Title
Prevention of Mother-to-Child Transmission of HIV in India: Lessons Learned from a Cohort of HIV-Infected Mothers and Their Children

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Prevention of Mother-to-Child Transmission of HIV in India: Lessons Learned from a Cohort of HIV-Infected Mothers and Their Children

By

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Professor Alan Hubbard
Professor Malcolm Potts

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Abstract

Prevention of Mother-to-Child Transmission of HIV in India: Lessons Learned from a Cohort of HIV-Infected Mothers and Their Children

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Women infected with the human immunodeficiency virus (HIV) can transmit their infection to their baby during pregnancy, delivery, or breastfeeding —a process known as mother-to-child transmission (MTCT). According to the World Health Organization (WHO), an estimated 3.4 million children under the age of 15 were living with HIV at the end of 2011. In 2011 alone, 330,000 children had newly acquired HIV from their mothers. 'Prevention of mother-to-child transmission of HIV' (PMTCT) refers to a series of interventions that help protect babies born to HIV-infected mothers against the virus. In order to be effective, these interventions need to be implemented as a cascade – starting with antenatal care and continuing during postpartum care. The maximum efficacy of the interventions to reduce MTCT differs by setting. In a developed country setting, the risk of MTCT has be reduced to less than two percent, whereas in a developing country setting, like India, the risk of MTCT still remains relatively higher. The elimination of mother-to-child transmission of HIV is now considered a realistic public health goal. Considerable efforts to expand PMTCT programs and guaranteeing access to antiretroviral therapy (ART) for pregnant and postpartum HIV-infected women has raised the possibility of achieving the virtual elimination of MTCT of HIV.

In order to achieve the maximum impact of PMTCT and realize the goal of virtually eliminating new HIV infections among children by 2015, high levels of coverage, access, utilization, and adherence to treatment regimens must be attained across India. However, 40 percent of HIV-infected women enrolled in the national PMTCT program in India are estimated to be lost to follow-up (LTF) even before they receive a single dose of Nevirapine (NVP). PRAYAS, a non-government organization (NGO) located in the city of Pune, Maharashtra, runs one of the largest private sector PMTCT programs in India. Between 2002 and 2008, PRAYAS collaborated with 43 hospitals in nine districts across Maharashtra and provided comprehensive antenatal care (ANC) counseling and HIV testing services to 122,005 pregnant women and enrolled 950 HIV-infected women in the PMTCT program. This dissertation uses de-identified data previously collected by PRAYAS for program purposes.

The first goal of this dissertation was to contribute to the knowledge on the factors associated with loss to follow-up during the PMTCT cascade in India. Univariate and multivariate analyses were conducted to estimate the associations between being LTF and socio-demographic factors, using generalized linear models. Results of the multivariate analysis showed that women with less than a college level education, women from poor families, women who were registered after 20 weeks of pregnancy, and women whose partners were HIV-uninfected or of unknown HIV status were more likely to be LTF before delivery. Similarly, the factors associated with being LTF after delivery were less than college level education, being in a poor family and registration after 20 weeks of pregnancy.

PMTCT programs are regarded as an entry point to continued care because they provide an opportunity to link an HIV-infected woman, her partner, and her child (if infected) to long-term treatment and care. However, little is known about the factors associated with utilization of continued care among women who have previously utilized PMTCT services. The second goal of this dissertation was to study the barriers associated with reduced utilization of HIV-related continued care in women who have previously accessed PMTCT services in India. After adjusting for potential confounders, results from the multivariate analysis showed that women with poor HIV-related knowledge, women who were currently married, women whose partners had never utilized HIV-related care and women who could not afford to travel to the HIV-care facility were less likely to utilize HIV-related continued treatment and care.

The number of HIV-exposed uninfected (HIV-EU) infants identified in India is likely to increase due to the scale up of programs aimed at realizing the goal of elimination of MTCT by 2015. While some studies from developed and developing countries have reported stunting in HIV-EU children compared to HIV-unexposed uninfected children, others have found no such association. No studies on the effect of HIV-exposure on postnatal growth patterns in HIV-EU children in India have been published to date. The final goal of this dissertation was also to assess the effect of *in utero* HIV exposure on birth weight and postnatal growth in HIV-uninfected children in India. Birth weight, height and weight of 297 HIV-EU children and 1611 HIV-unexposed uninfected children, in India, were compared. Linear regression models were used to evaluate the association between *in utero* HIV exposure and birth weight and *in utero* HIV exposure and postnatal height and weight, after adjusting for potential confounders. HIV-EU children weighed 123.5 g less ($p<0.01$) at birth compared to HIV-unexposed children. On an average, HIV-EU children were 2.9 cm shorter ($p<0.00$) compared to HIV-unexposed children. In children five years of age and younger, with every year of increase in age, HIV-EU children grew 0.8 cm less ($p<0.01$) than HIV-unexposed uninfected children. At ages three and five, the HIV-EU children were 0.22 cm ($p<0.05$) and 1.8 cm shorter ($p<0.05$) than HIV-unexposed uninfected children respectively. After adjusting for potential confounders, no significant difference in weight between HIV-EU and HIV unexposed uninfected children was found at different ages.

DEDICATION

I dedicate this dissertation to the love of my life- my husband, Amol. This dissertation would not have been possible without his patience, his unconditional love and his never-ending support. He was always there when I needed him, through the highs and the lows, and through the good times and the not so good times. He is and forever will be the source of my inspiration.

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And last but definitely not the least, I would like to thank my dear family, my father, Vijaykumar, my mother, Manik, and my brother, Shreenath, for always believing in me.

CHAPTER 1

PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HIV IN INDIA: AN OVERVIEW

Prevention of mother-to-child transmission of HIV

The human immunodeficiency virus (HIV) epidemic continues to affect women and children worldwide. According to the World Health Organization (WHO), an estimated 3.4 million children under the age of 15 were living with HIV at the end of 2011.[1] In 2011 alone, 330,000 children were newly infected with HIV.[1] Most of these children acquired the virus from their HIV-infected mothers during pregnancy, labor, delivery, or breastfeeding.[1] Mother-to-child transmission (MTCT), also known as vertical transmission of HIV have been studied in detail. Risk factors for MTCT include maternal factors during pregnancy and at the time of delivery, such as high HIV viral load, low CD4 cell count, and advanced clinical stage of the disease; obstetric factors, such as prolonged rupture of membranes and invasive obstetrical procedures; and postnatal factors, such as breastfeeding and the presence of mastitis.[2-4]

Since the groundbreaking clinical trial that demonstrated the efficacy of prophylactically administered azidothymidine (AZT), an antiretroviral drug (ARV), in reducing the rate MTCT of HIV by 68%,[5] numerous observational studies and clinical trials have evaluated the efficacy and the effectiveness of various other antiretroviral drug regimens and interventions.[6] ARV drugs work against HIV by stopping or interfering with the reproduction of the virus in the body. In the absence of any intervention, the risk of a HIV-infected woman passing on the infection to her infant is between 20 and 45 percent.[6] The maximum effect of the various interventions to reduce MTCT has differed by setting. In the developed country setting, the risk of MTCT can be reduced to less than two percent by a series of interventions that includes a combination of three ARVs (known as antiretroviral therapy (ART)) given to women during pregnancy and labor; obstetrical interventions, including cesarean delivery; the complete avoidance of breastfeeding; and ARVs given to the infant during the first several weeks of life.[6]

'Prevention of mother-to-child transmission of HIV' (PMTCT) refers to a series of interventions that help protect infants born to HIV-infected mothers. In order to be effective, these interventions need to be implemented as a cascade – starting with antenatal care and continuing during postpartum/natal care and beyond.

The United Nations promotes a comprehensive four-pronged approach to prevent HIV infection among infants and young children.[7] (See box below)

Prong 1	Primary prevention of HIV infection among women of childbearing age.
Prong 2	Prevention of unintended pregnancies among women living with HIV.
Prong 3	Prevention of HIV transmission from women living with HIV to their infants.
Prong 4	Provision of appropriate treatment, care, and support to mothers living with HIV and their children and families.

Prong 3 of the comprehensive four-prong PMTCT strategy is a vital component that is firmly based on years of experience and scientific findings from PMTCT programs

worldwide. This prong consists of a cascade of services, including HIV testing and counseling of all pregnant women; ARV prophylaxis (for HIV-infected pregnant women who are not eligible for ARV treatment of their own HIV infection) and ART (for HIV-infected pregnant women who are eligible for treatment of their own HIV infection); safe delivery; safe infant feeding practices and postpartum interventions such as cotrimoxazole prophylaxis for the infant; early infant diagnosis; and linkage of all HIV-infected children to treatment and care.[7]

Current guidelines on use of antiretroviral drugs for treating pregnant women for their own health and to prevent HIV infection in their infants

Moving away from single dose Nevirapine (sd-NVP)

The 2006 PMTCT guidelines issued by the WHO moved beyond recommending sd-NVP to recommending a more effective combination of ARVs for prophylaxis during the last trimester of pregnancy and in the early postpartum period.[8] Sd-NVP is the regimen of choice for preventing mother-to-child transmission of HIV in many developing countries due to the several reasons. First, the use of sd-NVP significantly reduces peripartum transmission of HIV.[8] The single dose regimen of NVP is suitable for women who first learn that they are HIV-positive at the onset of labor, a common occurrence in developing countries. Second, NVP is relatively inexpensive, can be stored at room temperature and is administered orally; making it feasible to use in developing countries.[9] However, recent evidence shows that sd-NVP is associated with a higher risk of development of resistance to ARV and is much less effective compared to combination ARV prophylaxis regimens.[6] Furthermore, sd-NVP does not provide protection during the breastfeeding period.[6] Postnatal transmission of HIV continues to be a major problem in developing countries, where prolonged breastfeeding is a common practice.[8] Safer alternatives to extended breastfeeding, such as formula, can help reduce the risk of transmission, but they require the availability of clean drinking water and substantial efforts in terms of nutritional counseling and care and therefore are not sustainable in many developing countries.[8]

Lowering the threshold for initiation of ART

The 2006 PMTCT guidelines recommended giving ART to a limited number of pregnant women; recommended prophylaxis regimens that focused only on the last trimester of pregnancy; and did not recommend continued ARV during breastfeeding.[8] Since the 2006 PMTCT guidelines were issued, important new scientific evidence on the use of ARV prophylaxis to prevent MTCT has emerged. This evidence led to the development of revised PMTCT guidelines in 2010. Highlights of the 2010 guidelines include a raising of the eligibility threshold for initiating ART among pregnant women from CD4 counts $\leq$200 cells/mm^3 to $\leq$350 cells/mm^3, irrespective of WHO clinical staging; immediate initiation of ART (regardless of gestational age) for all treatment-eligible women; expanded number of recommended first-line ART regimen options for pregnant women;

and initiating ARV prophylaxis at 14 weeks for HIV-infected pregnant women who are not eligible for ART to treat their own HIV infection.[6]

Provision of ARVs to non-treatment eligible women and/or their infants

HIV-infected pregnant women who are not eligible to receive ART to treat their own HIV infection (based on their CD4 count and clinical disease staging) require effective ARV prophylaxis to prevent HIV infection in their infants. The 2010 guidelines recommended that ARV prophylaxis be started as early as 14 weeks of gestation or as soon as feasible during pregnancy, labor and delivery.[6]

Three options (Option A, Option B and Option B+) are recommended for HIV-infected pregnant women who are *not* eligible to begin ART to treat their own HIV infection**,** as shown in Table 1.

Current guidelines on infant feeding

Complete and exclusive formula feeding eliminates the risk of transmission of HIV through breastfeeding and is the standard of care recommended in developed countries. However in the developing country setting, an infant who given formula or other substitutes (such as animal milk) often faces greater health risks than an infant who is exclusively breastfed by an HIV-infected mother.[10,11] Given that safe and affordable alternatives to breast feeding are not readily available in developing countries, the 2010 PMTCT guidelines recommend that mothers known to be HIV-infected exclusively breastfeed their infants for the first six months of life, introducing appropriate complementary foods thereafter, and continue breastfeeding until the infant is at least 12 months of age.[6] ARV prophylaxis decreases the amount of HIV in the mother's breast milk (i.e., the viral load), thus reducing the risk that she will transmit the infection to her infant.[6] Regardless of infant feeding choice, the provision of prophylaxis to the infant offers added protection from early postpartum transmission, particularly in situations where a mother has higher HIV viral loads.[6]

Eliminating mother-to-child transmission of HIV (EMTCT) by 2015

Provision of PMTCT to all women who need it is the most effective way to end mother-to-child transmission of HIV. The elimination of mother-to-child transmission of HIV is now considered a realistic public health goal and an important component of the campaign to achieve the Millennium Development Goals.[12] Considerable efforts to expand programs aimed at preventing MTCT and guaranteeing access to ART for pregnant and postpartum HIV-infected women have raised the possibility of reducing MTCT to very low levels and achieving the virtual elimination of vertical transmission.

In June 2011, world leaders gathered at the United Nation meeting on AIDS in New York and launched the 'Global plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive'. The goal of this global plan is to

virtually eliminate new HIV infections among children by 2015. The plan's objectives include reducing new pediatric HIV infections by 90%; reducing HIV-associated deaths among women during pregnancy, childbirth and postpartum by 50%; and reducing mother-to-child transmission of HIV to less than 5% at the population level.[13]

PMTCT: Developed countries versus developing countries

Although mother-to-child transmission of HIV has been virtually eliminated in the developed world, an estimated annual 430,000 new HIV infections in children living in developing countries have been attributed to MTCT. [13] In the year 2010, only 35% of all pregnant women in developing countries underwent HIV testing. Furthermore, of an estimated 1,490,000 HIV-infected pregnant women in these countries who needed antiretroviral drugs to prevent mother-to-child transmission of HIV, only 48% received the most effective regimen currently recommended by the WHO.[14] While, the number of children receiving ART increased from 71,500 at the end of 2005 to 456,000 in 2010, the proportion of HIV-infected children receiving ART is still substantially lower than the proportion of HIV-infected adults receiving ART.[15]

Deficiencies of PMTCT efforts in developing countries

Despite the efficacy of the various PMTCT regimens in the clinical trial setting, the translation of the findings into public health policy in developing countries has been slow compared to that in developed countries.[15] To reach the objective of providing PMTCT services to all women who need them, pregnant women across the developing world must be tested for HIV, and PMTCT programs need to be scaled up to include all mothers and babies who need them.[15]

A variety of factors impede the translation of clinical PMTCT guidelines into public health policy in developing countries in Asia and Africa. These factors include weak health care infrastructure, lack of integration of PMTCT programs into maternal and child health services, a high proportion of home-deliveries, and competing public health priorities in the context of limited overall health care funding. Other challenges include lack of male involvement in HIV testing and impediments to disclosure of HIV status by infected women due to the association of HIV status with stigma.[16]

Mother-to-child transmission of HIV in India

India has an estimated 2.4 million people living with HIV/AIDS -the highest number in Asia.[17] The prevalence of HIV infection among adults (ages 15-49) in India was estimated at 0.3% in 2009, with the higher prevalence in the south and southeast regions.[18] It is estimated that between 22,000 and 61,000 HIV-infected pregnant women were living with HIV in India, in 2010. Although the percentage of pregnant women tested for HIV increased from 2% in 2005 to 23% in 2010, the proportion being tested remains low.[19] It is also estimated that between 7,300- 21,000 infants in India were newly infected with HIV in the same year.[19] India has adopted the WHO PMTCT Option A

regimen, but the country is likely to switch to the Option B regimen in the near future.[20] In the light of the goal of eliminating new HIV infections among children by 2015, a national PMTCT scale up plan for India has also been developed.[21,22]

Healthcare delivery system in India

Healthcare delivery in India is complex, due to the existence of multiple health systems. Primary health care and preventive care are mainly available only in the public health sector, which in the rural setting consists of community health centers (CHCs) and primary health centers (PHCs). In the urban setting, the public health sector includes urban health centers and district and medical college hospitals. The private health sector, comprised of private practitioners, large and small hospitals and nursing homes primarily provides therapeutic care. In addition, the private health sector includes non-governmental organizations and faith-based organizations. Traditional systems of medicine such as ayurveda, unani, siddha and homeopathy, exist in parallel with the western medicine.[23]

The public sector PMTCT program in India

India's PMTCT program is known as the PPTCT (prevention of parent-to-child transmission) program. PMTCT services in the public health sector are provided at 5135 Integrated Counseling and Testing Centers (ICTC) across India. In 2008, the number of pregnant women counseled and tested through the national PPTCT program was approximately 4,631,000 (16% of total deliveries).[24] Only 21,483 (23%) of the estimated 92,000 HIV-infected pregnant women giving birth were identified in 2008.[25,26] Pregnant women who test positive for HIV under the PPTCT program are given sd-NVP prophylaxis during labor, and the newborn is given sd-NVP within 72 hours of birth. A total of 10,494 mother-baby pairs (49% of total women who tested positive for HIV) were given a dose of NVP under the national program in 2008.[24] In March 2010, the national PPTCT program began using the DNA PCR test for early infant diagnosis (at six weeks) in the four high prevalence states of Andhra Pradesh, Karnataka, Tamil Nadu and Maharashtra. However, between April and June 2010, only 45 children had undergone testing for HIV infection.[27]

PMTCT programs in the private sector in India

In addition to the public sector, the private sector plays an important role in the provision of maternal and child health-related services in India. According to the National Family Health Survey (NFHS-3) report, approximately 40% of pregnant women received their health care services in the private sector.[28] Numerous NGO-supported programs across India provide PMTCT-services to HIV-infected women. The first and largest private sector PMTCT program in India, initiated by the Elizabeth Glazer Pediatric AIDS Foundation, provided PMTCT care to approximately 692,000 women between 2002 and 2009.[29]

Knowledge gaps related to PMTCT in India

PMTCT programs present a unique opportunity to reach HIV-infected women of reproductive age and their families.[30,31] A woman who is diagnosed with HIV infection during her pregnancy is an ideal candidate for referral for treatment assessment and possible initiation of ART, prior to the development of AIDS manisfestations.[30] Her partner can also be encouraged to access voluntary HIV counseling and testing and referred for treatment, if needed. In addition, children born to HIV-infected mothers receiving care through PMTCT programs can benefit from medical follow-up and diagnosis, regardless of their HIV status.[31] Children who are HIV-infected require long-term care and follow-up, whereas children who are not HIV-infected typically need some degree of routine primary care.[30]

In order to achieve maximum impact of PMTCT and realize the goal of virtually eliminating new HIV infections among children by 2015, high levels of coverage, access, utilization, and adherence to treatment regimens must be attained across the country. However, in most developing countries, including India, retaining HIV-infected women in PMTCT care continues to be a major challenge. Loss to follow-up (LTF) of women enrolled in PMTCT programs at various stages has been recognized as a major problem by PMTCT programs in many resource-poor settings. Forty percent of HIV-infected women enrolled in the national PMTCT program in India are lost to follow-up before they receive a single dose of NVP. Although loss to follow-up in the PMTCT setting has been identified as a problem in India, factors associated with low utilization of PMTCT services and post-PMTCT treatment and care by HIV-infected women in India are largely unknown. An in-depth understanding of the factors associated with utilization of HIV-related care and treatment in women in India will assist in devising strategies to achieve higher rates of uptake and thus improve health outcomes and survival in women and their infants.

The number of HIV-exposed uninfected (HIV-EU) infants identified in India is likely to increase due to the scale up of programs aimed at realizing the goal of elimination of MTCT by 2015. Postnatal growth patterns in HIV-infected children have been studied in detail and impaired postnatal growth, especially stunting, has been reported as a common manifestation of HIV infection.[32-35] Some studies from developed and developing countries have reported stunting in HIV-EU children compared to HIV-unexposed uninfected children, while others have found no such association.[36-42] No studies on the effect of HIV-exposure on postnatal growth patterns in HIV-EU children in India have been published to date. Developing an understanding of postnatal growth and its determinants in HIV-EU children is thus critical.

Dissertation Goals and Specific Aims

The overall goals of this dissertation are:

1. To contribute to the knowledge on the factors associated with loss to follow-up during the PMTCT cascade in India.

2. To study the barriers associated with continued utilization of HIV-related care in women who have previously accessed PMTCT services in India.

3. To assess the effect of *in utero* HIV exposure on birth weight and postnatal growth in HIV-uninfected children in India.

Study 1: Socio-demographic factors associated with loss to follow-up of HIV-infected women attending a private sector PMTCT program in Maharashtra, India.

Specific aim

To determine the socio-demographic risk factors associated with loss to follow-up in HIV-infected women accessing PMTCT services in a private sector PMTCT program.

Study 2: Barriers associated with reduced utilization of continued care by HIV-infected women who had previously enrolled in a private sector PMTCT program in Maharashtra, India: results from the 'Linking to Care' study

Specific aim

To determine the barriers associated with continued utilization of HIV-related treatment and care in HIV-infected women after completing the PMTCT cascade.

Study 3: Effect of *in utero* HIV-exposure on birth weight and postnatal growth in HIV-uninfected children in India

Specific aim

To determine the effect of *in utero* HIV exposure on birth weight and postnatal height and weight in HIV-uninfected children.

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Table 1: Three ARV prophylaxis options that are currently recommended for HIV-infected pregnant women who are not eligible to initiate ART to treat their own HIV infection (have CD4 count ≥ 350 cells/mm^3).

Option A	Option B	Option B +
Mother	Mother	Mother
Consists of twice-daily AZT starting from as early as 14 weeks of gestation and continued during pregnancy. At onset of labor, sd-NVP and initiation of twice daily AZT + 3TC (Lamivudine) for 7 days postpartum.	Consists of triple ARV prophylaxis starting from as early as 14 weeks of gestation and continued until delivery, or, if breastfeeding, continued until 1 week after all infant exposure to breast milk has ended.	Regardless of CD4 count, triple ARVs starting as soon as diagnosed and continued for life
Infant	Infant	Infant
For breastfeeding infants: Daily NVP from birth for a minimum of 4 to 6 weeks, and until 1 week after all exposure to breast milk has ended. Infants receiving replacement feeding only: Daily NVP + twice-daily AZT from birth until 4 to 6 weeks of age.	Irrespective of mode of infant feeding: Daily NVP or twice daily AZT from birth until 4 to 6 weeks of age.	Daily NVP or AZT from birth through age 4–6 weeks regardless of infant feeding method

CHAPTER 2

SOCIO-DEMOGRAPHIC FACTORS ASSOCIATED WITH LOSS TO FOLLOW-UP OF HIV-INFECTED WOMEN ATTENDING A PRIVATE SECTOR PMTCT PROGRAM IN MAHARASHTRA, INDIA

ABSTRACT

Background

Currently, 40 percent of HIV-infected women enrolled in a national PMTCT program in India are lost to follow-up (LTF) before they can receive single dose Nevirapine. To date, no study from India has examined the reasons for inadequate utilization of PMTCT services. This study sought to examine the socio-demographic factors associated with LTF of HIV-infected women enrolled during 2002 to 2008 in a large-scale private sector PMTCT project in Maharashtra, India.

Methods

Data on HIV-infected women who were enrolled during pregnancy (N= 734) and who reported a live birth (N= 770) were used to analyze factors associated with LTF before delivery and after delivery, respectively. Univariate and multivariate analyses were conducted to estimate the associations between being LTF and socio-demographic factors, using generalized linear models.

Results

Eighty (10.9%) of 770 HIV-infected women were LTF before delivery and 151 (19.6%) women were LTF after delivery. Women with less than college level education (RR= 6.32), from a poor family (RR= 1.61), who were registered after the 20th week of pregnancy (RR= 2.02) and whose partner was HIV uninfected or of unknown HIV status (RR=2.69) were more likely to be LTF before delivery. Similarly, the factors associated with LTF after delivery were: less than college level education (RR=1.82), poor family (RR=1.42), and registration after the 20th week of pregnancy (RR=1.75).

Conclusions

This study highlights the need for innovative and effective counseling techniques for less educated women; economic empowerment of women; better strategies to increase up-take of partner's HIV testing; and early registration of women in the program for preventing LTF in PMTCT programs. This need for innovative counseling techniques is even greater for PMTCT programs in the public health sector, as the women accessing care in the public sector are likely to be less educated and economically more deprived.

Background

Prevention of HIV transmission from a HIV-infected pregnant woman to her child requires completion of a cascade of services, beginning with HIV testing and counseling for the pregnant woman followed by antiretroviral treatment (ART) or prophylaxis for the HIV-infected pregnant woman, safe obstetric interventions, and support for safer infant feeding options.[1] Adequate utilization of each service in this cascade contributes to the effectiveness of a program for prevention of mother to child transmission (PMTCT) of HIV.

Loss to follow-up (LTF) of women enrolled in a PMTCT program at different stages has been recognized as a major hurdle by PMTCT programs in resource poor settings. In a PMTCT project in Malawi, 68 percent of the HIV-infected pregnant women were LTF by delivery and 81 percent were LTF by the six-month post-natal visit.[2] A PMTCT program in Côte d'Ivoire reported that 84 percent of the HIV-infected pregnant women were LTF before they had started taking Zidovudine prophylaxis.[3] Similarly a program in Zimbabwe reported that 76 percent of the HIV-infected women were LTF before the mother and the baby could be given single dose Nevirapine (sdNVP),[4] while a study from South Africa reported that more than 70 percent of infants born to HIV-infected mothers were LTF by four months of age.[5] In India, more than 3.5 million pregnant women were tested for HIV in 2008.[6] However, approximately 40 percent of the identified HIV-infected women and their babies were LTF before they could be given sdNVP.[6] Owing to the large number of HIV-infected pregnant women who are LTF, the efficacy of a PMTCT program is substantially reduced, not only because the objective of reducing pediatric HIV transmissions is compromised, but also because of the missed opportunity to link HIV-infected women and their partners to further care and support activities.

There is dearth of literature on the risk factors for LTF of HIV-infected women within PMTCT programs. Almost all of the studies in the PMTCT setting to date have been carried out in African countries. However, factors found to be associated with LTF in the African PMTCT setting may be different from the Indian PMTCT setting due to substantial differences in the social, cultural, and economic contexts in which women's lives are embedded. Therefore, in order to increase the effectiveness of a PMTCT program, there is a need to study the factors associated with LTF in the local and cultural contexts, while identifying any common factors in the different geographic and cultural settings. Furthermore, the factors associated with LTF in previous studies have been mostly derived from qualitative data.[7,8] Previous qualitative studies in Africa have identified several risk factors for LTF, such as fear of stigma, discrimination, household conflict and even violence or divorce on disclosure of HIV status; lack of support from partners; social and cultural taboos associated with artificial infant feeding; long waiting times at the antenatal care (ANC) facility; and unaffordable transport costs to the hospital.[3,7,8]

Although LTF in the PMTCT setting has been identified as a problem in India, no data on risk factors for LTF in PMTCT programs are available. Understanding the factors

associated with LTF of HIV-infected women in the PMTCT programs in India will assist in devising strategies to achieve better follow-up and subsequently improve health outcomes and survival in women and infants seeking care at such facilities. Hence, the contributions of this paper are twofold: first, a quantitative analysis of risk factors associated with LTF of HIV-infected women in the PMTCT setting and second, a focus on a geographic site where such a study has never been carried out previously. This study analyzes the data from one of the largest private sector PMTCT programs in India. Therefore, the findings of this study will be useful to health care providers, as well as to the program managers and policy makers currently implementing or planning to implement PMTCT programs in the private and public sectors.

Methods

The PRAYAS PMTCT program

PRAYAS, a non-government organization (NGO) located in the city of Pune, Maharashtra, a state with an HIV prevalence of 0.67 percent [9] among adults, started implementing a PMTCT program in the private health sector in September 2002. This program is one of the largest private sector PMTCT programs in India. Between 2002 and 2008, the NGO collaborated with 43 hospitals in nine districts of Maharashtra and provided comprehensive antenatal care (ANC) counseling and HIV testing services to 122,005 pregnant women and enrolled 950 HIV-infected women in the PMTCT program. ANC and PMTCT counseling are provided by trained counselors located at these hospitals. HIV-infected women are offered AZT based ARV prophylaxis for PMTCT, following the WHO recommendation for resource poor countries. Infant feeding counseling is provided, and the options of breastfeeding and replacement feeding are given to women after a thorough discussion about the availability, affordability, feasibility, accessibility and sustainability (AAFAS) of replacement feeding. HIV-exposed infants are tested for HIV by DNA PCR test.

Data collection

I used de-identified data previously collected by PRAYAS for programmatic purposes. Trained counselors located at the collaborating hospitals collected data using a pre-designed semi-structured questionnaire.[*] The socio-demographic data were collected at the time of registration of pregnant women in the PMTCT project, and the data on each follow-up visit were recorded on separate follow-up sheets. Data validation was regularly conducted as a part of internal monitoring of the project, and these data were entered using a software specifically devised for monitoring the PMTCT project.

[*]PRAYAS had obtained institutional ethics review board approval for collecting these data.

Detailed information on socio-demographic factors, past obstetric and medical history of the woman, and socio-demographic information about the woman's partner was collected. Information on delivery was noted on a separate delivery sheet. Detailed information on adherence to ART and infant feeding practices was collected during follow-up visits.

Case definition

HIV-infected women registered during pregnancy and who were not known to have terminated the pregnancy were included in the analysis. Women were considered as LTF before delivery if they did not come to the hospital for delivery by the expected date (cut off date was 31st December 2008) and could not be contacted even after repeated attempts. Similarly, women were considered LTF after delivery if they came during labor and delivered a live baby but did not come for any post-natal visits. As a routine procedure, consent for contacting women is sought at the time of registration into the program and women are contacted by letter, phone calls or home visits when they miss their scheduled visit with the doctor or the counselor.

Statistical Analyses

We undertook a descriptive analysis of basic demographic characteristics of the HIV-infected women enrolled in the project. We conducted statistical analyses to determine the risk factors for LTF before delivery and after delivery for pregnant women registered in the PMTCT program. Univariate analyses were conducted using generalized linear regression to estimate the associations between being LTF and demographic as well as other social factors. Statistically significant covariates (in the univariate analysis) were tested in log-linear (binomial) multivariate models using generalized linear regression. We chose to estimate relative risks instead of odds ratios, because the outcome (being LTF) was not a rare occurrence. Estimating the odds ratios when the outcome is not rare would have overestimated the relative risk. Separate final models for analysis of LTF before delivery and after delivery were selected using backward stepwise elimination technique. All statistical analyses were performed with STATA for Windows (Version 9.0).

Results

Between 2002 and 2008, a total of 950 HIV-infected women were registered in the program (840 were enrolled during pregnancy and 110 were enrolled during labor). Of these women, 80(9.5%) women meeting the case definition of LTF before delivery and 151 (15.9%) women meeting the case definition of LTF after delivery were identified. Table 2 shows the results of the univariate analysis of factors associated with LTF before and after delivery. Presence of previous healthy children, woman's educational level, family's economic status, partner's HIV status, and whether woman was referred to the program were associated with being LTF before delivery. In addition to these factors, place of residence, stage of pregnancy at the time of registration, mode of delivery, birth

weight of baby, infant feeding option, and medication regimen given to the baby were found to be statistically associated with being LTF after delivery.

The results of the multivariate analysis conducted to identify the risk factors associated with LTF before delivery are shown in Table 3.

A woman with less than college level education (≤12 years of education) was 6.32 (95% CI: 1.57-25.44) times more likely to be LTF than a woman with college level education (≥ 12 years of education), after controlling for other covariates. A woman from a poor family was 1.61 (95% CI: 1.07-2.42) times more likely to be LTF than a woman from a middle-class or rich family. A woman who was registered after the 20th week of pregnancy was 2.02 (95% CI: 1.34-3.05) times more likely to be LTF than a woman who was registered within the first 20 weeks of the pregnancy. A woman whose partner was HIV seronegative or whose HIV infection status was unknown was 2.69(95% CI: 1.71-4.24) times more likely to be LTF than a woman whose partner was HIV seropositive. These results were found to be consistent across the different study sites.

The results of the multivariate analysis conducted to identify the risk factors associated with the woman's LTF after delivery are shown in Table 4.

A woman with less than college level education was 1.82 (95% CI: 1.03-3.22) times more likely to be LTF than a woman with college level or higher than college level education, after controlling for other covariates. A woman from a poor family was 1.42 (95% CI: 1.05-1.91) times more likely to be LTF than a woman from a middle-class or a rich family. A woman who was registered after the 20th week of pregnancy was 1.75 (95% CI: 1.12-2.73) times more likely to be LTF than a woman who was registered within the first 20 weeks of the pregnancy. These results did not differ across the different study sites.

Discussion

The results of the analyses of the risk factors for LTF in HIV-infected pregnant women before delivery and after delivery are discussed below in detail.

Woman's education level

Women with college level education were less likely to be LTF compared to women with less than college level education. Previous research in India on a nationally representative sample of women has identified woman's education as a significant factor influencing utilization of maternal and child health care services.[10] The results from this study suggest that woman's education is an important determinant for continued utilization of PMTCT services among HIV-infected women.

The relationship between maternal education and health care utilization is not straightforward and there are several pathways in which education may influence

maternal health care utilization. Educated women are better able to break away from the traditions to utilize modern means of safeguarding their own health,[11-13] they are able to make independent decisions,[11,14] and utilize what is available in the community for their advantage.[15-17] However, in the context of PMTCT, continued utilization of health care services is needed and therefore the exact role of education in reducing LTF needs to be studied further. This is particularly important when PMTCT and ART programs are being rolled out in rural areas among relatively less educated population.

Family's economic status

HIV-infected women whose families had a higher economic status were found to be less likely to be LTF before and after delivery, as compared to women of lower economic status. The need for economic empowerment of women to reduce LTF in PMTCT has been recently highlighted in the study from Malawi.[9] In this study, a family's economic status was subjectively assessed by the counselor. Such subjective assessments may not be as accurate as income-based or asset based assessments of economic status. It is important to note that HIV-infected women in this study were accessing health care in the private sector, where they had to bear the cost of obstetric care and medical care for the baby, although the PMTCT services were offered free of charge. During the project implementation it was noted that the cost of providing obstetric care to HIV-infected women was often higher than the cost of providing obstetric care to HIV negative women in the same private health facility. This finding suggests that there is an urgent need for for public private partnerships so that HIV-infected women from different economic backgrounds can access affordable health care.

Woman's stage of pregnancy at the time of registration into the program

Women who were pregnant for less than 20 weeks at the time of registration into the program were found to be less likely to be LTF compared to women who were pregnant for more than 20 weeks. The cut-off of 20 weeks was selected because medical termination of pregnancy (MTP) in India is legally allowed up to 20 weeks. It was hypothesized that women who were registered before 20 weeks of pregnancy would be more likely to be LTF because some of them would opt for terminating their pregnancy and would not return to the PMTCT site. However, the analyses suggest that women who are registered early during pregnancy are more likely to continue utilization of PMTCT services.

Early registration has previously been linked with higher uptake of sdNVP (WHO, 2009). Recognizing the importance of preventing LTF in PMTCT programs, in it's recent PMTCT guidelines, WHO recommends starting ARV prophylaxis at 14 weeks, despite the lack of direct evidence showing that starting prophylaxis earlier (than 28 weeks) is associated with a reduced risk of intrauterine transmission of HIV.[18] This analysis suggests that the quality of counselling is important for retaining women in the program. Women in this program who were registered before 28 weeks (and hence were advised to start ARV at 28 week) were less likely to be LTF (data not shown). Women who are

registered earlier get the opportunity to have more counseling sessions with the PMTCT counselor and also get more time to cope with their HIV diagnosis, which might result into better follow-up. The association between early registration during pregnancy and better follow-up indicates that it is important to concentrate efforts on enrolling women early in the pregnancy in order to retain them in the program.

Partner's HIV status

Women whose partners were known to be HIV-infected were less likely to be LTF before delivery, but this factor it was not a significant predictor of LTF after delivery. This finding underscores the importance of partner's involvement and support during pregnancy. Partners who are aware of their HIV positive status are known to be more supportive of their pregnant wives in seeking both antenatal care and care to prevent MTCT.[19] A few studies, mainly from Africa, have documented the benefits of partner involvement within PMTCT. In Zambia and Kenya, for example, women who received counseling together with their partners had improved uptake of HIV testing, improved uptake of antiretroviral prophylaxis, and better adherence to alternative infant feeding options.[20,21] However, there is limited knowledge about the different strategies for partner involvement and testing in the PMTCT set-up. Based on this finding, it can be suggested that it is important to counsel partners who are HIV negative or unaware of their HIV status to support and encourage their HIV-infected pregnant wives to seek antenatal and postnatal care. Innovative strategies to increase partner involvement in PMTCT are required.

This study focuses on the demographic risk factors for LTF among HIV-infected women before and after delivery in the PMTCT program setting in India. In the analyses, we found similar factors associated with LTF both before and after delivery. These factors may be the key factors associated with continued utilization of services for the mother and the child. However, based on program experience, there may be other factors (which we did not measure), such as distance to the clinic, quality of the counseling sessions, non-disclosure to family, and fear of discrimination at a hospital that may directly or indirectly affect whether a woman is LTF. Figure 1 shows possible ways in which these factors may be influencing a woman's risk of being LTF from the PMTCT program. One of the possible limitations of this study is that the data were not primarily collected to study LTF in the PMTCT setting. However, this is an inherent problem with research examining LTF as the study outcome.

Although quality of the counseling sessions could not be assessed, there was no significant difference in the LTF across different PMTCT sites, suggesting uniformity in the quality of counseling across study sites. In this study, we were not able to assess the impact of non-disclosure to family members and experiences of discrimination in the health care setting as risk factors for being LTF. Based on findings from previous studies, both these factors appear to have direct effect on women's follow-up. Further research is warranted to study the effect of these factors on risk of LTF in the PMTCT context.

These results have identified the need for innovative and effective counseling techniques for women with less than college level education, economic empowerment of women, better strategies to increase up-take of partner's HIV testing and early registration of women in the program for improving utilization of PMTCT services by HIV-infected women. The need is even greater for PMTCT programs in the public health sector as the women accessing care in the public sector are less likely to be educated and economically more deprived.

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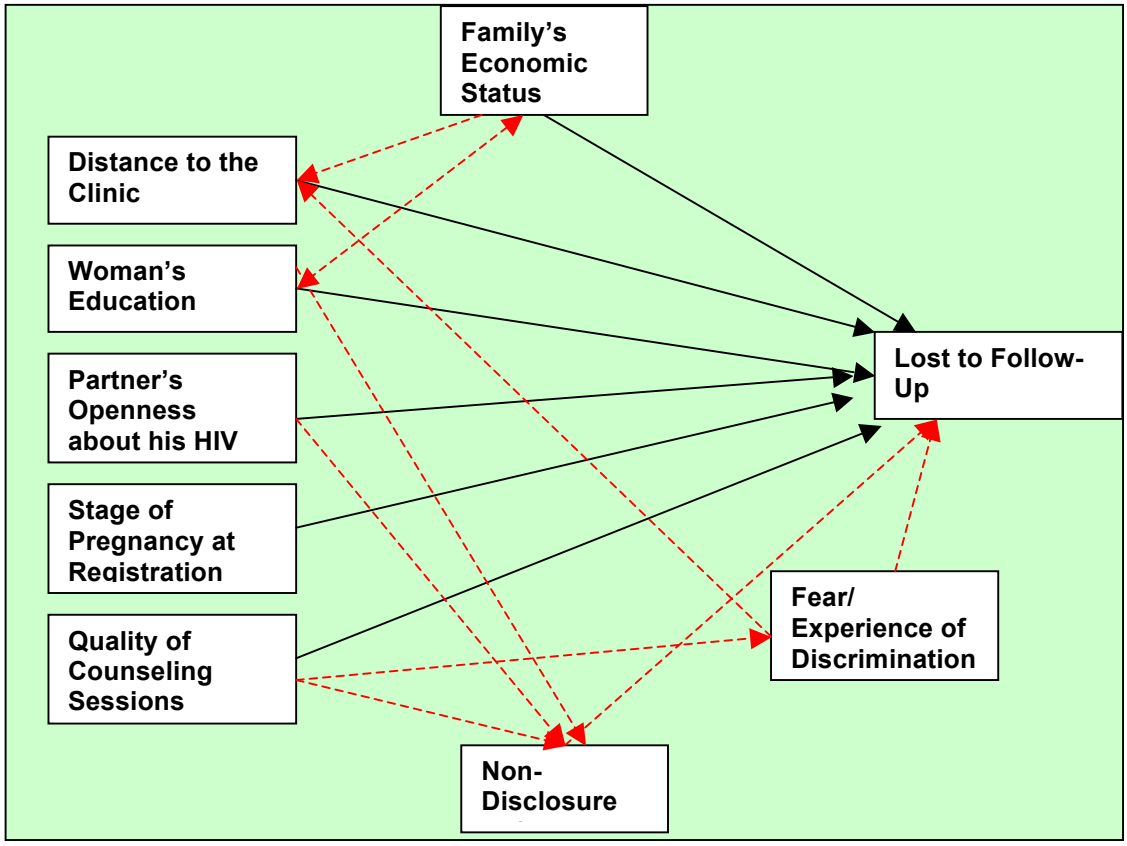

Figure 1: Schematic graph showing potential factors that may play a role in being lost to follow-up among pregnant women registered in the PMTCT program before and after delivery.

Table 2: Crude risk ratios and 95% confidence intervals of all potential risk factors for being lost to follow-up in HIV-infected pregnant women registered at study ANC sites providing PMTCT-related care

Variable	LTF Before Delivery			LTF After Delivery		
	n	RR	95% CI	n	RR	95% CI
Woman's Age Category (Years)						
<20	60			63		
20-24	367	0.70	0.37-1.32	362	0.86	0.53-1.40
25-29	209	0.52	0.25-1.06	229	0.70	0.41-1.18
≥30	94	0.57	0.25-1.33	109	0.85	0.48-1.51
Place of Residence						
Urban	353			358		
Rural	377	1.26	0.83-1.91	406	1.38	1.03-1.84
Previous Healthy Children						
No	446			468		
Yes	288	1.55	1.03-2.34	299	1.89	1.42-2.51
Woman's Education						
College	117			122		
Less than College	617	7.40	1.84-29.68	647	2.17	1.24-3.79
Family's Economic Status						
Middle Class/Rich	542			560		
Poor	192	2.20	1.46-3.76	207	1.65	1.23-2.20
Pregnancy Stage at Registration						
≤20 Weeks	208			179		
>20 Weeks	526	1.52	1.00-2.32	588	1.98	1.27-3.07
Partner's HIV Status						
Positive	526			429		
Negative/Not known	208	2.78	1.78-4.37	338	1.45	1.10-1.93
Partner's Occupation						
Driver	129			116		
Service/Professional	234	0.32	0.16-0.62	253	0.75	0.49-1.14
Agricultural/Non-agricultural Manual Laborer	233	0.84	0.51-1.40	251	0.94	0.63-1.41
Other	120	0.36	0.16-1.81	135	0.73	0.44-

Other	120	0.36	0.16-1.81	135	0.73	0.44-1.20
Type of Family						
Joint family	418			435		
Nuclear family	313	1.30	0.85-1.98	331	1.10	0.83-1.47
Referred to the Program by a Private Practitioner						
Yes	520			559		
No (Detected at Site)	214	1.71	1.13-2.59	211	1.67	1.25-2.23
Study Site						
Primary Program Clinic	135			135		
Partner Nursing Home	119	1.05	0.52-2.15	120	2.05	1.20-3.51
Partner Trust Hospital	480	1.06	0.61-1.86	516	1.57	0.97-2.53
Time of Delivery						
Full term				697		
Pre-term		-	-	74	0.82	0.48-1.40
Mode of Delivery						
Cesarian				388		
Normal		-	-	383	1.75	1.30-2.36
Gender of Baby						
Boy				407		
Girl		-	-	364	1.10	0.83-1.47
Birth weight (grams)						
>2000				695		
≤2000		-	-	54	1.61	1.04-2.50
Infant feeding option						
Formula/ Animal milk				633		
Breast milk		-	-	140	2.04	1.53-2.74
Medication Regimen for Baby						
Only ZDV/ZDV+NVP				648		
No ARV/ Only NVP		-	-	126	2.55	1.92-

Table 3: Crude and adjusted risk ratios and 95% confidence intervals for risk factors associated with being lost to follow-up before delivery in 734 HIV-infected pregnant women registered at study ANC sites providing PMTCT-related care

	Cases (Number in Subgroup)	RR (95% CI)	
		Crude	Adjusted
Woman's Education			
College* (>12 years)	2 (117)		
Less than College (≤12 years)	78 (617)	7.40 (1.84-29.68)	6.32 (1.57-25.44)
Family's Economic Status			
Middle Class/Rich*	40 (537)		
Poor	35(192)	2.20 (1.46-3.76)	1.61 (1.07-2.42)
Pregnancy Stage at Registration			
≤ 20 Weeks *	50 (526)		
> 20 Weeks	30 (208)	1.52 (1.00-2.32)	2.02 (1.34-3.05)
Partner's HIV Status			
Positive*	25 (410)		
Negative/Not known	55 (324)	2.78 (1.78-4.37)	2.69 (1.71-4.24)

Note: * represents the reference group

Table 4: Crude and adjusted risk ratios and 95% confidence intervals for risk factors associated with being lost to follow-up after delivery in 769 HIV-infected women registered at study ANC sites providing PMTCT-related care

	Cases (Number in Subgroup)	RR (95% CI)	
		Crude	Adjusted
Woman's Education			
College* (>12 years)	12(122)		
Less than College (≤12 years)	138(647)	2.17(1.24-3.79)	1.82(1.03-3.22)
Family's Economic Status			
Middle Class/Rich*	92(560)		
Poor	56(207)	1.65(1.23-2.20)	1.42(1.05-1.91)
Pregnancy Stage at Registration			
≤20 weeks*	20(179)		
>20 weeks	130(588)	1.98(1.27-3.07)	1.75(1.12-2.73)

Note: * represents the reference group

CHAPTER 3

BARRIERS ASSOCIATED WITH REDUCED UTILIZATION OF CONTINUED CARE AMONG HIV-INFECTED WOMEN WHO HAD PREVIOUSLY ENROLLED IN A PRIVATE SECTOR PMTCT PROGRAM IN MAHARASHTRA, INDIA: RESULTS FROM THE 'LINKING TO CARE' STUDY

ABSTRACT

Background

Prevention of mother-to-child transmission (PMTCT) programs are regarded as an entry point to continued care because they provide an opportunity to link an HIV-infected woman, her partner, and her child (if infected) to long-term treatment and care. However, little is known about the factors associated with utilization of continued care among women who have previously accessed PMTCT services. Better knowledge of the barriers to continued care in HIV-infected women could lead to effective strategies to increase the uptake of post PMTCT care.

Methods

The 'Linking to Care' study was designed to examine the factors associated with reduced utilization of continued care among HIV-infected women enrolled in the PRAYAS PMTCT program in Maharashtra, India, between 2002 and 2011. All consenting women who had completed the receipt of PMTCT services at least six months prior to the time of data collection were interviewed. Univariate and multivariate analyses were conducted to estimate the associations between not utilizing continued care and various hypothesized risk factors using generalized linear models.

Results

Of the 733 eligible HIV-positive women, 311 women consented to and completed a structured interview. Since their exit from the PMTCT program, 59 (19%) women had never accessed HIV-related care, 58 (19%) women had intermittently utilized HIV-related care, and 194 (62%) women had consistently utilized HIV-related care at regular intervals. After adjusting for potential confounders, women with poor HIV-related knowledge (RR= 1.83, 95% CI: 1.15-2.92), women who were currently married (RR=1.76, 95% CI 1.03-3.03), women whose partners had never utilized HIV-related care (RR=4.82, 95%CI: 2.57-9.04) and women who could not afford to travel to the HIV-care facility (RR=2.96, 95% CI 1.23-4.53) were less likely to utilize HIV-related care after exiting the PMTCT program.

Conclusions

This study highlights the need for enhanced techniques to impart HIV-related knowledge to all women who seek PMTCT services. This study also underlines the need for improved partner involvement during the PMTCT cascade to increase the uptake of post-PMTCT treatment and care.

Background

The inclusion of HIV testing and counseling services in antenatal care (ANC) has improved the identification and linking of HIV-infected women of reproductive age to prevention of mother-to-child transmission (PMTCT) services. PMTCT programs are widely regarded as an entry point to continued care because they can be utilized to ensure that the HIV-infected woman, her partner, and her child (if infected) continue to receive the necessary treatment and care. In fact, the four-pronged PMTCT approach promoted by the United Nations focuses not only on the prevention of vertical transmission of HIV from mother-to-child, but also emphasizes the utility of PMTCT programs as a pathway leading to continued treatment and care for HIV-infected women and their families.[1] A comprehensive understanding of the factors associated with access to continued care and treatment among HIV-infected women who have previously accessed PMTCT services and their partners and children (if infected) could help policymakers design effective strategies related to continuum of care for these women and their families.

Only a handful of studies exploring the factors associated with continued HIV-related care among women who have previously accessed PMTCT services in developing countries have been published to date. Most studies of HIV-infected women attending PMTCT programs or Antiretroviral Therapy (ART) clinics in resource poor populations have been carried out in Africa.[2-6] In India, little is known about utilization of continued care and treatment among women who have completed a PMTCT program. Only one qualitative report on utilization of continued care for HIV-infected women accessing PMTCT programs in India has been published to date.[7] Cultural and regional factors may influence a woman's decision in seeking and utilizing continued HIV-related care and treatment. It is important to study the barriers to continued care in a regional context. The identification of modifiable factors will help inform health care providers and policy makers in designing effective strategies to improve utilization of continued HIV-related care in women who have previously used PMTCT services.

Previous studies cite the presence of individual, community, and health system-level factors as potential barriers to continuing to receive HIV-related treatment. Individual-level barriers include demographic factors, such as marital status, lack of economic resources, and factors related to attitudes and beliefs regarding HIV and ART. Community-level barriers include the lack of family or social support, social stigma attached to HIV and discrimination against HIV-infected individuals. Health system-level barriers include insufficient supply of human resources, limited health infrastructure and lack of coordination in the process of providing care resulting in long waiting times.

A brief description of the factors that have been previously identified as barriers to utilizing continued treatment in HIV-infected women is given in the next section.

Overview of potential barriers to continued care in HIV-infected women

Individual-level barriers

Dalal et al. have identified socioeconomic factors, such as poverty and residence in a remote rural region, as risk factors for low utilization of continued treatment in women attending ART clinics in South Africa.[2] Qualitative studies from Malawi and Côte d'Ivoire have identified the inability to afford transportation required to travel to the clinic as a major barrier to continued utilization of HIV-related treatment among women attending PMTCT programs.[3-5] Financial constraints have also been reported as a major barrier to accessing post-PMTCT care among HIV-infected women living in Uganda.[6] The only quantitative study exploring risk factors for loss to follow-up among HIV-infected women enrolled in a PMTCT program in India has identified woman's education level and family's economic status as major risk factors for loss to follow-up.[8] A study from Nairobi, Kenya, reported that women who did not access care after completing a PMTCT program were less likely to believe that highly active antiretroviral therapy (HAART) is an effective treatment for HIV.[9]According to a Population Council report, South African migrants currently taking traditional medicine for their HIV infection or related co-morbid conditions were less likely to seek treatment from ART centers.[10]

Family and Community-level barriers

According to Bwirire et al., Painter et al., and Chinkonde et al., HIV-infected women attending PMTCT programs in Africa identified fear of household conflict, divorce, stigma, and discrimination on disclosure of HIV status as potential barriers to utilizing continued HIV-related care. Lack of emotional support from partners and their refusal to undergo HIV testing were also identified as barriers to utilization of continued HIV-related care. [4-6] The only study on HIV-infected women enrolled in a PMTCT program in India showed that women whose partner's HIV status was known or whose partner was seeking treatment for HIV were more likely to continue to utilize PMTCT services.[8] Nguyen et al. found that women who did not have a known HIV-positive family member and who had not disclosed their HIV status were less likely to utilize HIV care and treatment services in Vietnam.[11] The same study also reported that women who were randomly tested for HIV had four times the odds of failing to seek HIV care and women who were tested as a part of antenatal care had three times the odds for failure to seek HIV care compared to women who had been tested because their partners were sick or had died. Ahoua et al., in their recent paper on the evaluation of a five-year PMTCT program in Uganda, have showed that women with children suffering with a diagnosed acute illness were more likely to seek HIV-related continued care and treatment for themselves.[12]

Health system-level barriers

Bwirire et al. have identified long waiting times at ANC centers (due to scarcity of trained health staff) as a risk factor for not utilizing continued HIV-related care among women attending PMTCT programs in Africa.[4] Long waiting times at the clinic and suboptimal provider-patient interactions at the hospital have also been identified by HIV-infected women in Uganda as barriers to seeking post-PMTCT treatment and care.[7]

Methods

I used de-identified data previously collected by PRAYAS for programmatic purposes. The PRAYAS 'Linking to Care' study was designed to identify the modifiable factors associated with utilization of continued HIV-related treatment and care among HIV-infected women enrolled in the PRAYAS PMTCT program in Maharashtra, India.* Detailed information about potential barriers to utilization of continued HIV-related treatment and care from 311 consenting HIV-infected women who had previously enrolled in the PRAYAS PMTCT program was collected. Women were considered eligible for the study if they were enrolled at any one of the 43 PRAYAS PMTCT sites between September 2002 and March 2011 and if they had completed the receipt of PMTCT services at least six months prior to the date of data collection. Women who were on antiretroviral treatment (ART) at the time of enrollment into the PRAYAS PMTCT program were considered eligible for the study, irrespective of the six-month eligibility requirement. Prior to contacting the women, detailed information provided by each woman at the time of enrollment in the PMTCT program, including whether she had disclosed her HIV status to her partner and family, was reviewed by the interviewer in order to safeguard the woman's wish for non-disclosure. If it was found that a woman was deceased, her partner was contacted for information related to her utilization of treatment and care, along with information related to his own use of HIV-related care and that of their child's (if HIV-infected). If the woman and her partner were both deceased, no information was collected from the family members.

Utilization of continued HIV-related care was defined as ≥1 visit to any health facility for a general check-up, CD4 count, HIV viral load test, treatment for an opportunistic infection, or treatment with ART after completing the services provided by the PMTCT program. Trained interviewers used a structured questionnaire to collect information on potential barriers to utilization of continued HIV-related treatment and care. Information concerning knowledge and beliefs related to HIV and ART, disclosure of HIV status, socio-demographic status, obstetric and medical history of the woman, HIV serostatus of her partner and children and medical history of her partner and children (if HIV-infected) was collected at the time of the interview. Information related to previous use of antiretroviral drugs (ARVs) during pregnancy or at the time of delivery was collected from the PRAYAS PMTCT medical records.

Data Analysis

Distributions and frequencies of all the predictor variables were examined. Standard preliminary descriptive analyses of all study variables were calculated. All predictor variables and covariates in this study were categorical by design.

*PRAYAS had obtained institutional ethics review board approval for collecting these data.

Principal Component Analysis (PCA) was used to construct socioeconomic status quintiles. In addition to household ownership of durable assets, such as owning a house, television, refrigerator, motorcycle, car, etc., variables related to housing characteristics, such as source of drinking water, type of sanitation facility, type of fuel used for cooking, and type of materials used for making the floors, walls, and roof of the house were included in the construction of socioeconomic status quintiles. We drew on the framework outlined by the Demographic and Health Surveys (DHS) to decide which variables to include in the construction of the socioeconomic quintiles.[13]

Univariate analyses were conducted to estimate the associations between never utilizing continued care and various factors that were determined a priori. Multivariate analyses were conducted by including all relevant covariates in generalized linear models. We chose to estimate the relative risks instead of estimating the odds ratios, because the outcome (never utilizing HIV-related treatment and care) was not a rare occurrence. The final model was adjusted for woman's age, place of residence, education, occupation, disclosure of HIV status & family's socioeconomic status. All statistical analyses were performed using STATA for Macintosh (Version 12.0).

Results

Of the 1196 HIV-infected women who had enrolled in the PRAYAS PMTCT program between 2002 and 2011, 733 women met the eligibility criteria for the 'Linking to Care' study. Of those eligible for the study, 374 (51%) women could be contacted and informed about the study. Of those contacted, 316 (84%) women gave their consent for an interview. Table 5 gives a description of all eligible women who could and could not be contacted to participate in the 'Linking to Care' study. Of those who consented to an interview, five women could not complete the interview. Of those interviewed, 59 women had never utilized HIV-related care (i.e. never visited an HIV care or treatment facility), 58 women had intermittently utilized HIV-related care (i.e. had visited a HIV care facility at least once), and 194 women had consistently utilized HIV-related care at regular intervals (i.e. visited an HIV care or treatment facility at least every six months) after exiting the PMTCT program. Table 6 provides a detailed description of all eligible women who consented to participate in the 'Linking to Care' study. Fifty six percent (33 of 59) of women who never utilized HIV-related continued care lived in a rural area. Almost 30 percent (17 out of 59) of women who never utilized HIV-related continued care were in the lowest socio-economic quintile compared to 17 percent (43 out of 252) of women who utilized HIV-related continued care. The mean age of women who utilized HIV-related continued care was slightly higher (28.9 years) compared to that of women who never utilized HIV-related continued care (27.8 years). Almost 31 percent (18 out of 59) of women who never utilized HIV-related continued care had less than five years of education, whereas only 18 percent (45 out of 252) of women who utilized HIV-related continued care had less than five years of education. Only 19 percent (11 out of 59) of women who never utilized HIV-related continued care had partners who were seeking HIV-related care, whereas 61 percent (154 out of 252) of women who had

utilized HIV-related continue care had partners who were currently seeking continued care.

Table 7 gives the results of the final multivariate model. Women with little or poor HIV-related knowledge (RR= 1.83, 95% CI 1.15-2.92), women whose partners were not seeking continuous care (RR=4.82, 95% CI 2.57-9.04), and women who could not afford to travel to the HIV care facility (RR=2.36, 95% CI 1.23-4.53) were less likely to utilize continuous HIV-related care after adjusting for potential confounders. Although currently married women were more likely to utilize continued HIV-related care in the univariate analysis, after adjusting for potential confounders, currently married women were less likely to utilize follow-up HIV-related care (RR=1.76, 95% CI 1.03-3.03). Family wealth index (measured using durable asset ownership) and woman's level of education, occupation, and place of residence (rural/urban) were not statistically significantly associated with utilization of continued HIV-related care.

Discussion

Lack of integration of PMTCT services with follow-up HIV-related care and treatment services may result in a missed opportunity to improve health and post-partum follow-up of HIV-infected women. WHO's PMTCT Strategic Plan 2010-2015 calls for a high priority to be given to strengthening linkages between PMTCT and HIV care and treatment services for women, their children and other family members in order to support an effective continuum of care.[14] The integration of PMTCT services and follow-up HIV-related services could not only help in decreasing morbidity among HIV-infected women but also facilitate the provision of additional services to HIV-infected women, including counseling for family planning and improving nutritional status. The 'Linking to care' study is the first study to use quantitative techniques to identify key barriers to continued HIV-related care in women who have previously received PMTCT services in India. This study is critical to the understanding of key modifiable factors that are involved in preventing HIV-infected women of reproductive age from continuing to utilize HIV-related treatment and care in India. We found that 28 percent of the women who participated in the study were unable to answer basic questions related to HIV and HIV-related treatment. This number is especially alarming because all women who enroll in the PMTCT program are counseled and given a comprehensive overview of the disease and the available treatments. This study, therefore, highlights the need for enhanced techniques to impart HIV-related knowledge to all women who seek PMTCT services.

We also found that women whose partners were not seeking continued care were less likely to utilize continued HIV-related care. Men are often the key decision makers in Indian families. Hence, there is a need for increasing the involvement of men in issues related to women's health, including HIV-related treatment and care. According to the Population Council report on continuum of care for HIV-infected women seeking PMTCT services in India, of 176 women living with HIV-infected partners who were interviewed, 28 percent of the partners were on ART, whereas only seven percent of the

women were on ART. Almost all of these men had started ART earlier than their wives, although some of them had their HIV infection diagnosed after their wives.[7] This study underlines the need for improved partner counseling and involvement during the PMTCT cascade to increase the uptake of post PMTCT care in their wives. Although we found that currently married women were less likely to utilize continued care, this finding may be a result of the fact that most women who were not currently married had lost their partner to HIV and were seeking treatment because they themselves were at an advanced stage of the HIV infection.

According to this study, the family's socioeconomic status (measured using durable asset ownership) and the woman's education, occupation and place of residence (rural/urban) were not significantly associated with utilization of continued HIV-related treatment and care. However, we did find that the ability to afford travel to HIV-care facility was a significant barrier to utilization of continued treatment and care. This finding has also been reported by studies from Malawi, Côte d'Ivoire and Uganda.[3-6]

Fear of disclosure of HIV status to the family or community has been mentioned as a key barrier to utilization of HIV-related care in studies from the African sub-continent, However, only five women who participated in the 'Linking to Care' study reported that disclosing their HIV status to their family or the community was a barrier to utilizing HIV-related treatment and care.

One of the limitations of this study is that, despite painstaking efforts, we were able to reach only a little over half of all women who were eligible for this study. Change in addresses and telephone numbers provided at the time of the registering for the PMTCT program was the primary reason for the inability to reach the women. It is possible that the women who could not be contacted are systematically different from those who participated in the 'Linking to Care' study. However, comparing baseline socioeconomic and demographic indicators of eligible women who participated in the study and those who did not suggests no such difference (Table 5). In order to interpret the adjusted models with regards to the entire target population, we assume that conditional on covariates in the model, the decision to participate in the study was random. Hence, we may not be able to generalize these findings to the greater target population if this assumption is not met. Further research is needed to test this assumption. Second, we used a structured questionnaire to capture the information on barriers to continued care. Although such a questionnaire is easy to administer to a large number of women, it may not be sufficiently comprehensive to capture all barriers and may not enable the respondent to raise other relevant issues. It is important to note that the structured questionnaire was subjected to rigorous pilot testing with a variety of respondents before finalization.

Despite the availability of free ART at all government run hospitals in India, utilization of treatment and care for HIV remains low. In order to maximize the impact of the services provided by PMTCT programs and ART centers in India, it is therefore crucial

to develop strategies and policies to ensure that women completing the PMTCT program are linked to continued care.

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Table 5 : Covariates of all eligible women who could and could not be contacted to participate in the 'Linking to Care' study

Variables		Could be Contacted to Participate in the LTC study		Total	$\chi 2$ statistic	p-value
		Yes	**No**			
Lives in Rural Area	Yes	130	149	279		
	No	194	260	454		
				733	1.0	0.306
Woman's Education	≤5 years	181	242	423		
	>5 years	143	164	310	0.8	0.368
				733		
Woman's Occupation	Housewife	256	339	595		
	Working	68	70	138		
				733	1.8	0.183
Marital Status	Married	317	393	710		
	Not Married	7	16	23		
				733	1.8	0.177

Table 6: Covariates of all eligible women who consented to participate in the 'Linking to Care' study

Variables		Utilized HIV-related Continued Care		Total	$\chi 2$ statistic	p-value
		Ever	Never			
HIV-related Knowledge	Adequate Knowledge	197	28	225	22.5	0.000
	Poor Knowledge	55	31	87		
				311		
HIV Status Known before PMTCT	Yes	96	10	106	9.5	0.002
	No	156	49	205		
				311		
Lives in Rural Area	Yes	89	33	122	8.5	0.004
	No	163	26	189		
				311		
Asset Index Quintile	0	43	17	60	9.7	0.046
	1	48	15	63		
	2	49	11	60		
	3	59	5	64		
	4	53	11	64		
				311		
Woman's Age	≤20	6	4	10	12.4	0.029
	21-25	55	21	76		
	26-30	108	14	122		
	31-35	56	15	71		
	36-40	22	5	27		
	>40	5	0	5		
				311		
Woman's Education	≤5 years	45	18	63	4.7	0.030
	>5 years	207	41	248		
				311		
Woman's Occupation	Housewife	176	39	215	0.3	0.576
	Working	76	20	96		
				311		

Afford Travel to HIV Care Facility	Yes	107	10	117	13.3	0.000
	No	145	49	194		
				311		
Currently Married	Yes	214	48	262	0.5	0.499
	No	38	11	49		
				311		
Partner Linked to HIV Care	Yes	154	11	165	34.6	0.000
	No	98	48	146		
				311		

Table 7: Barriers associated with never utilizing HIV-related treatment and care after exiting the PMTCT program.

	Number of Women who Never Utilized HIV-related Continued Care (Total Number in Sub-group)	RR(95% CI) Crude	RR(95% CI) Adjusted
Woman's Basic HIV-related Knowledge			
Adequate knowledge*	28(225)	2.89(1.85-4.53)	1.83(1.15-2.92)
Poor knowledge	31(87)		
Partner Linked to HIV-related Continued Care			
Linked*	11(165)	4.93(2.66-9.14)	4.82(2.57-9.04)
Not-linked	48(146)		
Woman is Currently Married			
Yes	48(262)	0.82(0.46-1.46)	1.76(1.03-3.03)
No*	11(49)		
Could Afford Travel Expenses to HIV Care Facility			
Yes*	10(117)	2.96(1.56-5.61)	2.36(1.23-4.53)
No	49(194)		

Note: * represents the reference group.

Final model was adjusted for woman's age, place of residence, education, occupation, disclosure of HIV status & family's socioeconomic status.

CHAPTER 4

EFFECT OF *IN UTERO* HIV EXPOSURE ON BIRTH WEIGHT AND POSTNATAL GROWTH IN HIV-UNINFECTED CHILDREN IN INDIA

ABSTRACT

Background

Postnatal growth patterns in HIV-infected children have been studied in detail, and impaired postnatal growth, especially stunting, has been reported as a common manifestation of HIV infection. Some studies have reported stunting in HIV-exposed uninfected children (HIV-EU) compared to HIV-unexposed children, while others have found no such association. No studies on the effect of HIV-exposure on postnatal growth patterns in HIV-EU children in India have been published to date.

Methods

We compared birth weight, height and weight of 297 HIV-EU children born to mothers who had previously registered in a prevention of mother-to-child transmission (PMTCT) program and 1611 HIV-unexposed children residing in the state of Maharashtra from the National Family Health Survey (NFHS) 2005-06 database. We used linear regression models to evaluate the association between *in utero* HIV exposure and birth weight and *in utero* HIV exposure and postnatal height and weight, after adjusting for potential confounders.

Results

HIV-EU children weighed 123.5g less at birth ($p<0.01$) compared to HIV-unexposed children, after adjusting for potential confounders. On average, HIV-EU children were 2.9 cm shorter ($p<0.00$) compared to HIV-unexposed children after adjusting for potential confounders. In children ≤ 5 years of age, with every year of increase in age, HIV-EU children grew 0.8 cm ($p<0.01$) less than HIV-unexposed uninfected children. At ages three and five, the HIV-EU children were 0.22 cm ($p<0.05$) and 1.8 cm shorter ($p<0.05$) than HIV-unexposed uninfected children respectively. When we only considered children ≤ 3 years of age, HIV-EU children grew 1.6 cm ($p<0.05$) less than HIV-unexposed uninfected children. At age three, the HIV-EU children were 2.34 cm shorter ($p<0.05$) than HIV-unexposed uninfected children. We did not find a significant difference in weight between HIV-EU and HIV unexposed After adjusting for potential confounders, no significant difference in weight between HIV-EU and HIV unexposed uninfected children was found at different ages.

Conclusions

HIV-EU children from India are more likely to be of lower birth weight and shorter stature compared to children born to HIV negative mothers. We did not find any association between *in utero* HIV exposure and weight at any age. Developing an understanding of the determinants of growth impairment in HIV-EU children in India is critical, given that the number of HIV-EU infants detected is likely to increase due to

implementation of programs that aim at reducing mother-to-child transmission of HIV.

Background

Growth is an indicator of overall infant and child health. Human growth can be described as a complex process, with interactions between multiple environmental, genetic, and nutritional factors (Figure 2). Abnormalities in somatic growth typically appear in one of several patterns. Stunting (decreased height for age), wasting (decreased weight for height), and underweight (decreased weight for age) are the most common postnatal growth abnormalities.[1]The associations between infant and child HIV infection and impaired postnatal growth in height and weight over time have been studied in detail and the results are fairly consistent across studies.[2-21] Although the pathophysiology of impaired postnatal growth among HIV-infected infants and children is not completely understood, typically, HIV-infected children with growth failure are short for age but normally proportioned (i.e. have normal weight-for-height ratios).[22] Inadequate weight gain or frank weight loss (i.e., wasting) is also seen in HIV-infected children,[16] but less commonly than stunting.[2-5, 7-21] Height-for-age growth velocity has been reported as the growth index most closely associated with poor health outcomes and clinical progression among HIV-infected children receiving antiretroviral (ARV) therapy in the United States.[23]

Several factors, including inadequate nutritional intake, HIV-related infectious illnesses, and low socioeconomic status, have been hypothesized to be associated with poor height-for-age outcomes in HIV-infected children.[22] Studies published before the advent of ARV therapy showed that increasing the nutritional intake of HIV-infected infants and children with supplemental feeding improved weight but did not affect height-for-age in children with HIV-associated growth failure.[24] Deficits in height-for-age in HIV-infected children are detectable well before the onset of HIV-related symptomatic infections and hence cannot be completely attributed to these illnesses.[22]

Recent scientific evidence points to associations between immunological abnormalities and low height-for-age among HIV-infected infants and children (see below). Although exposure to HIV continues in HIV-infected children, leading to several immune abnormalities, it has been shown that *in utero* exposure to HIV without infection leads to similar immunologic abnormalities.[30-32, 37,38]

HIV infection in infancy initiates a series of complex events, culminating in profound immunosuppression caused by prolonged immune activation and subsequent alterations in T-cell homeostasis. In particular, naïve CD4 and CD8 cells are progressively depleted as a consequence of their frequent activation and differentiation into memory cells.[25-27] Sustained immune activation in children infected with HIV early in infancy has been linked to poor health indicators, including poor growth and progression to AIDS.[28, 29] *In utero* exposure to HIV does not always result in HIV infection in the baby. Data from previous studies show that *in utero* exposure to HIV or its soluble proteins, without infection, induces premature immune activation and impairs T-cell homeostasis.[30, 31] These abnormal immune responses are similar to those seen in HIV-infected infants.[32] Moreover, these abnormal immune responses have been shown to persist for years, long

after exposure to the virus or its proteins has ceased.[31]

The human thymus is the primary site of *de novo* T-cell development and is highly active during early life. Human thymocytes synthesize and secrete growth hormone (GH) and insulin-like growth factor -1 (IGF-1). GH functions as a growth factor in the human thymus via locally synthesized IGF-1.[33] Reduced thymic output, along with GH resistance, has been shown in HIV-infected children.[26, 34,35]GH resistance and reduced levels of IGF-1 are associated with deficits in height-for-age and weight-for-age in HIV-infected children.[34-36] *In utero* exposure to HIV without infection is associated with significantly reduced thymic output in infants.[37, 38] In spite of the similar reduction in thymic output seen in HIV-EU children, GH and IGF-1 levels and their associations with postnatal growth have not yet been studied in HIV-EU children.

In addition to the immunologic abnormalities mentioned above, maternal HIV-infection has been shown to be associated with reduced placental antibody transfer to infants born to these mothers.[39, 40] Such reductions in antibody transfer can compromise postnatal infant protection and affect immune development and hence growth, in not only HIV-infected infants, but also in HIV-EU infants.[41]

Few studies to date have explored the association between exposure to HIV and impaired postnatal growth. Although there is some evidence that exposure to HIV without infection may be associated with poor postnatal height-for-age, the results of prior studies on this subject have not been consistent. The discrepancy in results could be due to certain methodological limitations of these studies.

No studies on the effects of exposure to HIV in infancy on postnatal growth patterns in children in India have been published to date. Differences in the levels of total lymphocyte count and its subsets, as well as neutrophil counts, have been shown in HIV-EU children across different countries. These differences have been attributed to genetic and environmental factors, including nutrition and exposure to infectious agents.[42] It is therefore important to study the growth patterns of HIV-EU children in India, as results from other countries may not be applicable to the Indian setting.

Epidemiological studies of HIV exposure and postnatal growth

Studies from developed countries

A study from Italy that followed 92 HIV-EU infants and 65 infants born to HIV-uninfected mothers found that HIV-EU infants had lower length-for-age compared to infants born to HIV- seronegative women at six, 12, and 24 months of age (z scores being 0.06, 0.26, and 0.46 lower in HIV-EU infants, respectively, $p<0.05$) even after adjustment for infant's sex and birth order, father's occupation, maternal age at the time of birth, mother's education, maternal drug use and smoking habits during pregnancy, and mother's immunologic status, categorized using the HIV disease staging and classification system as described by the CDC and the WHO.[43]

In a cohort study of 77 HIV-EU children and 86 children born to HIV- uninfected mothers in the U.S, height-for-age was measured at regular intervals from birth to 14 years of age. This study reported a greater risk of growth failure (defined as height-for-age z <-2, growth <4 cm/year or height deceleration of >10%) in HIV-EU infants compared to children born to HIV uninfected mothers. This study did not provide information on whether any potential confounding factors were adjusted for in the analysis.[44]

Children born to HIV-infected mothers in eight European countries were enrolled at birth in the European Collaborative Study and followed prospectively. Serial measurements of height and weight from birth to ten years of age of 1403 HIV-EU and 184 HIV-infected children were assessed. Growth patterns of HIV-EU and HIV-infected children were compared with British growth standards in 1990. At an early age, the length-for-age and height-for-age z scores of HIV-EU children were lower compared to those of children in the 1990 British Growth Standards. However, after four years of age the HIV-EU children in this cohort were found to have higher length-for-age and height-for-age z scores than children in the reference group. This study failed to control for any of a number of potential confounding factors, such as infant feeding practices, maternal education, maternal health status, maternal smoking or drug use, and household income.[45]

Studies from developing countries

A prospective cohort study in the Democratic Republic of Congo (DRC) compared length, weight, and weight-for-length of 190 HIV-EU children, and 256 HIV uninfected children born to HIV uninfected mothers. The risk of falling below -2.0 *z*-scores from the reference values for weight-for-age, and height-for-age was estimated as a function of child and maternal immunological, clinical, and socio-demographic variables. The HIV-EU children in this study were found to be stunted (0.15 *z* lower in HIV-EU children, $p<0.05$) but not underweight compared to the unexposed infants at eight months of age. The study concluded that exposure to HIV placed children at increased risk for growth retardation.[16]

In another study, HIV-infected and uninfected women in Lusaka, Zambia were followed regularly from late pregnancy to 16 weeks postpartum. Infant weight and length were measured at birth, and at six and 16 weeks of age. Infant anthropometric *z* scores, both with and without correction for gestational age at delivery, were calculated from the British growth standards. At all time points, HIV uninfected infants of HIV-infected mothers tended to have lower weight and length standard deviation *z* scores, even after adjustment for their lower gestational age at birth, compared with infants born to HIV-uninfected mothers ($p<0.05$). In multivariate analyses, the major factors affecting weight or length at six or 16 weeks of age were birth weight and length, maternal subclinical mastitis, primiparity, and maternal weight during pregnancy. In this study, the infants' HIV sero-status was not determined through laboratory methods. Analyses were limited to comparisons of postnatal growth by maternal HIV infection status among children who appeared 'healthy' at follow-up.[46]

In a prospective cohort study of 140 HIV-EU children born to HIV seropositive mothers and 218 children born to HIV seronegative mothers in Kigali, Rwanda, weight, height, and head circumference of HIV-EU children, and HIV uninfected children born to seronegative mothers were compared. Anthropometric measurements were taken at birth, every three months during the first year of life, and every six months thereafter. Weight-for-age, height-for-age, head circumference- for-age, and weight for-height mean *z* scores were calculated using the data from the National Center for Health Statistics (NCHS) as the reference standard. Statistically significant differences for weight-for-age, height-for-age and head circumference-for-age mean z scores ($p < 0.01$) between HIV-EU children and those born to HIV-seronegative mothers were observed only early in life (at six months of age) for the height-for-age mean *z* score. However, the inability to detect a statistically significant difference beyond six months of age may have been influenced by lower survival of children born to HIV-infected mothers compared to those born to HIV seronegative mothers.[15]

To evaluate the longitudinal growth patterns of HIV uninfected infants born to HIV-infected and uninfected mothers in Malawi, Henderson et al. studied weight and length among 270 HIV-EU infants and 686 infants born to HIV uninfected mothers from birth to 24 months of life. HIV-EU children were compared with uninfected children born to HIV- uninfected mothers and to the NCHS growth standards. Mean growth curves constructed using generalized estimating equations showed that HIV-EU infants weighed less and were smaller initially than infants born to HIV uninfected mothers.[47] There was no discussion in the paper of the control for any potential confounders, such as infant feeding practices, mother's health status, and family's socioeconomic status.

Sherry et al. followed a cohort of 155 HIV-EU and 139 HIV uninfected children born to HIV seronegative mothers in a maternity hospital in Nairobi, Kenya, between 1991 and 1994. Children in the cohort had similar socio-demographic characteristics, lived in similar housing in similar geographical areas, had mothers as their primary care givers, and similar feeding practices. HIV-EU children were more compromised in length-for-age at 1.5 months of age ($p < 0.05$) compared to HIV uninfected children. This study had considerable loss to follow-up in both groups and the researchers were unable to verify if the children who were lost to follow-up had the same growth patterns as those who remained in the study.[48]

After reviewing the published literature, it is apparent that there is consistent evidence for an association between *in utero* HIV exposure and impaired postnatal height-for-age in both the developed and developing country setting. It is important, however, to note that many of the studies evaluating the association between HIV exposure and postnatal growth have failed to control for potentially important confounders, such as infant feeding practices, mother's health status, and family's socioeconomic status. In addition to failing to adequately control confounding, many of the studies lacked precision in estimating the effect measure of interest, owing to their small sample sizes. Further, many studies conducted in the developing country setting did not describe methods for confirming the child's HIV status i.e. whether the child was subsequently infected via

breast milk. Most studies exploring the association between HIV exposure and postnatal growth have evaluated only the short-term effects of HIV on postnatal growth. Data beyond two years of age are limited, and the follow-up periods of less than six months found in some studies may not be long enough to capture the complete pattern of change in growth outcomes. The aim of this study was to evaluate the association between *in utero* HIV-exposure and postnatal growth without the limitations of previous studies.

Methods

I used de-identified data previously collected by PRAYAS for programmatic purposes.* Data on height (cms), weight (kgs), age (months), and gender of 297 HIV-EU children born to mothers who had previously registered in the PRAYAS prevention of mother-to-child transmission of HIV (PMTCT) program was used. HIV-EU children were considered eligible for the study if their mothers had completed the receipt of PMTCT related services between September 2002- March 2011 from any of the PRAYAS PMTCT sites and if they had been confirmed to be HIV uninfected by DNA PCR. Information on birth weight was obtained from the PRAYAS PMTCT birth record for each HIV-EU child. Information on potential confounders, including socio-demographic variables, child's birth order, infant feeding option, and mother's medical history, was collected from the mothers of the HIV-EU children by trained interviewers using a pre-designed structured questionnaire. Height and weight measurements of all HIV-EU children were carried out using calibrated equipment and according to WHO guidelines.

All HIV-unexposed children born to mothers who were confirmed to be HIV seronegative and residing in the state of Maharashtra at the time of the third National Family Health Survey (n=1611) were used as controls in this study. The National Family Health Survey (NFHS) is a large, multi-round survey conducted in a representative sample of households throughout India. This survey dataset provides detailed information on key biological variables and socio-economic variables.[49]

Data Analysis

Distributions and frequencies of all the predictor variables were examined. Standard preliminary descriptive analyses of all study variables were calculated (Table 8). Figure 3 gives a schematic of all covariates and their potential associations with HIV exposure and the outcome (postnatal growth).

Principal Component Analysis (PCA) was used to construct socioeconomic status quintiles. In addition to household ownership of durable assets, such as house, television, refrigerator, car, motorcycle, etc., variables related to housing characteristics such as source of drinking water, sanitation facility, etc. were included in the construction of socioeconomic status quintiles. We drew on the framework outlined by the Demographic

* PRAYAS had obtained institutional ethics review board approval for collecting these data.

and Health Surveys (DHS) to decide which variables to include in the construction of the socioeconomic quintiles.[50]

Relevant covariates were tested in multivariate models using linear regression. Separate final models for analysis of HIV exposure and birth weight, HIV exposure and current height and *in utero* HIV exposure and current weight were selected using backward stepwise elimination technique. All statistical analyses were performed using STATA for Macintosh (Version 12.0).

Results

As shown in Table 8, more children from the control group belonged to the lowest and second lowest socioeconomic quintile compared to the HIV-EU children (17% versus 13% and 22% versus 17%, respectively). However, more children from the control group lived in urban areas compared to HIV-EU children (70% versus 58%). Almost 99% of mothers of children in the control group were currently married, whereas only 85% of mothers of HIV-EU children were currently married. Almost 70% of mothers of controls had more than one living child versus 57% of mothers of HIV-EU children. Only one percent of controls were not breastfed versus 66% of HIV-EU children.

Table 9 gives the adjusted values of birth weight in HIV-EU compared to HIV-unexposed children. On average, HIV-EU children weighed 123 g less at birth (95% CI: -31.9 to -215.1) compared to HIV-unexposed children, after adjusting for the child's gender, socio-economic status, place of residence and other variables related to the mother such as marital status, age at delivery, parity, occupation, education and whether the mother was on ART during pregnancy. Having more than one living child was significantly associated with a higher birth weight (98.6 g, 95% CI 33.8 to 163.3). Taking ART during pregnancy was significantly associated with a lower birth weight (-308 g, 95% CI: -42.3 to -573.9). Male sex was found to be statistically significantly associated with a higher birth weight (97.1 g, 95% CI: 40.1 to 154.2).

Table 10a gives the adjusted differences in values of height in HIV-EU compared to HIV-unexposed children under four different models. Model 1 includes children of all ages (including those over the age of five). Model 2 only includes children five years or younger. Model 3 includes the interaction term of HIV exposure and child's age for children five years or younger. Model 4 includes the interaction term of HIV exposure and child's age for children three years or younger. The rationale for including children five years or younger is that the control group only includes children up to the age of five. Models 3 and 4 include the interaction term of HIV exposure and child's age to evaluate how the effect of HIV exposure on child's height varied with age. Model 4 was run to assess whether a similar effect was seen if younger children (three years or younger) were included in the analysis. Although we show results of a sensitivity analysis at age three years or younger, sensitivity analyses for each age bracket were carried out. On average, HIV-EU children were 2.9 cm shorter (95% CI: -1.4 to -4.4) compared to HIV-unexposed uninfected children, after adjusting for child's age, gender, whether the child was

breastfed, socio-economic status, place of residence, mother's age, occupation, education and whether mother was on ART during pregnancy (Model 1). Breastfeeding was significantly associated with lower height (-4.1 cm, 95% CI: -2.5 to -5.7). Unit increase in mother's age at the time of delivery was significantly associated with an increase in height (0.2 cm, 95% CI: 0.1 to 0.3). Male sex was significantly associated with increased height (1.5 cm, 95% CI: 0.9 to 2.2).

When we considered children five years or younger, we failed to find a statistically significant effect of HIV exposure on child's height after controlling for known confounders (Model 2). When we added an interaction term of HIV exposure and child's age, we found that with every year of increase in age, HIV-EU children grew 0.8 cm (95% CI: -0.01 to -1.6) less than HIV-unexposed uninfected children. At ages three and five, the HIV-EU children were 0.22 cm ($p<0.05$) and 1.8 cm shorter ($p<0.05$) than HIV-unexposed uninfected children respectively (Model 3, Table 10b). Similar results were seen when we only considered children three years or younger. HIV-EU children grew 1.6 cm (95% CI: -0.2 to -2.9) less than HIV-unexposed uninfected children. At age three, the HIV-EU children were 2.34 cm shorter ($p<0.03$) than HIV-unexposed uninfected children (Model 4, Table 10b).

We carried out similar analyses to determine the adjusted differences in values of weight in HIV-EU compared to HIV-unexposed children (Tables 11a and 11b). When we considered children of all ages, we found that there was no significant difference in the values of weight for HIV-EU children and HIV-unexposed children, after adjusting for known confounders (Model 1). On average, in children five years and younger, HIV-EU children weighed 430 g more (95% CI: 40 to 830) compared to HIV-unexposed children, after adjusting for child's age, gender, whether the child was breastfed, socio-economic status, place of residence, mother's age, occupation, education and whether the child's mother was on ART during pregnancy (Model 2). Unit increase in mother's age at the time of delivery was significantly associated with an increase in weight (30g, 95% CI: 10 to 50). Unit increase in mother's education was also associated with an increase in weight (40g, 95% CI: 20 to 70) Multi-parity was significantly associated with a decrease in weight (-260g, 95% CI: -70 to -450). Male sex was significantly associated with an increase in weight (560 g, 95% CI: 80 to 6690). We did not find a significant difference in weight between HIV-EU and HIV unexposed children at different ages after adjusting for potential confounders.

Discussion

Few studies worldwide have evaluated the association between exposure to HIV and postnatal growth. While some prior studies have found an association between *in utero* exposure to HIV and impaired height-for-age, others have found no such association. Most of these studies evaluating the association between *in utero* exposure to HIV and postnatal growth have suffered from one or more methodological limitations, including insufficient control for potential confounders, small sample sizes, lack of an appropriate control group and inability to study growth beyond the age of two years. Following is a

detailed outline of limitations of previous studies exploring the association between HIV exposure and postnatal growth.

i) Insufficient control for confounders

Control for factors that could be associated with postnatal growth was found to be inconsistent across studies exploring the association between *in utero* exposure to HIV and postnatal growth. Potential confounding due to covariates associated with growth, such as gender, infant feeding practice, and maternal factors, was not controlled for in a few studies. Here we would like to discuss the possible role of these confounders:

Maternal ill health or death resulting in reduced care of infants

The UNICEF model of causes of malnutrition recognizes the important contribution of care to child health.[51] Care has many components that are not easy to measure in large studies or community surveys. Although a study in Kenya found no difference in infant care practices between HIV- infected and HIV uninfected women[48] there is evidence for an effect of infant feeding (a key component of care) on infant growth, with ill HIV-infected mothers being less likely to breastfeed their infants.[52]

Breastfeeding

A likely major cause of impaired health outcomes in both HIV-infected and HIV-EU infants is reduced exposure to breast milk, as HIV-infected mothers are either less likely to breastfeed (due to ill health) or to avoid breastfeeding to protect their infant from HIV infection.[52] Reduced breastfeeding by HIV-infected mothers could be responsible for increased morbidity and mortality, increased exposure to infectious agents, and altered immune function, and thus potentially hinder the development of HIV-EU infants compared to unexposed infants.[40] WHO summarizes the results of extensive research in their recommendation that 'Exclusive breastfeeding is recommended during the first few months of life unless replacement feeding is acceptable, feasible, affordable, sustainable and safe' (AFASS).[53] Due to a lack of availability of replacement foods, diets of non-breastfed infants of HIV-infected Zimbabwean women were found to be insufficient in energy and most essential micronutrients required for optimal growth.[54] The low infant feeding score of infants born to HIV-infected women in Cote d'Ivoire at six months of age was attributed to limited dietary diversity and food frequency and was found to be associated with a subsequent risk of stunting.[55]

Low socio-economic status

In addition to infant feeding, there is evidence from several countries that HIV-affected households are poorer than HIV- unaffected households in the same area, because of a combination of decreased ability to work and earn by adults and increased expenditures on health care. In a study in Zambia, although the mothers were knowledgeable about optimal infant feeding practices, actual feeding practices were constrained by the cost of

high quality foods.[56] Hence, economic hardship contributes to sub-optimal postnatal growth.

Given the independent associations of maternal health, infant feeding practices, and socioeconomic status with HIV-exposure, as well as with postnatal growth, it is crucial to collect detailed information on all these factors and adjust for these potential confounding factors in the analysis.

ii) Sample size

Studies exploring the association between HIV exposure and postnatal growth often included only a small number of subjects and experienced considerable drop-out.[16, 43,44,48] With the exception of the European Collaborative study,[45] few studies exploring the association between HIV exposure and postnatal growth included sufficient number of infants in each exposure group. Studies with small sample sizes often lack the precision to estimate small effect sizes. This often leads to wide confidence intervals and inconclusive results.

iii) Lack of an appropriate control group

The inclusion and choice of HIV unexposed controls is important in studies on the postnatal growth of HIV-EU children, because in many African countries, even relatively healthy children born to HIV uninfected mothers may have impaired growth patterns compared with international standards.[40] Further, HIV-infected mothers from Europe and North America often come from socially disadvantaged sub- population, and their children may grow poorly for reasons not associated with HIV exposure.[43]

iv) Effect of HIV exposure on children above the age of two

Most studies exploring the association between *in utero* HIV exposure and postnatal growth evaluated only the short-term effects of HIV on postnatal growth.[43, 46,48] Data beyond two years of age are limited, and the follow-up periods of less than six months found in some studies may not be long enough to capture the complete pattern of change in growth outcomes.

This is the first study to explore the association between *in utero* HIV-exposure and birth weight and postnatal growth patterns in HIV-EU children in India. This is also the first study to collect detailed information on potential confounders and adjust for them appropriately in the analysis. With its large sample size, this study has adequate statistical power to evaluate the association between *in utero* HIV exposure and impaired postnatal growth. The study enrolled only those HIV-EU children whose HIV infection status was confirmed by DNA PCR either at six months of age (or after breastfeeding was stopped). As a result, we were able to exclude any potentially HIV-infected children in the study.

Because almost 34% of the women who enrolled in the PRAYAS PMTCT program chose to breastfeed their infants, this study was able to evaluate the impact of breastfeeding versus formula feeding on postnatal growth in HIV-EU children. It is also important to note that there is a good representation of different socioeconomic classes among the women who enrolled in the PMTCT program. Most of the HIV-infected women were recently infected with HIV at the time of enrollment into the PRAYAS PMTCT program and did not require ART to control their disease progression. Hence, it is very unlikely that the mothers who enrolled in the PMTCT program were unable to care for their infants for reasons related to their health.

It is possible that the anthropometric measurements in this study were subject to measurement error. However we expect that the biases resulting from these errors would be non-differential and hence would result in an underestimation of the association between HIV exposure and the outcome variables.

We used HIV uninfected children born to HIV-negative mothers from the NFHS dataset as controls in this study. The NFHS dataset contains detailed information on birth history, nutrition, health, and anthropometric measurements of these children. The dataset also contains information on their mother's health, parity, and family's socioeconomic status. Controls were chosen from the same state (Maharashtra) as the study participants. Hence, it is very unlikely that these children are systematically different in terms of unmeasured confounder distributions (diet, care practices, etc.) from the HIV-EU children participating in the study.

This study found that HIV-EU children in India were more likely to have smaller birth weights compared to HIV-unexposed uninfected children. On an average, the HIV-EU children were found to be shorter compared to HIV-unexposed children after adjusting for potential confounders. In children five years and younger, with every year of increase in age, HIV-EU children grew 0.8 cm less than HIV-unexposed uninfected children. Similar results were seen when we considered children three years or younger. No statistically significant result was seen for children under the age of one. One reason for this finding could be the relatively smaller number of HIV-EU children (N=22) in this age bracket. Of the previous studies that found evidence for an association between *in utero* HIV exposure and impaired postnatal height-for-age, three studies assessed the association between HIV exposure and postnatal growth only up to two years of age,[16,43,46,48] while one study found an association up to four years of age.[45] In this study, we did not find a significant difference in weight between HIV-EU and HIV-unexposed uninfected children at different ages after adjusting for potential confounders.

Similar results have been shown by previous studies.[16,43,44,48] Interestingly, in this study, breastfeeding was associated with both lower height and lower weight, when we considered children of all ages in the analysis. In India, as in many resource-poor countries, the advice to HIV-infected women to breastfeed is often given to those women who lack access to safe drinking water and cannot afford to buy formula. Hence, it is

possible that exposure to breast milk is correlated with (and hence is a proxy for) other economic indicators that have not been sufficiently controlled for in the analysis.

Growth hormone resistance and reduced levels of IGF-1 have been directly linked to deficits in height-for-age growth and weight-for-age in HIV-infected children. In spite of the reduction in thymic output reported in HIV-EU children (as seen in HIV-infected children), GH and IGF-1 levels and their associations with postnatal growth have not yet been studied in HIV-EU children. Given the association between HIV-exposure and impaired postnatal height after controlling for the key confounding variables, there is merit in evaluating the levels of GH and IGF-1 in HIV-EU children.

Forty six percent of all children under the age of three in India are stunted.[57] Further, the number of HIV-EU infants detected in India is likely to increase due to implementation programs targeting the prevention of mother-to-child transmission of HIV. Developing an understanding of postnatal growth and its determinants in HIV-EU children is hence critical and has important policy implications for the country.

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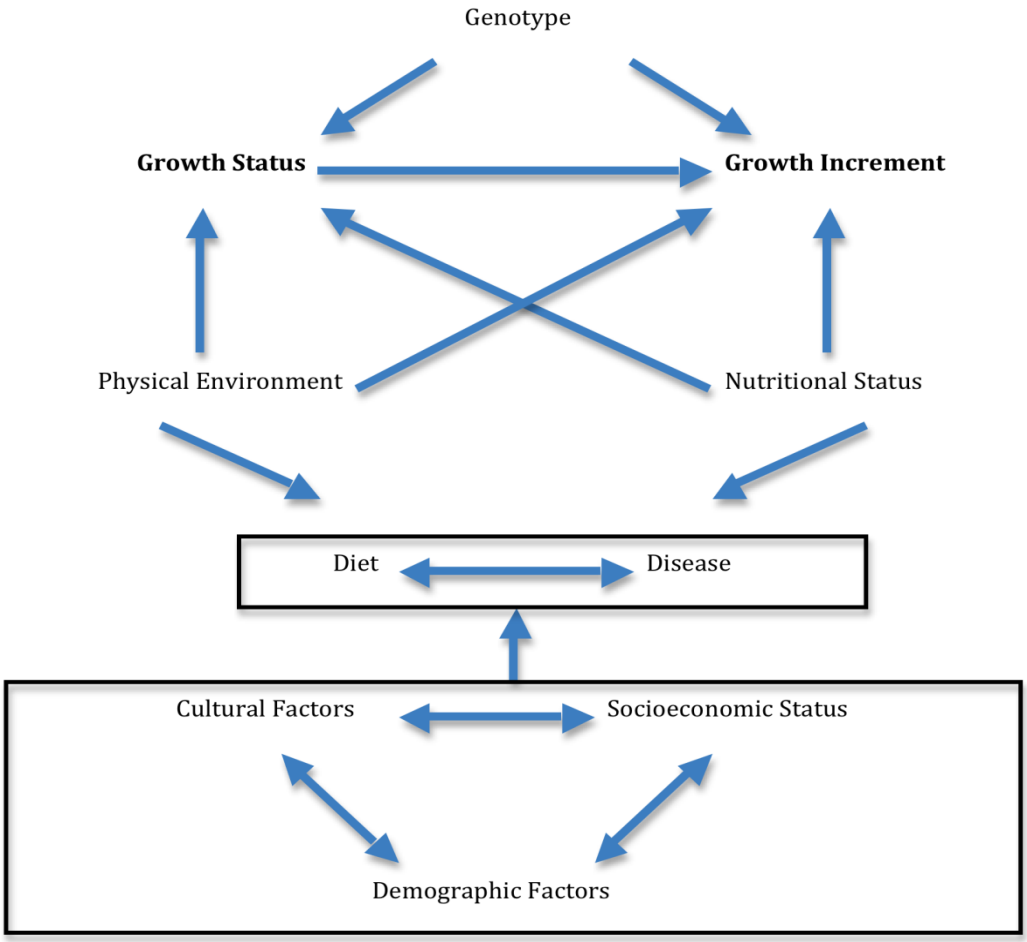

Figure 2: Ecosystem of Human Growth (modified from Ulijaszek, S., Johnston, E., & Preece, M. (1998)) This figure represents human growth as a complex process involving interactions between environmental, genetic and nutritional factors.
*This is not a Directed Acyclic Graph (DAG).

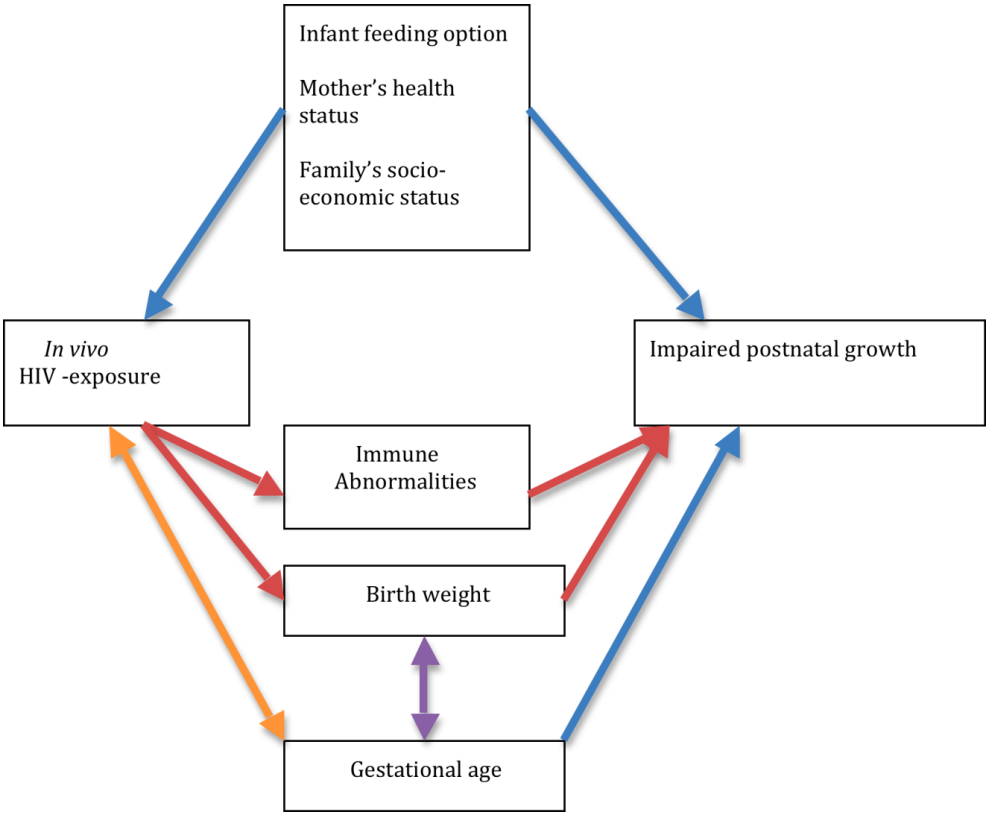

Figure 3: Covariates in the association between HIV exposure and postnatal growth

Table 8: Covariates included in the analysis of the effect of *in utero* HIV-exposure on birth weight and postnatal height and weight.

Variable		Number of HIV exposed (% of total exposed)	Number of HIV unexposed (% of total unexposed)	Total
Socio-demographic variables				
Family's socio-economic status quintile	Quintile 1 (lowest)	38 (12.8%)	277 (17.2%)	315
	Quintile 2	51 (17.2%)	349 (21.7%)	400
	Quintile 3	66 (22.2%)	385 (23.9%)	451
	Quintile 4	100 (33.7%)	369 (22.9%)	469
	Quintile 5 (highest)	42 (14.1%)	231 (14.3%)	273
		297	1611	1908
Place of residence	Rural	125 (42.2%)	488(30.3%)	613
	Urban	171 (57.8%)	1123(69.7%)	1294
		296	1611	1907
Mother				
Marital status	Married	253 (85.2%)	1589 (98.6%)	1842
	Widowed/Separated/ Divorced	44 (14.8%)	22 (1.4%)	66
		297	1611	1908
Age at delivery (years)	<=20	63 (21.3%)	342(21.2%)	405
	>20 and <=30	191 (64.5)	1146 (71.1)	1337
	>30 and <=40	40 (13.5%)	122 (7.6%)	162
	>40	2 (0.7%)	1 (0.06%)	3
		296	1611	1907
Education	No education	30 (10.1%)	200 (12.4%)	230
	<=5 years (Primary school)	31 (10.5%)	115 (7.1%)	146
	>5 and <=10 (Secondary school)	133 (44.9%)	794 (49.3%)	927
	>10 and <=12 (Junior College)	46 (15.5%)	268 (16.6%)	314
	>12 and <=15 (Graduate)	45 (15.2%)	177 (11.0)	222

	>15 (Post-Graduate)	11 (3.7%)	57 (3.5%)	68
		296	1611	1907
Occupation	Working	87 (29.3%)	446 (27.7%)	533
	Not working (Housewife)	209 (70.7%)	1165 (72.3%)	1374
		296	1611	1907
Parity	More than one living child	170 (57.4%)	1120 (69.5%)	1290
	Only one living child	126 (42.6%)	491 (30.5%)	617
		296	1611	1907
Child Sex	Boy	145 (49.1%)	884 (54.8%)	1029
	Girl	150 (50.9%)	727 (45.2%)	877
		295	1611	1906
Breastfed	Yes	100 (33.7%)	1589 (98.6%)	1689
	No	196 (66.3%)	22 (1.4%)	218
		296	1611	1907
Age (years)	<1 year	24 (8.1%)	325 (20.2%)	349
	1-3 years	135 (45.6%)	691 (42.9%)	826
	3-5 years	74 (25.1%)	595 (36.9%)	669
	>5 years	63 (21.2%)	0 (0%)	63
		296	1611	1907
Birth weight (grams)	<2500	76 (27.1%)	353 (21.9%)	429
	>=2500	204 (72.9%)	1258 (78.1%)	1462
		280	1611	1891

Table 9: Adjusted estimates of differences in birth weight (in g) in HIV-EU children compared to HIV-unexposed uninfected children.

Covariate	n	Adjusted Estimate (in g)	95% CI
HIV exposure			
No*	1611	-	-
Yes	297	-123.5	(-215.1 to -31.9)
Family's SES			
Quintile 1*	273	-	-
Quintile 2	315	100.7	(-8.1 to 209.4)
Quintile 3	400	61.9	(-51.3 to 175.2)
Quintile 4	451	108.2	(-10.1 to 226.5)
Quintile 5	469	158.8	(27.2 to 290.4)
Residence in rural area			
No*	1295	-	-
Yes	613	-7.5	(-83.1 to 68.2)
Marital status			
Not Married*	66	-	-
Married	1842	-55.8	(-227.9 to 116.4)
Parity			
One child*	617	-	-
More than one child	1291	98.6	(33.8 to 163.3)
Housewife			
No*	534	-	-
Yes	1374	-16.1	(-84.7 to 52.5)
Education (in years)	1891	4.5	(-3.3 to 12.4)
Age at delivery (in years)	1891	-1.7	(-8.8 to 5.3)
Mother on ART			
No*	1878	-	-
Yes	30	-308.1	(-573.9 to -42.3)
Sex			
Female*	877	-	-
Male	1030	97.1	(40.1 to 154.2)

Note: * Indicates the reference group

Table 10a: Adjusted estimates of differences in postnatal height (in cm) in HIV-EU children compared to HIV-unexposed uninfected children.

	Model 1		**Model 2**		**Model 3**		**Model 4**	
Age category	All ages		Age <=5		Age <=5		Age<=3	
	β	P-value	β	P-value	β	P-value	β	P-value
HIV exposure (Exposed=1)	-2.88	0.00	0.06	0.94	2.15	0.10	2.34	0.16
Child's Age	7.75	0.00	8.45	0.00	8.53	0.00	10.34	0.00
Child's Age*HIV exposure	NA	NA	NA	NA	-0.79	0.05	-1.56	0.03
Breastfed (Yes=1)	-4.06	0.00	-1.61	0.06	-1.67	0.05	-1.95	0.05
Child's Sex (Male=1)	1.52	0.00	1.42	0.00	1.40	0.00	1.62	0.00
SES Quintile 2	0.40	0.53	0.39	0.52	0.42	0.49	0.93	0.19
SES Quintile 3	1.03	0.12	1.02	0.11	1.03	0.11	1.10	0.15
SES Quintile 4	1.60	0.02	1.76	0.01	1.78	0.01	2.12	0.01
SES Quintile 5	2.44	0.00	2.65	0.00	2.68	0.00	2.69	0.00
Residence area (Rural=1)	0.82	0.06	1.16	0.01	1.19	0.01	1.24	0.01
Mother's Parity (>1 Child=1)	-0.59	0.12	-0.70	0.06	-0.76	0.05	-1.00	0.02
Mother's occupation (Housewife=1)	0.33	0.42	0.63	0.10	0.66	0.09	0.67	0.15
Mother's education	0.13	0.01	0.14	0.00	0.14	0.00	0.09	0.08
Mother's age at delivery	0.18	0.00	0.16	0.00	0.16	0.00	0.18	0.00
Mother on ART (Yes=1)	-0.09	0.96	0.12	0.94	0.19	0.91	0.49	0.81
Constant	59.71	0.00	55.65	0.00	55.58	0.00	53.12	0.00
Number of observations (N)	1864		1810		1810		1155	
R-squared	0.77		0.76		0.76		0.66	

Table 10b: Adjusted estimates of differences in postnatal height (in cm) in HIV-EU children compared to HIV-unexposed uninfected children at ages three and five.

	Model 1		**Model 2**		**Model 3**		**Model 4**	
Age category	All ages		Age <=5		Age <=5		Age<=3	
	β	P-value	β	P-value	β	P-value	β	P-value
HIV exposure (Exposed=1) at Child's age=3	-2.88	0.00	0.06	0.94	-0.22	0.05	-2.34	0.03
HIV exposure (Exposed=1) at Child's age=5	-2.88	0.00	0.06	0.94	-1.8	0.05	NA	NA

Table 11a: Adjusted estimates of differences in postnatal weight (in kg) in HIV-EU children compared to HIV-unexposed uninfected children.

	Model 1		**Model 2**		**Model 3**		**Model 4**	
Age category	All ages		Age <=5		Age <=5		Age<=3	
	β	P-value	β	P-value	β	P-value	β	P-value
HIV exposure (Exposed=1)	0.18	0.38	0.43	0.03	0.60	0.08	0.64	0.09
Child's Age	1.91	0.00	1.87	0.00	1.87	0.00	2.18	0.00
Child's Age*HIV exposure	NA	NA	NA	NA	-0.06	0.54	-0.11	0.50
Breastfed (Yes=1)	-0.78	0.00	-0.32	0.16	-0.32	0.15	-0.19	0.41
Child's Sex (Male=1)	0.55	0.00	0.56	0.00	0.56	0.00	0.60	0.00
SES Quintile 2	0.01	0.97	0.07	0.64	0.08	0.63	0.15	0.37
SES Quintile 3	0.11	0.55	0.16	0.32	0.17	0.32	0.15	0.38
SES Quintile 4	0.37	0.05	0.42	0.02	0.42	0.02	0.44	0.01
SES Quintile 5	0.57	0.01	0.60	0.00	0.60	0.00	0.69	0.00
Residence area (Rural=1)	-0.01	0.92	0.02	0.88	0.02	0.86	0.08	0.46
Mother's Parity (>1 Child=1)	-0.43	0.00	-0.26	0.01	-0.27	0.01	-0.18	0.06
Mother's occupation (Housewife=1)	0.09	0.39	0.08	0.41	0.09	0.40	-0.07	0.49
Mother's education	0.04	0.00	0.04	0.00	0.04	0.00	0.03	0.03
Mother's age at delivery	0.04	0.00	0.03	0.01	0.03	0.01	0.02	0.11
Mother on ART (Yes=1)	0.07	0.87	0.31	0.47	0.31	0.46	0.33	0.47
Constant	4.95	0.00	4.67	0.00	4.67	0.00	4.49	0.00
Number of observations (N)	1860		1810		1810		1155	
R-squared	0.75		0.70		0.70		0.65	

Table 11b: Adjusted estimates of differences in postnatal weight (in kg) in HIV-EU children compared to HIV-unexposed uninfected children at ages three and five.

	Model 1		**Model 2**		**Model 3**		**Model 4**	
Age category	All ages		Age <=5		Age <=5		Age<=3	
	β	P-value	β	P-value	β	P-value	β	P-value
HIV exposure (Exposed=1) at Child's age=3	0.18	0.38	0.43	0.03	0.42	0.54	0.31	0.50
HIV exposure (Exposed=1) at Child's age=5	0.18	0.38	0.43	0.03	0.3	0.54	NA	NA

CHAPTER 5

SUMMARY OF RESEARCH FINDINGS AND IMPLICATIONS FOR PUBLIC HEALTH AND FUTURE RESEARCH

Context

Over the last two decades, our understanding of mother-to-child transmission (MTCT) of HIV has grown significantly. The risk of MTCT can now be effectively reduced to less than two percent by a series of interventions that includes a combination of three antiretroviral drugs (ARVs) given to women during pregnancy and labor; obstetrical interventions, including cesarean delivery; the complete avoidance of breastfeeding; and ARVs given to the infant for the first several weeks of life. However, despite remarkable gains in coverage and uptake of PMTCT services in developed countries, where MTCT has been virtually eliminated, the translation of research findings into successful health policies and practice in developing countries like India has been far from optimal.

Study1: Summary

In addition to making HIV testing and counseling available to all pregnant women, ensuring that all HIV-infected pregnant women receive the cascade of PMTCT interventions (including antiretroviral treatment (ART) or prophylaxis for the HIV-infected pregnant woman, safe obstetric interventions and counseling, and support for safer infant feeding options) is key to realizing the goal of eliminating mother-to-child transmission of HIV. Loss to follow-up (LTF) of women enrolled in a PMTCT program has been recognized as a major problem by PMTCT programs in resource-poor settings. Forty percent of HIV-infected women enrolled in the national PMTCT program in India are lost to follow-up before they can receive a single dose of Nevirapine (NVP). Although loss to follow-up in the PMTCT setting has been identified as a problem in India, factors associated with loss to follow-up are largely unknown.

This study was the first to examine the socio-demographic factors associated with LTF of HIV-infected women enrolled in a large-scale private sector PMTCT project in Maharashtra, India. We found that 80 (10.9%) women were LTF before delivery and 151 (19.6%) women were LTF after delivery. Women with less than college level education, women who were from a poor family, women who were registered after 20 weeks of pregnancy, and women whose partners were HIV uninfected or of unknown HIV status were more likely to be LTF before delivery. Similarly, the factors associated with being LTF after delivery were less than college level education, being in a poor family and registration after 20 weeks of pregnancy.

Implications for public health practice and future research

This study highlights the need for innovative and effective counseling techniques for less educated women, economic empowerment of women, better strategies to increase the up-take of partner's HIV testing, and early registration of women in the program for preventing loss to follow-up in PMTCT programs. Because there is no information on the reasons for loss to follow-up in women who access services from the public sector PMTCT program in India, it may be useful to analyze the data collected from the public

sector PMTCT program to see if the reasons for LTF differ from the findings of this study.

Study 2: Summary

PMTCT programs are widely regarded as an entry point to continued HIV-related treatment and care, presenting a unique opportunity to reach HIV-infected women of reproductive age and their families. However, in most developing countries, including India, retaining HIV-infected women in PMTCT care and beyond continues to be a major challenge. In-depth understanding of the factors associated with utilization of post-PMTCT HIV-related treatment and care, in women in India, will assist in devising strategies to achieve higher uptake rates and subsequently improve health outcomes and survival in women and infants seeking care at such facilities.

The 'Linking to Care' study was designed to examine the factors associated with reduced utilization of continued treatment and care among HIV-infected women enrolled in the PRAYAS PMTCT program in Maharashtra, India. Of the 733 eligible women, 311 women consented to and completed a structured interview. After adjusting for potential confounders, women with poor HIV-related knowledge, women who were currently married, women whose partners had never utilized HIV-related care and women who could not afford to travel to the HIV-care facility were less likely to utilize HIV-related care after exiting the PMTCT program.

Implications for public health practice and future research

This study highlights the need for enhanced techniques to impart HIV-related knowledge to all women who seek PMTCT services. This study also underscores the need for greater partner involvement during the PMTCT cascade to increase the uptake of post- PMTCT treatment and care.

Study 3: Summary

The number of HIV-exposed uninfected (HIV-EU) infants identified in India is likely to increase, due to the scale up of programs aimed at realizing the goal of elimination of MTCT by 2015. Postnatal growth patterns in HIV-infected children have been studied in detail, and impaired postnatal growth, especially stunting, has been reported as a common manifestation of HIV infection. Some studies from developed and developing countries have reported stunting in HIV-EU children compared to HIV-unexposed uninfected children while others have found no such association. No studies on the effect of HIV-exposure on postnatal growth patterns in HIV-EU children in India have been published to date. We compared birth weight, height and weight of 297 HIV-EU children born to mothers who had previously registered in a PMTCT program and 1611 HIV-unexposed children residing in the state of Maharashtra from the National Family Health Survey (NFHS) 2005-06 database. We found that HIV-EU children weighed 123.5g less at birth compared to HIV-unexposed children, after adjusting for potential confounders. On an

average, HIV-EU children were 2.9 cm shorter compared to HIV-unexposed children, after adjusting for potential confounders. In children five years of age and younger, with every year of increase in age, HIV-EU children grew 0.8 cm less than HIV-unexposed uninfected children. At ages three and five, the HIV-EU children were 0.22 cm (p=0.05) and 1.8 cm shorter (p=0.05) than HIV-unexposed uninfected children respectively. When we only considered children three years or younger, HIV-EU children grew 1.6 cm (95% CI: -0.2 to -2.9) less than HIV-unexposed uninfected children. At age three, the HIV-EU children were 2.34 cm shorter (p=0.03) than HIV-unexposed uninfected children. We did not find a statistically significant difference in weight between HIV-EU and HIV unexposed children at different ages after adjusting for potential confounders.

Implications for public health practice and future research

Developing a better understanding of the determinants of growth impairment in HIV-EU children in India is critical, given that the number of HIV-EU infants identified is likely to go up due to implementation of programs that aim at reducing mother-to-child transmission of HIV. Growth hormone resistance and reduced levels of IGF-1 have been directly linked to deficits in height-for-age growth and weight-for-age in HIV-infected children. In spite of the reduction in thymic output reported in HIV-EU children (as seen in HIV-infected children), GH and IGF-1 levels and their associations with postnatal growth have not yet been studied in HIV-EU children. Given the association between HIV-exposure and impaired postnatal height after controlling for the key confounding variables, there is merit in evaluating the levels of GH and IGF-1 in HIV-EU children.