HIV positive during the study period. The primary goal of this review would have been to document rates of infant testing, infant HIV status, and the provision of infant follow-up care as a measurement of overall PMTCT program effectiveness. However, since mother-infant pairs could not be linked, a retrospective review of infant PCR testing was conducted in lieu of infant medical record review. This review included all infants documented to have received HIV PCR testing at EDH Family Clinic between December 2006 and June 2007 (n = 276). Of note, all available test results logged during this time period were included. Information was collected regarding: (i) infant date of birth; (ii) date of PCR test; and (iii) PCR test result. Given South

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Africa's national policy of testing HIV-exposed infants at six weeks of age and given national immunization guidelines requiring immunizations at both six and ten weeks of age, allowing for a two-week delay in presentation, particular attention was paid to infants both less than eight and 12 weeks of age at the time of testing. As part of the retrospective review of infant PCR testing, birthdates associated with the infant PCR tests were compared with the birthdates of the HIV-exposed infants from the primary retrospective review who were expected to have returned for PCR testing during the review period (n = 70). Assuming that mothers who received antenatal care at EDH would return to EDH for all follow-up infant care, any matching birthdates were assumed to represent an idealized rate of infant follow-up testing.

A summary of the research methods used in this study is outlined in Table 1.

TABLE 1: Summary of Research Methods

REVIEW	ELIGIBILITY CRITERIA
Testing in Pregnancy (n = 240)	Pregnant women who: • Received antenatal care at EDH • Delivered at EDH between December 2006 and June 2007
Testing at Delivery (n = 105)	Pregnant women who: • Presented for delivery with unknown HIV status • Delivered at EDH between December 2006 and June 2007
Infant PCR Testing (n = 276)	Infants who: • Received HIV PCR testing at EDH Family Clinic between December 2006 and June 2007

Data Collection & Analysis

Eligible subjects for both retrospective medical record reviews were identified using EDH Labor Ward delivery registers. Both antenatal cards and delivery records for each subject were acquired from the hospital medical records department using each subject's medical record number. Eligible subjects for the review of infant PCR testing were identified using EDH Family Clinic PCR testing registers. All data were collected on-site by the primary author during the months of July and August 2007. Study data for all three reviews were recorded on pre-designed paper forms and subsequently entered into Excel. Standard statistical measures were performed

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using Excel after data collection was completed. Sample size chosen for the study was sufficiently large to provide reliable descriptive data, while at the same time taking into consideration the length of the research period.

Ethical Considerations

This study received approval from both the Yale Institutional Review Board and EDH Ethics Board. Confidentiality of data and protection of privacy were maintained throughout the study.

Challenges / Limitations

This study was limited by the availability of records, the quality of record keeping, and the prevalence of patients who were lost to follow-up. Due to the nature of the study, data collection relied solely on written documentation in hospital registers and patient records. There was no way to differentiate between interventions that were not given and interventions that were not documented; therefore, any apparent low uptake of services may reflect poor documentation.

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RESULTS

Testing in Pregnancy

A total of 240 subjects were included in the retrospective review of pregnant women who accessed ANC services at EDH. A summary of key findings from this review are presented in Table 2. Subjects ranged from 16.1 to 45.8 years of age (average age: 26.0, 18 subjects with age not documented), with an average gravida/para of 2.0/0.9 (range: 1-6/0-5); a total of 90 (37.5%) women were primigravida. On average, women presented to the ANC for their first visit at an estimated 23.9 weeks' gestation (range: 0.9-40). Subjects averaged a total of 5.6 (range 1-14) documented ANC visits prior to delivery.

TABLE 2: Testing in Pregnancy

	YES		NO		Not Documented		Total Subjects
HIV TESTING	n	(%)	n	(%)	n	(%)	N
For all mothers:							
Offered PMTCT during pregnancy	227	(94.6)	-	-	13	(5.4)	240
Accepted HIV testing during pregnancy	219	(96.5)	8	(3.5)	-	-	227
Tested HIV+ during pregnancy	105	(47.9)	114	(52.1)	-	-	219
HIV RETESTING							
For HIV- mothers:							
HIV tested ≥ 3 months before delivery	70	(58.3)	38	(31.7)	12	(10.0)	120
Retested during pregnancy	17	(24.3)	-	-	53	(75.7)	70
DOCUMENTATION OF HIV STATUS							
For all mothers:							
HIV status in antenatal card	234	(97.5)	-	-	6	(2.5)	240
HIV status in delivery record	143	(59.6)	-	-	97	(40.4)	240
CD4 TESTING & HAART TREATMENT							
For HIV+ mothers:							
Documentation of CD4 count	83	(71.6)	-	-	33	(28.4)	116
CD4 < 250	22	(26.5)	61	(73.5)	-	-	83
Initiated HAART during pregnancy	14	(63.6)	8	(36.4)	-	-	22
NVP ADMINISTRATION							
For HIV+ mothers:							
Received NVP during pregnancy	78	(67.2)	6	(5.2)	32	(27.6)	116
Took NVP before delivery	86	(74.1)	12	(10.3)	18	(15.5)	116
Took NVP at correct time	58	(67.4)	17	(19.8)	11	(12.8)	86
For infants born to HIV+ mothers:							
Received NVP after delivery	100	(82.6)	-	-	21	(17.4)	121
Received correct dose of NVP	59	(59.0)	16	(16.0)	25	(25.0)	100
Received NVP at correct time	41	(69.5)	4	(6.8)	14	(23.7)	59

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Of the 240 pregnant women who accessed antenatal services at EDH and delivered at EDH between December 2006 and June 2007, 227 (94.6%) were documented as being offered PMTCT during pregnancy. Among these 227 women, there was a substantially high rate of HIV testing documented (96.5%). Of the 219 women who consented to HIV testing, 201 (91.8%) had the date the test was performed documented in their antenatal card, and 179 (89.1%) of these women were tested during their first ANC visit. Of the 22 women not tested during their first ANC visit, 11 (50%) were tested during their second visit, and seven (31.8%) were tested during their third visit. The remaining four women included two who were tested at the sixth visit, one who was tested at the seventh visit, and one at the ninth visit.

Of the 219 women who consented to HIV testing, 105 (47.9%) were found to be HIV positive. Of the 120 women documented to be HIV negative (114 documented to be HIV negative after accepting HIV testing during pregnancy plus an additional six women documented to be HIV negative although there was no evidence of testing being done), 70 (58.3%) were documented to have been tested at least three months prior to their ultimate delivery date. Among these women, only 17 (24.3%) were retested during pregnancy; all retested HIV negative. The average amount of time between initial HIV test and retest was 117 days (range: 56-177). Among the 53 women eligible for retesting who were not retested, seven were lost to follow-up. The remaining 46 women continued to attend the ANC during which time they could have been retested; on average, each had a total of at least 2.2 ANC visits (range: 1-7) which took place at least three months after the date of original HIV testing.

Of the 116 women documented to be HIV positive (105 documented to be HIV positive after accepting HIV testing during pregnancy plus an additional nine women documented to be HIV positive although there was no evidence of testing being done), 104 (89.7%) were documented as having received infant feeding counseling during pregnancy. Among the women who were counseled, despite KZN policy promoting six months of exclusive breastfeeding, 73

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(70.2%) were documented to have chosen formula feeding; the remaining 31 (29.8%) women were documented to have chosen breastfeeding.

Among all women included in the review, a total of 234 (97.5%) had their HIV status (positive, negative or unknown) documented in their antenatal card and a total of 143 (59.6%) had their status documented in their delivery record. Notably, rates of documentation of HIV status did not differ between those who were HIV negative and those who were HIV positive. Of the 120 women documented to be HIV negative, 119 (99.2%) had their status documented in their antenatal card while 73 (60.8%) had their status documented in their delivery record. Of the 116 women documented to be HIV positive, 112 (96.6%) had their status documented in their antenatal card while 66 (56.9%) had their status documented in their delivery record. There were two instances (1.7%) in which a woman's HIV-positive status was recorded in the Labor Ward register but not documented in either the antenatal card or the delivery record.

Of the 116 HIV-positive women, 83 (71.6%) had CD4 counts documented in their antenatal card. Of the 22 (26.5%) women with CD4 counts less than 250 and who were therefore eligible for HAART treatment, 14 (63.6%) were documented to have initiated HAART during pregnancy. On average, HAART treatment was started at an estimated 30.4 weeks' gestation (range: 22.4-38.6). While all of these women had the date of HAART initiation documented in their antenatal card, only nine had the date of their HIV test date documented in the antenatal card. Among these nine women with a known date of HIV testing, time to HAART treatment was on average 50.4 days (range: 17-112) after HIV testing. Of the eight women with CD4 counts less than 250 who did not initiate HAART during pregnancy, one was documented to have refused HAART treatment, four did not have a reason for their failure to start HAART documented in the antenatal card, and three were lost to follow-up.

In examining NVP treatment, of the 116 women documented to be HIV positive, a total of 78 (67.2%) were documented to have been given single-dose NVP during pregnancy to be taken at the onset of labor. On average, these women were provided with single-dose NVP at an

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estimated 30.1 weeks' gestation (range: 24.9-39.9). In contrast, a total of 86 (74.1%) women were documented to have taken single-dose NVP prior to delivery, and 58 (67.4%) of these women were documented to have taken NVP at the correct time (between two and 48 hours prior to delivery).

A total of 121 infants were born to the 116 HIV-positive mothers identified in this review (due to the addition of six twin births and one infant death). Of these 121 HIV-exposed infants, 100 (82.6%) were documented to have received NVP after delivery. In 90 (74.4%) cases, the required dose of NVP could be determined based on available documentation; conversely, in 31 (25.6%) cases, the required dose of NVP could not be determined. Of the 100 infants documented to have received NVP, 59 (59%) could be identified as having received the correct dose of NVP, of which 41 (69.5%) received NVP at the correct time (between six and 72 hours after delivery). Based on documentation, it was not possible to determine whether the remaining 41 (41%) of the 100 infants who had received NVP had received the correct dose.

Testing at Delivery

During the study review period between December 2006 and June 2007, EDH had a total of 4,580 pregnant women presenting for delivery (monthly average of 654 women). Of these women, according to Labor Ward delivery registers, a total of 1,509 (32.9%) were documented as being HIV positive, 2,241 (48.9%) were documented as being HIV negative, and 830 (18.1%) were documented as having unknown HIV status (i.e., no prior history of HIV testing). Of the 830 women with no prior history of testing, 153 (3.3% of total / 18.5% of women with unknown status) had no prior history of antenatal care. The monthly totals for each of these groups are depicted in Figure 2.

In order to evaluate HIV testing at delivery, a total of 105 subjects were included in the retrospective review of pregnant women who had not accessed antenatal services at EDH and with no prior history of HIV testing. Subjects were selected at random and in monthly proportion

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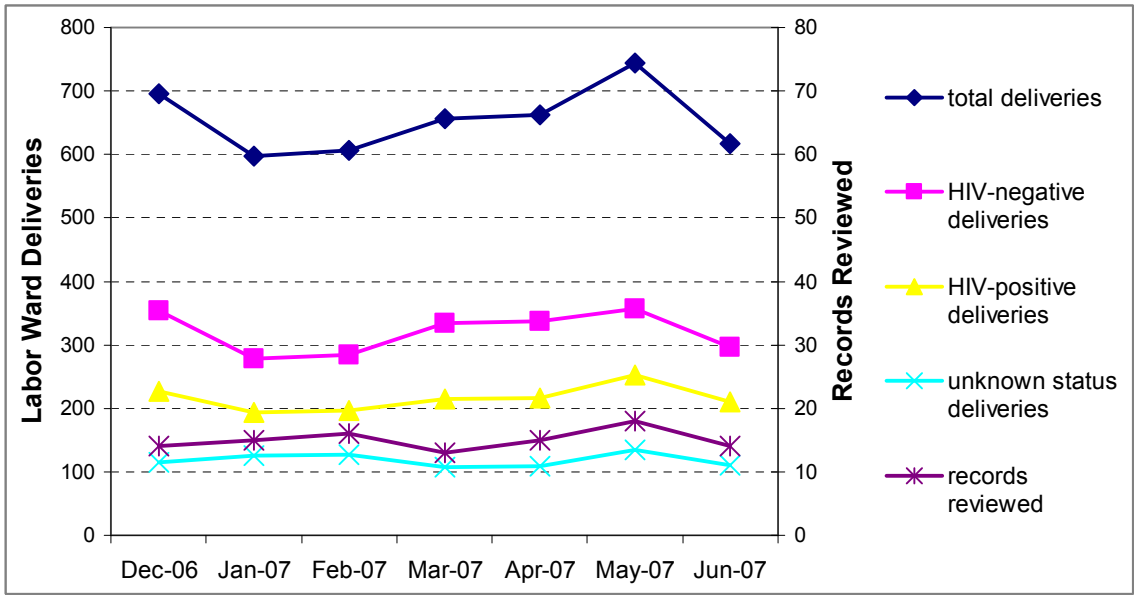
to the total number of women presenting with unknown HIV status–according to Labor Ward delivery registers–during the review period (see Figure 2). A summary of key findings from this review are presented in Table 3. Among the 105 women included in the review, 87 (82.9%) had received antenatal care at a facility other than EDH while 18 (17.1%) had received no antenatal care during their pregnancy. Subjects ranged from 15.9 to 43.6 years of age (average age: 25.2, 7 subjects with age not documented), with an average gravida/para of 1.9/0.8 (range: 1-4/0-3); a total of 41 (39.0%) women were primigravida. Among those who received antenatal care, subjects averaged a total of 3.7 (range 1-10) documented ANC visits prior to delivery.

FIGURE 2: EDH Labor Ward Deliveries & Records Reviewed
December 2006 – June 2007



Of the 105 pregnant women who presented for delivery with no prior history of HIV testing, 42 (40%) had their unknown HIV status documented in the antenatal card, and 66 (62.9%) had their unknown status documented in the delivery record; 25 (23.8%) women with no prior history of HIV testing did not have their unknown HIV status documented in either record. Of the total 105 women with unknown HIV status, 11(10.5%) were documented to have been offered HIV testing prior to delivery, and ten (90.9%) of these women were documented to have

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refused testing. The one woman (9.1%) who consented to HIV testing prior to delivery was found to be HIV positive. After delivery, there were 41 (39.0%) documented instances of HIV testing being offered, and of the 23 (56.1%) women who consented to HIV testing, eight (34.8%) had a positive test result, 13 (56.5%) had a negative test result, and two (8.7%) did not have a test result documented.

TABLE 3: Testing at Delivery

	YES	NO	Not Documented	Total Subjects
DOCUMENTATION OF HIV STATUS	n (%)	n (%)	n (%)	N
For all mothers:				
Unknown status in antenatal card	42 (40.0)	- -	63 (60.0)	105
Unknown status in delivery record	66 (62.9)	- -	39 (37.1)	105
HIV TESTING				
Before delivery:				
Offered VCT before delivery	11 (10.5)	- -	94 (89.5)	105
Accepted HIV testing before delivery	1 (9.1)	10 (90.9)	- -	11
Tested HIV+ before delivery	1 (100.0)	- -	- -	1
After delivery:				
Offered VCT after delivery	41 (39.0)	- -	64 (61.0)	105
Accepted HIV testing after delivery	23 (56.1)	18 (43.9)	- -	41
Tested HIV+ after delivery	8 (34.8)	13 (56.5)	2 (8.7)	23
NVP ADMINISTRATION				
For infants born to HIV+ mothers:				
Received NVP after delivery	6 (66.7)	- -	3 (33.3)	9

In examining NVP administration, the one woman found to be HIV positive prior to delivery was not documented to have been offered or given NVP. Among the nine infants born to those women found to be HIV positive (one woman identified prior to delivery and eight women identified after delivery), six (66.7%) infants were documented to have received NVP after delivery. In all cases, NVP was administered at the correct time (between six and 72 hours after delivery). With the three (37.5%) remaining infants born to HIV-positive mothers, there was no documentation of NVP administration. Of note, there were two additional infants–one whose mother was documented to have been HIV tested after delivery with no documented test result and one whose mother was not documented to have received any HIV testing during the intrapartum period–who were documented to have received NVP after delivery.

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Infant PCR Testing

A total of 276 infants were included in the retrospective review of infant PCR testing. A summary of key findings from this review are presented in Table 4. Infants included in this review ranged in age from 12 days to 17.6 months (average age: 4.4 months). Among the 276 infants tested, 66 (23.9%) were found to be HIV positive, 169 (61.2%) were found to be HIV negative, and 41 (14.9%) did not have the result of their PCR test documented. Among all infants tested during the review period, a total of 125 (45.3%) were tested at less than eight weeks of age; among these infants, 21 (16.8%) tested HIV positive. Allowing for further delay in presentation, among all infants tested, a total of 159 (57.6%) were tested at less than 12 weeks of age; among this larger cohort of infants, HIV prevalence remained approximately the same (16.4%) as among infants tested at less than 8 weeks of age

TABLE 4: Infant PCR Testing

	YES		NO		Not Documented		Total Subjects
HIV TESTING	n	(%)	n	(%)	n	(%)	N
For all infants tested:							
Tested HIV+	66	(23.9)	169	(61.2)	41	(14.9)	276
For infants tested at < 12 weeks of age:							
Tested at < 12 weeks of age	159	(57.6)	117	(42.4)	-	-	276
Tested HIV+	26	(16.4)	113	(71.0)	20	(12.6)	159
For infants tested at < 8 weeks of age:							
Tested at < 8 weeks of age	125	(45.3)	151	(54.7)	-	-	276
Tested HIV+	21	(16.8)	88	(70.4)	16	(12.8)	125

The total number of PCR tests performed and the percentage of HIV-positive test results by age group are depicted in Figure 3. While the number of PCR tests performed decreased with increasing age at the time of testing, the percentage of infants testing HIV positive substantially increased. A total of 25.0% of infants tested between 12 weeks and six months of age were found to be HIV positive, and over half (52.6%) of the infants tested between 12 and 24 months of age were found to be HIV positive.

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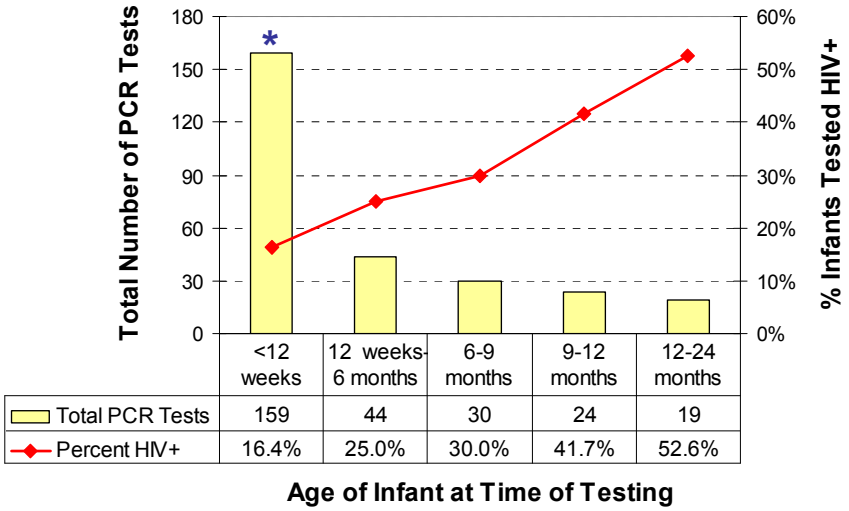
In order to estimate the rate of infant follow-up, since mother-infant pairs could not be linked, a comparison of birthdates was performed; specifically, birthdates from the PCR tests for infants tested at less than 12 weeks of age were compared with the birthdates of HIV-exposed infants from the primary retrospective review expected to have returned for six-week PCR testing during the review period (n = 70). Through this comparison, it was found that only 36 (51.4%) of the birthdates from these two groups matched. Since mothers who receive antenatal care at EDH were expected to receive their follow-up infant care at EDH, and assuming each matching birthdate pair correctly identified an infant from the primary retrospective review, then at best only half of HIV-exposed infants from the primary retrospective review returned for six-week PCR testing by 12 weeks of age.

FIGURE 3: Total PCR Tests & Percentage Infants Tested HIV+ by Age of Infant
December 2006 – June 2007



* Only 36 of these PCR tests (51.4%) matched birthdates with the 70 HIV-exposed infants from medical record review who were expected to have returned for HIV testing during the review period.

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DISCUSSION

Multiple gaps in service delivery were demonstrated in this study by low rates of repeat testing among women found to be HIV negative at first testing, low rates of testing at delivery among women with no prior history of HIV testing, extended time to HAART treatment among HIV-positive eligible women, and incomplete NVP provision and administration with both HIV-positive mothers and their infants. There were failures in documentation at each step in the PMTCT continuum of care. An inability to link mother-infant pairs, poor follow-up of HIV-exposed infants, and a lack of coordination of services further limit overall PMTCT program effectiveness. A summary of study findings is outlined in Table 5.

Table 5: Summary of Findings

- Almost all pregnant women receiving antenatal care at EDH were offered PMTCT. High rates of testing reveal that half of pregnant women presenting for care were HIV positive.
- Documented rates of repeat testing and testing at delivery were low. This is particularly concerning as the risk of transmission is highest during acute HIV infection.
- A majority of HIV-positive mothers had a CD4 count documented, though less than two-thirds of eligible mothers initiated HAART.
- Among those who initiated HAART, average time to treatment was over 50 days.
- Over 70% of HIV-positive mothers and 80% of HIV-exposed infants were documented as having received NVP, though only one-third of infants received NVP correctly.
- Less than 60% of PCR tests were on infants at twelve weeks of age or less. Of those tested, over 16% of infants were found to be HIV positive.
- At most, only half of HIV-exposed infants expected to return for HIV testing during the review period were tested at EDH by twelve weeks of age.

Gaps in Service Delivery

Almost all pregnant women receiving antenatal care at EDH were offered PMTCT. High rates of testing during the first clinic visit are suggestive of effective pre-test counseling and demonstrate that HIV testing is well accepted by women attending the ANC. High uptake of VCT at this stage is also reassuring, given the important opportunity it provides for education and counseling regarding prevention and risk reduction for those women who test HIV negative. [165-167] While other studies have demonstrated high numbers of women who do not return for

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test results, [110-111] this was not seen given EDH's use of rapid HIV testing. The fact that essentially half of the women presenting for antenatal care tested HIV positive confirms a high HIV prevalence rate in the area, strongly underscoring the need for timely and effective PMTCT interventions.

Despite high rates of initial HIV testing at EDH, the documented rates of repeat testing during pregnancy among women found to be HIV negative at first testing (24.3%) were low. Documented rates of testing at delivery, both before and after childbirth for those women without a prior HIV test, were also found to be low (10.5% and 39.0%, respectively). Low rates of repeat testing during pregnancy are concerning given the increased risk for MTCT during acute HIV infection. [65] Though the uptake of HIV testing was high at EDH, there was a lower rate of testing among outside antenatal clinics. This was demonstrated by the fact that over 18% of women presented for delivery with unknown HIV status. Given the sizeable proportion of pregnant women with no history of HIV testing, the low rate of intrapartum VCT further represents a significant missed opportunity to identify HIV-infected mothers and prevent pediatric HIV infection

Given the extremely high local incidence of HIV, the use of routine intrapartum testing could detect a substantial number of HIV-infected women and HIV-exposed infants who would otherwise not receive interventions to prevent MTCT. [88, 110, 168-169] The near universal acceptance of HIV testing among pregnant women who receive counseling illustrates a general openness to HIV treatment and prevention services in this population. [145] The acceptability, feasibility and effectiveness of intrapartum HIV testing have been demonstrated in multiple studies. [144, 170-172] Notably, as a result of preliminary study findings, the EDH PMTCT program initiated staffing changes in order to provide more extensive VCT in the Labor Ward. Prior to this, counselors had to be called from the ANC or GOPD if there was a perceived need for HIV testing at delivery. The impact of this staffing change could not be measured given its implementation at the end of the data collection period of the study, though the physical presence

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of a VCT counselor in the Labor Ward presumably has had a substantial impact on the rate of intrapartum testing.

Despite infant feeding counseling and EDH's promotion of exclusive breastfeeding, over 70% of HIV-positive mothers in our study chose to formula feed. This is concerning given the well-known risks associated with formula feeding [23] and the increased risk for postnatal MTCT if the mother continues to breastfeed while also giving formula. [25, 121] Given the nature of this study, it is difficult to comment on the quality of the counseling provided and the reasons behind the majority preference for formula feeding. However, lack of knowledge and inadequate counseling are likely contributing factors. Studies in South Africa evaluating infant feeding counseling found gaps in counselors' knowledge and a low level of knowledge among pregnant women regarding the risks of MTCT through breastfeeding. [173] Another recent study conducted in South Africa, Swaziland and Namibia found infant feeding counseling sessions were often demotivating, with mothers reporting feeling "judged, stigmatized and shamed." [174]

While a majority of HIV-positive mothers had a CD4 count documented in their antenatal card, less than two-thirds of eligible pregnant women initiated HAART. This is comparable to what has been found in other studies examining HAART coverage of HIV-positive pregnant women. [150] In addition, time to HAART initiation in our study was also unacceptably long (average > 50 days). This is concerning given the increased risk for MTCT with advanced maternal disease progression [61], and the risk for rapidly progressive disease among infected infants born to mothers with more advanced disease. [7, 54] While both maternal and infant uptake of NVP were incomplete, maternal NVP coverage was higher than the average reported in South Africa, [148] and both rates of coverage are comparable or higher than those found in other studies. [87, 107, 146, 175] When considering the timing of NVP, rates of coverage are lower. Only one-half of mothers were documented as having taken NVP correctly and only one-third of infants were administered NVP correctly. Similar rates of coverage have been reported in other

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studies. [95, 110, 125, 159, 176] This highlights the need for maternal education and staff training regarding PMTCT protocol for medication administration.

Failures in Documentation

This study revealed failures in documentation at each step of the PMTCT continuum of care, from antenatal VCT and NVP administration through follow-up infant PCR testing. The lack of documentation was most pronounced with maternal HIV status, particularly among women with no prior history of HIV testing, and NVP administration for both HIV-positive mothers and infants. In addition to preventing accurate data collection in terms of coverage and interventions provided, such failures in documentation can lead to substantial gaps in service and missed opportunities to prevent pediatric HIV infection. If a mother's HIV-positive status is not clearly documented, there is an increased chance that mother and/or infant will not receive the necessary NVP prophylaxis. Similarly, when a mother's unknown status is not clearly documented, she is less likely to be offered intrapartum VCT, again missing a key opportunity for PMTCT intervention. Of note, though not reported in this study, EDH had extremely limited data available on the pregnant women who had been referred for HAART, as well as limited data on those who had initiated HAART. It was impossible to follow pregnant women from the ANC–where they had tested HIV positive and found to be eligible for HAART–to the GOPD ARV Clinic, where pregnant women eligible for HAART were managed. Additionally, overall program statistics for the PMTCT ARV Clinic were not recorded.

At EDH, the difficulty of accurate data collection was compounded by the multiplicity of registers necessitated by the multiple locations where care is provided to pregnant women and their infants. The multiple locations included but were not limited to the ANC, GOPD, Labor and Delivery Wards, ARV Clinic and Family Clinic. Program indicator data only existed in the form of unlinked monthly summary reports, and data collection was hindered by inconsistent documentation within each register and record. Each hospital department designed and managed

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its own registers, and each register was completed by a various number of hospital staff on any given day. Documentation on antenatal cards was especially varied, as they were completed according to the local standards of each antenatal referral clinic. This allowed for greater opportunities for human error, and across the board, there was a lack of consistency in reporting.

The duplication of records and complexity of data monitoring found in this study has been noted in other studies evaluating PMTCT and data management systems in South Africa. [83, 159, 177-178] The need for improved documentation and reporting is also well recognized. [146, 179] In South Africa, it has been noted that PMTCT program management is severely hindered by major problems related to data collection and data quality, as well as program indicators that are "less than optimal." [53] A study evaluating health information management in ten rural clinics in KZN over a 12-month period found a high perceived work burden among staff associated with data collection and management. Data collection tools were not used correctly, and there was minimal analysis or utilization of the data available. In the clinics surveyed in this study, 2.5% of data values were missing, and one-fourth of the data were outside expected ranges. [178] Another recent study evaluating reporting in three KZN districts found that routine PMTCT health system data suffered from substantial problems of both completeness and accuracy. Notably, program data for the initial components of the PMTCT continuum of care was generally found to be most available, while data related to later components in the continuum were progressively less available. [177]

Improved documentation throughout all steps of the PMTCT pathway could have a profound impact on the provision of care. Routine testing in pregnancy with documentation of all results in the antenatal card–regardless of a woman's HIV status–would facilitate treatment later in pregnancy and labor. Routine documentation of a mother's status on some form of permanent medical record would facilitate maternal follow-up after delivery. Routine documentation of a mother's status on the infant Road-to-Health card would enable providers to identify all at-risk

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infants from the first post-natal visit, allowing for timely HIV testing for all HIV-exposed infants and early treatment initiation for all HIV-infected infants. [180]

The development of an essential data set–one that is comprehensive, accurate and timely–is necessary for effective program management and evaluation. [181] The WHO recommends "simplified data collection tools, a minimal common set of indicators, reduced numbers of registers, and allocation of dedicated, trained personnel at the local level to maintain patient records and reports," [182-183] but in resource-limited settings, this can be difficult to achieve. Various factors have been positively associated with higher data quality performance, including trained staff with longer experience with an ARV program, visits by ARV supervisors, a high volume of patients, and dedicated clerks for recordkeeping. [177] Improved staff understanding of the need for accurate data and documentation has also been demonstrated to improve overall reporting. [178] The development of internal protocols and regular staff training are therefore essential.

Poor Infant Follow-up

There was no means by which to follow mother-infant pairs through the PMTCT continuum, preventing one of the original goals of this study: to document rates of infant testing, infant HIV status, and the provision of infant follow-up care as a measurement of overall PMTCT program effectiveness. Given the complete absence of connecting data between both antenatal cards and delivery records and infant records, it was impossible to track individual infants born to HIV-positive mothers included in the study. As is the practice with antenatal cards, infant health records are kept by each family. The limited records maintained by the Family Clinic contain a child's name, but parents' names are not included, and it is impossible to know an infant's name based on retrospective review of antenatal cards and delivery records. Delivery records do not include an infant's name due to the custom of naming infants after hospital discharge. Infants also often receive their father's surname, which is not commonly documented in either the antenatal

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card or delivery record. It was therefore impossible to link mother-infant pairs based on retrospective review.

Utilizing the information available, our retrospective review of infant PCR testing revealed that while PMTCT guidelines call for testing at six weeks of age, even allowing for significantly delayed testing up to 12 weeks of age, less than two-thirds of PCR tests performed were on infants at twelve weeks of age or less. The timing of tests is notable, given that testing at four to six weeks of age can identify more than 95% of infants who acquired early HIV infection, either during pregnancy or delivery. [184] Among HIV-exposed infants tested in our study by 12 weeks of age, over 16% were found to be HIV positive. Assuming all HIV-positive mothers had been identified prior to childbirth and both mothers and infants received NVP prophylaxis as indicated, a transmission rate of approximately 12% would be expected at 6-8 weeks. A slightly higher transmission rate of 13% would be expected at 14-16 weeks of age. [39] Our findings estimate a transmission rate of 16.4%, higher than would be expected assuming effective PMTCT intervention, suggesting health system failures in the PMTCT continuum of care.

Our study also revealed that at most, only half of the infants expected to return for HIV testing during the study period were tested by 12 weeks of age. Since this analysis assumed that if a tested infant's birthdate matched the birthdate of one of the HIV-exposed infants from the primary retrospective review, those infants were one and the same, in all likelihood, the actual number of HIV-exposed infants who returned for HIV testing was substantially lower. While high rates of loss to follow-up have been reported in other studies, [83, 154] high rates of return are achievable. In a recent study in a large hospital in KZN, the uptake of infant PCR testing at six weeks of age was over 80%. [185] The high loss to follow-up in our study is concerning, given the significant risks for child mortality and morbidity in HIV-infected infants, [4, 161] and the small window for diagnosis to allow for effective early treatment. Since completion of this study, a study by Kurewa et al. demonstrated that HIV-exposed infants are at significant risk for higher mortality, especially in the first four months of life. [186] The need for early treatment was also

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recently demonstrated by the CHER trial, which showed quite profoundly that initiation of ARV therapy among HIV-infected infants before 12 weeks of age reduced early infant mortality by 76%. [187]

Other studies have similarly found high rates of loss to follow-up, [83, 107, 137, 188-189] which may be due to various factors. Many families have difficulties with access, either due to limited finances and/or transportation. As a referral hospital, EDH serves families throughout the district, many of whom must travel far distances to receive care. Other factors contributing to poor follow-up of HIV-exposed infants may include a family's lack of knowledge regarding the inherent risks of infection, the need for testing, and fear of stigmatization. [180, 190] Socio-economic factors including poverty, geographical relocation, and lack of paternal support may also play a role. [154]

It is important to note, however, that a low rate of infant PCR testing may not necessarily be due a family's failure to return for follow-up care. In KZN, infant attendance rates at immunization clinics are generally high, especially at six weeks of age. [191] Since infant health records commonly do not reflect maternal HIV status, unless providers are informed by parents, infants may be seen in a well child clinic for care without ever being identified as HIV-exposed. At EDH, families may be bringing their infants for follow-up care but choosing not to attend the Family Clinic, again either due to lack of knowledge or stigma. Regardless of the underlying reasons, HIV-positive children are often not identified early and only gain access to comprehensive HIV care and treatment late in their disease. [152-153] This is demonstrated in our study by the proportion of children testing HIV positive up to two years of age.

Improved rates of infant follow-up could be achieved by various means. Improved counseling during pregnancy and prior to hospital discharge could help to educate mothers about the importance of infant HIV testing and follow-up care. The routine documentation of maternal HIV status on each infant's Road-to-Health card would allow for the immediate identification of all HIV-exposed infants, regardless of the location of presentation for follow-up care. The use of

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home visits and support groups for HIV-positive parents have also been shown to be effective at improving rates of infant follow-up. [192] Peer support programs, such as the UNICEF-supported mothers2mothers program, provide education and social support to HIV-positive mothers, facilitating continuation of care. [193] Given the high prevalence of HIV among EDH's patient population, universal testing of all infants may also be beneficial. In a recent study in KZN, Rollins et al. demonstrated that universal HIV testing of infants at immunization clinics was both acceptable and feasible. [153]

Integration of Services

EDH had no integrated system in place to track HIV-positive pregnant women and their infants through the PMTCT continuum of care, including diagnosis, referral, enrollment, and treatment. Though necessary for effective programmatic management and required by the government PMTCT program, statistics of testing, referral, and enrollment were often unavailable or inaccurate, possibly due to short-staffing, lack of trained personnel, lack of uniform data collection tools, and lack of a computerized data collection system. [88, 96, 194] Program effectiveness was also severely limited by the inability to track mother-infant pairs after delivery. [195]

The provision of PMTCT services at EDH was further hindered by the functional, as well as physical, separation of the various components of the PMTCT program. At the time of this study, the EDH PMTCT program was divided among multiple sites, including the ANC, GOPD, Labor and Delivery Wards, and Family Clinic. Notably, there was no clinic site dedicated to the follow-up of HIV-positive mothers after delivery, except for those mothers initiated on HAART during pregnancy. This separation of services interfered with continuity of care for both mothers and their children and likely contributed to loss to follow-up between component services. [161, 196] Especially in high-prevalence areas, various studies have cited the need to improve linkages between the various departments and to integrate key components of PMTCT services into the

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routine continuum of care, whenever possible. [88, 146, 159, 164, 197] Such improvements have been demonstrated to increase uptake of VCT, [137] improve maternal ARV coverage, [198] reduce time-to-treatment initiation, [199] and improve rates of infant follow-up. [146]

Of note, while data collection for this study was being completed, EDH was in process of developing plans to build an on-site integrated PMTCT clinic to allow for the provision of counseling, testing and treatment of HIV-positive mothers in one location (as opposed to divided between the ANC and GOPD, as was the case during the study period).

New Directions

Since completion of this study, there have been substantial changes in PMTCT worldwide and specifically in South Africa. In 2006, partly due to the availability of more potent ARV prophylaxis and concerns for drug resistance, the WHO issued new guidelines recommending the use of more complex regimens–specifically, regimens including the use of AZT and lamivudine (3TC) in addition to single-dose NVP–over single-dose NVP alone to prevent MTCT in resource-limited settings. [8] In February 2008, South Africa revised its own national guidelines to include AZT in the prevention of MTCT. [200] According to these guidelines, all HIV-positive women who are not eligible for HAART (i.e., CD4 counts > 200 cells/mm^3) should receive AZT from 28 weeks of pregnancy, as well as single-dose NVP to be taken in labor. HIV-exposed infants should receive single-dose NVP at birth followed by AZT for seven days after birth; this is extended to 28 days if a mother has received anything less than the full maternal prophylaxis regimen. In addition, all pregnant women found to be HIV negative should be retested by 36 weeks' gestation.

Most recently, on World AIDS Day on December 1, 2009, South African President Jacob Zuma announced further revisions to the country's national PMTCT program. Starting April 2010, all HIV-positive women with CD4 counts < 350 cells/mm^3 (increased from the current threshold of 200 cells/mm^3) will be eligible for HAART. All other HIV-positive pregnant women

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will begin receiving AZT treatment from 14 weeks of pregnancy. In addition, all HIV-positive children under one year of age will receive ARV treatment, regardless of CD4 measures. [201] This is in line with the most recent WHO recommendations that all infants under 12 months of age with confirmed HIV infection be started on ARV therapy, irrespective of clinical or immunological stage. [184]

Preliminary findings from the recently completed and still unpublished KwaZulu-Natal Impact Study, which involved 38,000 mothers from 347 clinics in six districts of KZN, demonstrated that the rate of mother-to-child HIV transmission has dropped by nearly two-thirds since the addition of AZT to PMTCT national guidelines in early 2008. Overall, among infants born to HIV-positive mothers who received both AZT from 28 weeks of pregnancy and single-dose NVP in labor, 5.6% tested HIV positive four-to-eight weeks after delivery compared to 13.5% of infants born to HIV-positive mothers who received only NVP. Even this study, however, demonstrated that there is potential for even lower rates of transmission; in two of the studied districts, transmission rates were found to be as low as 4.3% and 7%. However, the KZN Impact Study also highlighted significant health system failures in the provision of PMTCT interventions. Many women in the study did not access antenatal care until later in their pregnancy. As a result, while almost all had been tested for HIV, more than two-thirds were tested in their final trimester, after the point at which they should have started AZT according to current guidelines. Additionally, a third of the women who tested HIV positive did not get a CD4 count measured, a necessary step for HAART referral. Despite the apparent dramatic success of adding AZT to PMTCT regimens, many HIV-infected pregnant women in need of treatment are still not being identified. [202]

CONCLUSION

Despite significant enrollment in PMTCT and high acceptance of HIV testing in pregnancy, gaps in service delivery and/or failures in documentation result in multiple missed

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opportunities to prevent pediatric HIV infection. The inability to link mother and infant records further contributes to incomplete follow-up care of HIV-exposed infants. While recent revisions of PMTCT treatment guidelines allowing for the use of combination therapy instead of only single-dose NVP will allow for considerable reductions in mother-to-child HIV transmission, more effective regimens will continue to have limited success without fundamental improvements in service delivery. Improved training and protocols for care, as well as the development of uniform data collection tools, are critical to PMTCT program effectiveness.

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