HIV Vertical Transmission and Survival of the HIV-Infected and HIV-Exposed Uninfected Children in Resource Limited Settings

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1 HIV Vertical Transmission

1.1 Introduction

According to UNAIDS, the joint United Nations Program on HIV/AIDS, 34 million people were living with HIV throughout the world at the end of 2011 (UNAIDS, 2012). In 2011, 330,000 children acquired HIV infection of which 90% of the children who acquired HIV infection live in sub-Saharan Africa (UNAIDS, 2012). Mother-to-child transmission (MTCT) was the major route of infection, and from 2009 to 2011, antiretroviral prophylaxis prevented 409,000 children from acquiring HIV infection in low- and middle-income countries (UNAIDS, 2012). In low- and middle-income countries, 35% of pregnant women were tested for HIV and coverage of antiretroviral prophylaxis was 48% (excluding the single dose Nevirapine) in 2010 (WHO, 2011). With prevention of mother-to-child transmission, PMTCT there are striking differences between the developed and developing countries (Buchanan & Cunningham, 2009). In the United States, Europe and other resource rich countries, PMTCT has been one of the major success stories (Buchanan & Cunningham, 2009; Dorenauma et al., 2002). Prior to effective perinatal HIV interventions, about 1 in 4 babies born to HIV-infected women became infected; whereas today an HIV-infected pregnant woman in these countries receiving combination antiretroviral therapy (cART) and with an undetectable viral load has only about 1-2% chance of transmitting HIV to her infant (Dorenaum et al., 2002; Dao et al., 2006; Jamieson et al., 2007; Jaspan & Garry, 2003, Newell, 2006; Thorne & Newell, 2003; 2007). In the absence of any interventions, rates of mother-to-child transmission can reach as high as 30 to 45% in developing countries (Fowler & Newell, 2002). The research achievements in PMTCT are remarkable; however, it has proved much more difficult to translate the findings into practice in resource limited settings. The translation of successful interventions into public health policy has been slow because of a variety of factors such as inadequate funding and cultural, social, and institutional barriers. The issue of HIV and infant feeding in settings that lack culturally acceptable, feasible, affordable, safe, and sustainable nutritional substitutes for breast milk is a continuing dilemma. Several questions and challenges remain, which include choice, availability, affordability, duration, long term safety of optimal antiretroviral agents to be used during pregnancy and early neonatal life. Drugs to reduce HIV transmission whilst also protecting treatment options to women and children are required and the issue of transmission via breast milk in situations where alternatives to breastfeeding are not available or safe need to be considered (Fowler et al., 2007). This chapter seeks to outline some PMTCT issues pertinent to resource limited settings that are to be considered in achieving the WHO strategic plan of reduction of pediatric HIV infection by 2015.

1.2 Risk factors for HIV vertical transmission

Mother-to-child transmission can occur during pregnancy especially in the last trimester, during delivery, and postnatal during breastfeeding (Fowler & Newell, 2002; Mofenson, 2003). The fetus can get infected “in utero” through maternal blood, transplacental hemorrhage, and infection through the gastrointestinal mucosa while swallowing infected amniotic fluid. Contact with the mother’s blood and/or vaginal secretions during labor and delivery increases the risk of HIV transmission to the infant (Mofenson, 2003). Of the 30% of babies who get infected vertically, the relative frequency of timing is 2% early in gestation, 3% late in gestation, 15% during labor, 5% in the early postpartum and 5% in late postpartum (DeCock et al., 2000).
1.2.1 Antenatal risk factors

Maternal factors like seroconversion during pregnancy, advanced stage of disease, concomitant malnutrition and micronutrient deficiencies, sexually transmitted diseases in the mother and poor adherence to antiretroviral therapy after initiation, are some important factors which increase transmission in the antenatal period (John-Stewart et al., 2004). Other factors implicated in MTCT antenatal are elevated maternal viral loads, low CD4 counts and HIV viral subtype C (Delicio et al., 2011; Renjifo et al., 2004). Maternal hard drug use has also been implicated “in utero” HIV transmission (Magder et al., 2005).

1.2.2 Intrapartum risk factors

Infant gestational age and birth weight have been associated with presumed intrapartum HIV transmission (Magder et al., 2005). Prematurity is a risk factor for increased transmission due to thin skin, susceptible mucous membranes, immature immune functions and low levels of maternal antibodies in the premature infant (Coustoudis, 2000). The association between premature birth and intrapartum transmission appears to be strongest among those with prolonged rupture of membranes (Magder et al., 2005).

At delivery, factors such as: vaginal delivery, prolonged contact with maternal blood and cervico-vaginal secretions, prolonged rupture of membranes and chorioamnionitis increase the HIV transmission (Magder et al., 2005; Goldenberg, 1998). Procedures that increase exposure of the infant to maternal blood, (like instrumentation during delivery, episiotomy and fetal scalp electrode), are associated with increased risk of transmission (Goldenberg, 1998). Performing caesarean section before the onset of labor and the rupture of membranes was shown to decrease the risk of HIV transmission. The effect was independent of the effects of treatment with Zidovudine in a meta-analysis of 15 prospective cohort studies (The International Perinatal Group, 1999).

1.2.3 Postpartum risk factors

Breast feeding has been associated with 4%-12% absolute risk of mother to child transmission of HIV through 6 months (Fowler & Newell, 2002; The Breastfeeding and HIV International Transmission Study Group, 2004; Thior et al., 2006; Miotti et al., 1999; Coustoudis et al., 2001). Infant feeding practices in the developing world comprise almost universally of breast feeding for prolonged duration (Fowler & Newell, 2002; Coustoudis et al., 2004).

Feeding in the presence of cracked nipples or mastitis, mixed feeding, continuation of breastfeeds for prolonged periods of time, seroconversion of the mother during the postnatal period, high viral load and low CD4 cell counts, all increase the risk of transmission of HIV (Marston et al., 2005; Coustoudis et al., 1999). In a randomized clinical trial done in Botswana, maternal HIV-1 RNA level (p=0.005) and maternal CD4 count (p=0.06) predicted MTCT in multivariable analysis which excluded breast milk HIV-1 RNA level (Shapiro et al., 2009). Exclusive breastfeeding, though better than other forms of infant feeding and associated with improved child survival, is uncommon. The HIV-1 transmission risks and survival associated with exclusive breastfeeding was assessed in KwaZulu natal, South Africa. Eighty-three percent infants born to HIV infected mothers initiated exclusive breast feeding at birth. The median duration of exclusive breastfeeding was 159 days (122,174). About 14.1% of exclusively breastfed infants were infected with HIV by 6 weeks, and 19.5% by 6 months, risk was significantly associated with maternal CD4 counts below 200 cells per µL and birth weight less than 2500g. Kaplan- Meier estimated risk of acquisition of infection at 6 months of age was 4.04%. Breastfed infants
who also received solids were significantly more likely to acquire infection than were exclusively breastfed children (p=0.018). Cumulative 3 month mortality in exclusively breastfed infants was 6.1% versus 15.1% in infants given replacement feeds (HR 2.06, 1.00-4.27, p=0.051) (Coovadia et al., 2007).

In a Cochrane review of randomized clinical trials assessing the efficacy of interventions to prevent MTCT of HIV through breast milk the summary is as follows. In a trial of breast feeding versus formula feeding, formula feeding was efficacious in preventing MTCT of HIV (the cumulative probability of HIV infection at 24 months was 36.7% in the breast feeding arm and 20.5% in the formula arm (p=0.001) but the mortality and malnutrition rates during the first two years of life were similar in the two groups (Horvath et al., 2009). An intervention cohort study evaluated the risks of MTCT among breastfed children who also received solids (HR 10.87) as well mortality rates (HR 2.06) among infants given non-breast milk feedings (Horvath et al., 2009). Complete avoidance of breast feeding is efficacious in preventing MTCT of HIV, but this intervention has significant associated morbidity. Breastfeeding is a cornerstone for child survival especially in resource limited settings where replacement feeding may not be feasible to many. Avoidance of breastfeeding eliminates the risk of HIV transmission through breast milk but is detrimental to child survival. Increased infant morbidity and mortality have been reported in several sub-Saharan African countries (Abrams et al., 2003; Creek et al., 2006; Doherty et al., 2007; Homsy et al., 2010; Jackson et al., 2007). Breast feeding mothers who need combination antiretroviral therapy for their own health should be treated early. This help reduces vertical transmission rates and offer improved survival among the HIV exposed infants, whether infected or not (Gona et al., 2006).

In 2009, new findings showed improved outcomes if life-long ART was started at a CD4 count of 350 instead of 200. The WHO recommended early CD4 dependent initiation of ART in patients with CD4 count <350 cells/mm³ [38]. The WHO guidelines include two new PMTCT options for mothers with a CD4 count above 350. Option A is prophylactic single ART daily to the infant until after exposure to breast milk, or option B prophylactic triple ART to the mother during the entire breastfeeding period (WHO, 2009). Recent trials in sub-Saharan Africa have shown that if the mother and/or the baby instead are treated throughout the breast feeding period, MTCT may be reduced to less than 5% (Peltier et al. n, 2009). Recent developments suggest that substantial clinical and programmatic advantages can come from adopting a single, universal regimen both to treat HIV infected pregnant women and to prevent mother to child transmission of HIV. Now a new third option (Option B+) proposes further evolution—not only providing the same triple ARV drugs to all HIV-infected pregnant women beginning in the antenatal clinic setting but also continuing this therapy for all these women for life (WHO, 2012).

2 Nevirapine Resistance

The simplicity, efficacy and low cost of the nevirapine regimen which is no longer recommended by WHO is attractive for resource poor countries, however, single mutations in HIV-RT can cause high level NVP-resistance and are likely to exist in most HIV-1 infected patients at low levels prior to antiretroviral drug exposure. This favors emergence of NVP-resistant HIV-1 following NVP exposure (Eshleman & Jackson, 2002; Eshleman et al., 2005). NVP-resistant HIV-1 has been shown to emerge in some women and infants following a single dose nevirapine. This has been reported in Malawi were nevirapine resistance was more frequent in infants with subtype C than with subtypes A and D (87 versus 50%, p=0.016). Emergence of NVP-resistant HIV-1 is more common among women with high baseline viral
loads and low baseline CD4 cell counts. The resistant virus fades from detection in women and infants overtime (Martinson et al., 2007), but because of these issues the outcome of nevirapine exposed infants is very important. In the SWEN study in Ethiopia 56% of the infants who received the extended nevirapine with nevirapine resistance at 6 months still had nevirapine resistance mutations present at high frequencies at 1 year of age. Infants infected before 6 weeks of age who received either single dose nevirapine or extended nevirapine were more likely to have Y181C or K103N; these mutations were also more likely to persist at high frequencies through 1 year of age (Persaud et al., 2011). A large clinical trial demonstrated that 83.2% of single-dose nevirapine exposed children who maintained resistance prior to cART therapy at levels detected by standard genotyping failed nevirapine based cART, compared with 18.2 % of nevirapine exposed children without detectable resistance (Violari et al., 2012).

3 Survival among HIV-Infected and HIV-Exposed Uninfected Children

3.1 Pediatric HIV infection

Pediatric HIV is a leading cause of morbidity and mortality worldwide. The burden among these newly HIV infected infants is high, with an estimated 50% mortality rate by their second year (Newell et al., 2004). The substantial interest in PMTCT has generated information on rates of transmission and associated factors, but there is a paucity of information on disease progression and mortality in vertically infected children, especially from resource poor settings. Majority of paediatric HIV infections are acquired through mother-to-child transmission. Child mortality is independently associated with maternal HIV status and maternal death (Kurewa et al., 2010). HIV/AIDS is now responsible for about 8% of all child deaths in sub-Saharan Africa and more than a third of young children mortality in Southern African countries (Black et al., 2003). The Child Problem Identification Programme (PIP) in South Africa showed that between 2005 and 2007 inclusive, almost half of all the deaths had been classified with stage 3 or 4 HIV diseases (Newell, 1998). Morbidities seen in infected children are similar to those seen in uninfected children, although the rates and recurrences of illnesses are greater. There are many factors which contribute to mortality in the HIV-infected children and hence affect their survival. Without antiretroviral therapy, more than half to a third of children with vertically transmitted HIV will have died by one year of age (Coovadia & Wittenberg, 1998) and most by five years (Coovadia & Wittenberg, 1998). Mortality and morbidity are due to common childhood illnesses such as pneumonia and gastroenteritis that are much higher in children with HIV than those who are not infected. There is some evidence that progression to AIDS may be more rapid in resource poor settings, than elsewhere although data on this are very limited. Pediatric cART has been shown to be successful in resource-limited settings (Little et al., 2007).

Diagnosis of HIV infected children remains a challenge in resource limited setting where the majority of women breast feed. Efforts to provide widespread access to cART have been limited by the unavailability of infant diagnostic methods (Lambert et al., 2003; Rouet et al., 2005; Mellors et al., 1997; Sherman et al., 2005). Methods to diagnose and monitor HIV-1 infection in resource-poor settings are usually limited to serologic assays and CD4/CD8 counts (Rouet et al., 2005; Mellors et al., 1997). However, antibody based assays can reliably guide diagnosis and management after 18 months of age following clearance of passively transferred maternal antibodies (Sherman et al., 2005). PCR based nucleic acid amplification and quantification of HIV-1 are the gold standard for early HIV-1 diagnosis in infants and
for evaluating ART efficacy (Moodley et al., 2003). The emergence of Dried Blood Spots PCR assays has enabled resource limited settings to diagnose HIV infection in children early because of the reduction in technical and economic obstacles (Mehta et al., 2009).

In the pre-antiretroviral era and before development of potent combination ART regimens, opportunistic infections (OIs) were the primary cause of death in HIV-infected children (Danker et al., 2001). Current ART regimens suppress viral replication, provide significant immune reconstitution, and have resulted in a substantial and dramatic decrease in AIDS-related OIs and deaths in both adults and children (Gortmaker et al., 2001; Gona et al., 2006; Nesheim et al., 2007). In resource poor settings children with known HIV infection, may have problems in accessing care, due to socioeconomic circumstances related to parental ill health. HIV-infected children eligible for primary or secondary OI prophylaxis might fail to be treated because they are receiving suboptimal medical care. Additionally, adherence to multiple drugs (antiretroviral drugs and concomitant OI prophylactic drugs) may prove difficult for the child or family. This has an impact on long term outcome. A pooled analysis by Newell et al showed that irrespective of their own HIV infection status, all children born to mothers who were at an advanced stage of HIV or who died during follow up were at considerable risk of death compared to those whose mothers survived or were at a less advanced stage of HIV, and this association was stronger for uninfected children (Newell et al., 2005).

### 3.2 Mortality among HIV-Infected Children

As expected, mortality has been shown to be higher among HIV infected children compared to HIV-exposed, uninfected children (Dabis et al., 2002). Mortality varies by geographical regions. Children from European countries where antiretroviral therapy has been long standing show better survival than in most African countries. Several studies have reported early mortality in HIV infected infants but few on long term outcome in Africa (Zijenah et al., 1998; 2004). Kuhn et al reported 77.1% mortality by 24 months in Zambia among HIV-infected children (Kuhn et al., 2008).

Studies from African countries have shown some of the factors which contribute to mortality in HIV infected children:

1. Maternal death, advanced maternal HIV infection with a high viral load and low CD4+ cell counts <200/µL. Mothers who have advanced HIV disease are unlikely to care for their children adequately and/or may carry infectious pathogens which are harmful to their children (Newell et al., 2004; Becquet et al., 2012).

2. Early HIV infection. A pooled analysis by Newell at all of randomised control clinical trials on seven MTCT intervention trials from African countries and several other studies have shown that children who acquire HIV in ‘uterus’ or those who get infected before 4 weeks of age are more likely to die within 12-24 months (Newell et al., 2004; Becquet et al., 2012; Fawzi et al., 2002; Rouet et al., 2003; Wamalwa et al., 2010).

3. Untreated HIV infection progresses from asymptomatic infection to full blown AIDS and children will succumb to opportunistic infections and die. Mortality is highest in the first 12-24 months of infection (Zanoni et al., 2011). ART offers improved survival rates among HIV-infected children.
For children who have been commenced on ART, factors which have been shown to be associated with high mortality are haemoglobin <9g/dL (Wamalwa et al., 2010; Zanoni et al., 2011), weight-for-height z-score less than -2 (Wamalwa et al., 2010), lower weight-for-age z-score, WHO clinical stage 4 (Zanoni et al., 2011; Lumbiganon et al., 2011; Van Kooten et al., 2006) and low baseline CD4 percentage (Zanoni et al., 2011; Lumbiganon et al., 2011). In addition, Lumbiganon et al in Asia showed that mortality was highest in the first 3 months of starting ART which corresponds to the period with the highest frequency of the immune reconstitution inflammatory syndrome (Lumbiganon et al., 2011). Children aged less than 3 years have been noted to have higher mortality and less chance of survival (Van Kooten et al., 2006). In Thai children, similar findings have been documented with hospitalisation rates of 30.7% during the first 24 week period and 2.0% during weeks 120-144 after initiation of ART (Puthanakit et al., 2007). The reason for hospitalisation among these children included OIs such as pneumonia, IRIS and drug related toxicities and non-infectious causes (Puthanakit et al., 2007).

To improve child survival, infant diagnosis should be done on all HIV exposed children at the age of 6 weeks. If the child is found to be infected or at any point thereafter, highly active antiretroviral therapy should be started as soon as the child is ready in order to ensure child survival. A breakthrough in the management of HIV-infected children came during a clinical trial, Children with HIV Early Antiretroviral Treatment (CHER) study in South Africa. Children aged 6-12 weeks with confirmed HIV infection were randomised into one of 3 treatment groups: immediate antiretroviral therapy for 40 weeks, immediate antiretroviral therapy for 96 weeks and one in which ART was delayed until the children met immunological or clinical criteria for starting ART. On June 20, 2007 the data and safety monitoring board reviewed the interim data and showed significant improved survival rates (96%) in the early ART group compared to 84% in the deferred ART group. There was also reduced HIV progression by 75% in children commenced on ART early. The study was stopped, and those children in the deferred ART group were commenced on ART so as to improve survival (Violari et al., 2008). Collins et al also showed high survival rates among children on ART, with older children more likely to survive than infants. The probability of survival among infants aged less than 12 months at baseline was 84.3% at 1 year and 76.7% at 5 years of ART, compared with 95.7% and 94.8%, respectively, among children aged older or equal to 1 year (Collins et al., 2010). Early, timely initiation of ART in children is essential for survival. The WHO recommends treatment of all HIV infected children less than 2 years of age irrespective of immunological status since mortality is higher in these children with early infection (WHO, 2010) and treatment offers a chance of survival and slows disease progression (Violari et al., 2008). Treatment ensures improved growth, neurodevelopment, reduction in frequency of opportunistic infections and hospitalisation.

Antiretroviral therapy is one component of a comprehensive clinical care for the HIV infected child (WHO, 2010), which is prong 4 of the PMTCT strategy. The other components include the following:

1. Cotrimoxazole preventive therapy
2. Growth monitoring
3. Immunisation
4. Counselling and support of the mothers and caregivers
5. Nutritional advice and micronutrient supplementation
6. Prompt and adequate treatment of opportunistic infections
7. Counselling and support of infant feeding choice
8. Routine treatment of intestinal worms
9. Monitoring and follow up

3.3 Mortality among HIV-Exposed Uninfected Children

The increasing success of the programmes of preventing mother-to-child transmission of HIV in Africa means that a very large numbers of HIV-exposed, uninfected children are being born. This group forms a unique group of children. Their survival is different from HIV uninfected children born to HIV uninfected mothers. A study in Uganda showed that the 2-year mortality in HIV infected children was 3-fold that of HIV exposed, uninfected children and 4-fold that of children born to uninfected mothers (Kagaayi et al., 2008). In a study from Central Africa, the mortality of HIV-exposed but uninfected children was already double that of those who were not HIV exposed by six months of age (Kafulafula et al., 2010). The HIV-infected mother with advanced disease and a high viral load has reduced ability to care for her ill child and other family members. Her income generating potential, food production and strength to feed or to take children for preventive or curative health care is also affected (Kafulafula et al., 2010). All the children of the HIV affected household are vulnerable. They may suffer malnutrition, infections due to increased risk of carriage by the HIV infected parent/s or as a result of incomplete immunisation. Other risk factors for mortality which have been identified by studies include low birth weight (Marinda et al., 2007; Wei et al., 2004), male sex, maternal death, low maternal CD4 count, severe maternal anaemia, single or widowed mother and low household income (Marinda et al., 2007). Figure 1 (adapted from Tropical Medicine International Health 2009; 14(3)) below shows the mortality among HIV-exposed uninfected and HIV-unexposed children in some African series (Filteau, 2009).

![Figure 1: Mortality Among HIV exposed uninfected and unexposed African Children.](image)

Data are percentages of deaths among Botswanan children to age 24 months (Shapiro et al., 2007), Ugandan children to age 24 months (Brahmbhatt et al., 2006), Gambian children to age 5 years (Schim van der Loeff et al., 2003), Malawian children ages between 12 and 36 months (Taha et al.,
To ensure survival of the HIV-exposed, uninfected child, prevention is the first strategy. The first 3 prongs of PMTCT help to reduce number of HIV-exposed children (WHO, 2010).

1. Prevent HIV infection in the community
2. Avoid unplanned pregnancies among HIV-infected women by using effective reliable contraception
3. Prevent MTCT of HIV by use of prophylactic antiretroviral therapy or combination ART during pregnancy using WHO guidelines. This is especially important since studies have shown that perinatal and early HIV infections are associated with higher mortality than late infections.
4. Treat HIV-infected parents and caregivers to ensure adequate care of all the HIV affected children.
5. Exclusive breastfeeding for the first 6 months and continued breastfeeding to at least 12 months while giving combination ART to mother or antiretroviral prophylaxis to baby. This is especially so in resource limited settings where replacement feeding may not be feasible.
6. Routine childhood care such as immunisations, nutritional education and supplementation and adequate management of common illnesses such as diarrhoea, respiratory tract infections and malnutrition.

4 Conclusions

Effective PMTCT programme is essential for child survival, and every infected child represents a failure of the system. Since studies show that early infection is associated with a higher mortality, a greater focus on prevention of early infection, earlier screening for HIV infection and access to antiretroviral treatment for eligible children is recommended. The WHO has developed the Global Monitoring Framework and Strategy for the global planning towards the elimination of new HIV infection among children by 2015 and keeping mothers alive (EMTCT) (WHO, 2012). The targets are as follows

1. Reduce HIV incidence in women 15-49 by 50%
2. Reduce unmet needs for family planning among women to zero
3. Reduce mother-to-child transmission of HIV to 5%. Ninety percent of mothers receive perinatal antiretroviral therapy or prophylaxis and 90% of infant-mother pairs receive antiretroviral therapy or prophylaxis
4. Provide 90% of pregnant women in need of antiretroviral therapy for their own health with lifelong treatment

Comprehensive care of these HIV exposed children offer better chances of child survival for both the infected and uninfected child.
References


