

Prevention of Mother-to-child Transmission of HIV

a report by

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DOI: 10.17925/EOH.2008.02.1.67

Mother-to-child transmission (MTCT) of HIV causes significant morbidity and mortality among children. Our understanding of the epidemiology, pathogenesis, diagnosis and prevention of MTCT of HIV infection has improved dramatically in recent years, and the objectives of this review are to summarise current understanding of the prevention of MTCT of HIV.

Most children acquire HIV infection through MTCT.¹ Although major successes have been achieved in prevention of MTCT, these successes have occurred primarily in those countries with the greatest resources and the lowest burden of HIV infection among women and children. Significant challenges remain, particularly in those countries with more limited resources and a greater population burden of HIV infection.

Rates of MTCT of HIV were calculated in studies conducted in various countries prior to the development and implementation of interventions to decrease transmission.² Usually a transmission rate in the range of 25–30% was reported, and higher transmission rates were observed in resource-poor settings (13–42%) than in resource-rich settings (14–25%).

MTCT of HIV can occur during pregnancy, around the time of labour and delivery, and post-natally (through breastfeeding).³ Most transmission is estimated to occur during the intrapartum period (both in breastfeeding and non-breastfeeding populations).⁴

Various risk factors for MTCT of HIV have been identified or are under investigation,¹ and can be categorised as follows:

- the amount of virus to which the child is exposed (i.e. maternal viral load);^{5–9}
- the duration of such exposure (i.e. the duration of ruptured membranes¹⁰ or of breastfeeding¹¹); and
- factors facilitating the transfer of virus from mother to child (e.g., mixed breastfeeding,^{12,13} maternal breast pathology^{7,8,14,16} and infant oral candidiasis).^{15,16}

In addition to these risk factors, characteristics of the virus and the child's susceptibility to infection are important.

Prevention of Mother-to-child Transmission of HIV

Although different interventions to prevent MTCT of HIV have been and are being investigated, efficacy has been demonstrated to date only for the following (see *Table 1*): antiretroviral (ARV) prophylaxis,¹⁷ Caesarean section before labour and before ruptured membranes,¹⁸ complete avoidance of breastfeeding¹⁹ and (in settings where complete avoidance of breastfeeding is not feasible) exclusive breastfeeding²⁰ and ARV prophylaxis administered

to the infant while breastfeeding.^{21–23} In addition to these interventions, observational data strongly suggest that maternal use of combination ARV regimens including highly active ARV therapy (HAART) during pregnancy is associated with very low rates of transmission.²⁴

Antiretroviral Prophylaxis

Maternal use of ARVs during pregnancy (whether for treatment of the woman's HIV disease itself or, for women who do not meet criteria for treatment, for prevention of MTCT) and ARV prophylaxis during the intrapartum and post-natal periods are associated with significantly lower rates of MTCT. In the first efficacy trial of ARV prophylaxis, zidovudine alone was given to the mother during pregnancy and the intrapartum period and to the infant.¹⁷ Subsequently, the US Public Health Service (USPHS) issued guidelines regarding the use of zidovudine prophylaxis,²⁵ and such prophylaxis has played a central role in the prevention of MTCT in the US²⁶ and other resource-rich settings. More recently, an increasing number of HIV-infected women are receiving combination ARV regimens, including HAART, during pregnancy.²⁴ Guidelines for initiation of ARV therapy in adults and adolescents have been developed by the USPHS²⁷ and other groups. In addition, guidelines addressing the use of ARVs, including combination ARV regimens, in pregnant women have been developed by the USPHS²⁸ and other groups.

Caesarean Delivery Before Labour and Before Ruptured Membranes

Among women receiving no ARVs or zidovudine alone, Caesarean section before labour and before ruptured membranes is associated with a lower risk of MTCT of HIV²⁹ and is efficacious in preventing MTCT.¹⁸ Based on these studies, the American College of Obstetricians and Gynecologists (ACOG)³⁰ and the USPHS²⁸ recommend Caesarean section for prevention of MTCT be considered for HIV-infected women with peripheral blood viral loads greater than 1,000 copies/ml, irrespective of receipt of ARVs. Caesarean delivery for HIV-infected women has been performed with increasing frequency in clinical centres in the US over the past several years.³¹ However, Caesarean section for prevention of MTCT of HIV is generally not



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Table 1: Efficacious Interventions for the Prevention of Mother-to-child Transmission of HIV

Antiretroviral prophylaxis:

- To the mother (antepartum, intrapartum) and to the non-breastfeeding infant (early post-natal period)
- To the breastfeeding infant*

Caesarean section before labour and before ruptured membranes

Complete avoidance of breastfeeding

Exclusive breastfeeding*

*When complete avoidance of breastfeeding is not feasible or safe.

feasible in resource-poor settings because of the lack of a skilled attendant during labour and other reasons.

Interventions to Prevent Breast Milk Transmission of HIV

Both the Centers for Disease Control and Prevention (CDC)³² and the American Academy of Pediatrics (AAP)³³ recommend that HIV-infected women in the US do not breastfeed. These recommendations are supported by the results of a randomised clinical trial conducted in Kenya, where the observed rate of MTCT of HIV among mothers randomised to not breastfeed (i.e. they fed their children formula milk) was significantly lower than among mothers randomised to breastfeed (20.5 versus 36.7% at two years; $p < 0.001$)¹⁹ (see *Table 2*).

However, if complete avoidance of breastfeeding is not safe or feasible, specific interventions to prevent breast milk transmission of HIV could be considered (see *Table 2*). Some of these interventions have been evaluated in phase III clinical trials, while others are currently under study. First, a longer duration of breastfeeding is associated with a greater risk of transmission¹¹ and, therefore, if breastfeeding is initiated, early weaning was thought to be a reasonable intervention to decrease the risk of transmission. However, the morbidity associated with complete avoidance of breastfeeding (formula feeding) and with early weaning, due to contaminated water used in the preparation of replacement feeds, serves to counteract the benefits of such interventions with regard to prevention of MTCT of HIV. For example, in the clinical trial of formula feeding versus breastfeeding, the two groups of children experienced similar mortality and malnutrition rates during the first

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two years of life.³⁴ Subsequently, in a randomised trial evaluating the safety and efficacy of early weaning,³⁵ HIV-free survival was similar between those children who ceased breastfeeding around four months of age and those who continued breastfeeding.

Second, a higher maternal viral load is associated with a greater risk of MTCT and two types of interventions have been proposed to decrease the infectiousness of the breast milk of HIV-infected mothers: maternal use of ARVs while breastfeeding and treatment (chemical or heat) of breast milk. Two randomised clinical trials are being conducted in sub-Saharan Africa to evaluate use of ARV prophylaxis by breastfeeding

women for the first few months of breastfeeding.^{36,37} Heat and chemical (e.g. sodium dodecyl sulphate) treatment of breast milk in order to decrease the amount of cell-free and cell-associated HIV have been evaluated in several studies.^{38,39} In addition, a method of 'flash-heating' of breast milk⁴⁰ will be evaluated further in East Africa.

Third, because various factors may facilitate the transfer of HIV from the breastfeeding mother to the child (e.g. maternal breast abnormalities, infant candidiasis, mixed breastfeeding), interventions to prevent or treat such factors have been developed. For example, programmes have been developed to educate HIV-infected women who choose to breastfeed, addressing proper positioning during breastfeeding; prompt seeking of

There remain a number of significant challenges if the goal of complete eradication of mother-to-child transmission is to be realised.

medical care if breast abnormalities develop or if the infant develops oral candidiasis or other lesions; and avoiding breastfeeding from a breast with mastitis or other abnormalities. Early findings from studies in Brazil and South Africa suggesting a lower risk of transmission with exclusive breastfeeding compared with mixed breastfeeding^{12,41} prompted the development of additional studies in Zimbabwe,¹³ South Africa²⁰ and Zambia;³⁵ they support the association of exclusive breastfeeding with a lower risk of MTCT of HIV. For example, the transmission rate at six months of age among infants who were still exclusively breastfeeding at six months was 15%, but was higher among those with mixed feeding at six months (27% among those who initiated mixed feeding before 14 weeks and 26% for those who initiated mixed breastfeeding after 14 weeks).²⁰

Finally, interventions to decrease infant susceptibility to infection while breastfeeding (e.g. active and passive immunisation of the infant, administration of ARV prophylaxis to the infant while breastfeeding) have been or are being evaluated. Studies of the safety and immunogenicity of active immunisation for prevention of MTCT of HIV have been initiated.⁴² Similarly, passive immunisation with polyclonal immunoglobulin has been evaluated in phase III studies in the US (formula-fed infants) and Uganda (predominantly breastfed infants).⁴² Large studies of monoclonal antibody preparations with proven neutralising activity have been proposed.

Three major studies have evaluated the efficacy of chronic administration of ARV prophylaxis to breastfeeding infants.²¹⁻²³ First, in a clinical trial in Botswana, infants were randomised to six months of breastfeeding with zidovudine prophylaxis or formula feeding with one month of zidovudine. HIV-free survival at 18 months was similar with both strategies.²¹ However, in a combined analysis from three separate but co-ordinated randomised controlled trials in Ethiopia, India and Uganda, extended (six-week) infant prophylaxis with nevirapine was compared with a single infant dose of nevirapine in terms of HIV-free survival at six weeks and six months of age among infants who were uninfected at birth. The risk of HIV infection or death was significantly lower at six weeks (relative risk [RR] 0.54), but not at six months, with the extended prophylaxis.²³ Finally, in a trial in

Table 2: Possible Interventions to Prevent Breast Milk Transmission of HIV

Risk Factor for Transmission	Related Intervention
Duration of exposure to breast milk of an HIV-1-infected woman	Complete avoidance of breastfeeding*
Higher maternal viral load	Maternal antiretrovirals (while breastfeeding) to decrease viral load Chemical or heat treatment of breast milk to decrease viral load
Factors facilitating transfer of HIV-1 from the breastfeeding mother to the child	Prevention and treatment of maternal breast abnormalities and infant candidiasis Exclusive breastfeeding (avoidance of mixed breastfeeding)*
Child's susceptibility to HIV infection while breastfeeding	Active immunisation Passive immunisation Antiretroviral prophylaxis to the infant while breastfeeding*

*Efficacy demonstrated.

Malawi, all infants received one dose of nevirapine at birth with one week of zidovudine, and then were randomised to no subsequent prophylaxis, nevirapine until the age of 14 weeks or nevirapine with zidovudine until the age of 14 weeks. Among infants uninfected at birth, both of the extended prophylaxis regimens conveyed a significantly lower risk of HIV infection (and a greater likelihood of HIV-free survival) among infants at nine months of age compared with the control arm.²²

Future Challenges

Despite major successes in the prevention of MTCT of HIV, such transmission continues to occur, and there remain a number of significant challenges if the goal of complete eradication of MTCT is to be realised. First, primary prevention is essential (i.e. prevention of acquisition of HIV infection by adolescent girls and women). Next, increasing the proportion of women accessing pre-natal care contributes to prevention of MTCT. As part of pre-natal care, pregnant women can access HIV diagnostic testing and, if found to be HIV-infected, can initiate one or more interventions to prevent transmission (in addition to accessing appropriate care and treatment for her own HIV infection). The greatest effectiveness of current preventative interventions is predicated upon a pregnant woman knowing her HIV infection status before becoming pregnant, or else as early as possible during pregnancy. The CDC has recommended 'opt-out' HIV testing for all individuals aged 13–64 years receiving care in healthcare settings (including pregnant women).⁴³ HIV testing is treated as part of routine care, and it is performed unless the patient objects (opts out). General consent for medical care is considered to encompass consent for HIV testing, and no specific consent for HIV testing would be requested or required in order for the testing to be performed. It is specifically recommended that women who arrive in labour with unknown or undocumented HIV infection status be screened with a rapid HIV test, and ARV prophylaxis be initiated based on a positive result on the rapid HIV test (without awaiting confirmation).⁴³ Re-screening for HIV infection during pregnancy is emphasised in these guidelines.⁴³

In addition, adverse events and other issues related to utilisation of existing efficacious interventions for prevention of MTCT of HIV must be considered. Potential safety problems related to ARVs for prevention of MTCT include⁴⁴ foetal toxicity (e.g. congenital anomalies, low birth weight, pre-term birth); short-term adverse effects on the mother and/or on the infant (e.g. anaemia or other laboratory abnormalities); and long-term adverse consequences for the child (e.g. cancer).

Relatively limited information has been published regarding the use of ARVs for prevention of MTCT of HIV and the development of resistance.

The USPHS guidelines²⁸ recommend resistance testing for all pregnant women not currently using ARVs (before starting treatment or prophylaxis) and for all pregnant women receiving ARV therapy who have persistently detectable plasma viral loads or sub-optimal viral suppression.

In settings where adequate staffing and infrastructure exist for utilisation of Caesarean section before labour and before ruptured membranes as an intervention to prevent MTCT of HIV, various issues have been raised. First, its effectiveness among women with low viral loads or women who are receiving combination ARV regimens has been questioned. However, published data indicate that Caesarean section before labour and before ruptured membranes is effective in preventing MTCT even among those pregnant women who have viral loads of less than 1,000 copies/ml^{45–49} or who are receiving combination ARV regimens. Second, cost-effectiveness analyses suggest this intervention remains cost-effective even at very low rates of MTCT.⁵⁰ Third, the potential benefit of Caesarean section before labour and ruptured membranes for prevention of MTCT must be weighed against possible deleterious effects of surgical delivery for the mother, for the infant and for the obstetrician.^{51–54} Caesarean delivery may be associated with an increased risk of post-partum morbidity among HIV-infected women compared with uninfected women, but assessment of currently available data suggest post-partum morbidity rates among HIV-infected women are not sufficiently frequent or severe to outweigh the potential benefit of Caesarean section for the prevention of MTCT.²⁸ Analyses of

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morbidity of infants of HIV-infected women associated with the mother's mode of delivery are under way. Although we know the risk must be extremely small, there are essentially no data regarding the relative risk of accidental acquisition of HIV infection by obstetricians or other healthcare workers according to mode of delivery.⁵⁴

Finally, further research is needed regarding not only the pathogenesis of and risk factors for MTCT of HIV, but also to develop new or to adapt existing interventions for the realities of different settings, especially resource-poor settings. In resource-poor settings, where the burden of HIV disease is much greater than in resource-rich settings, complete

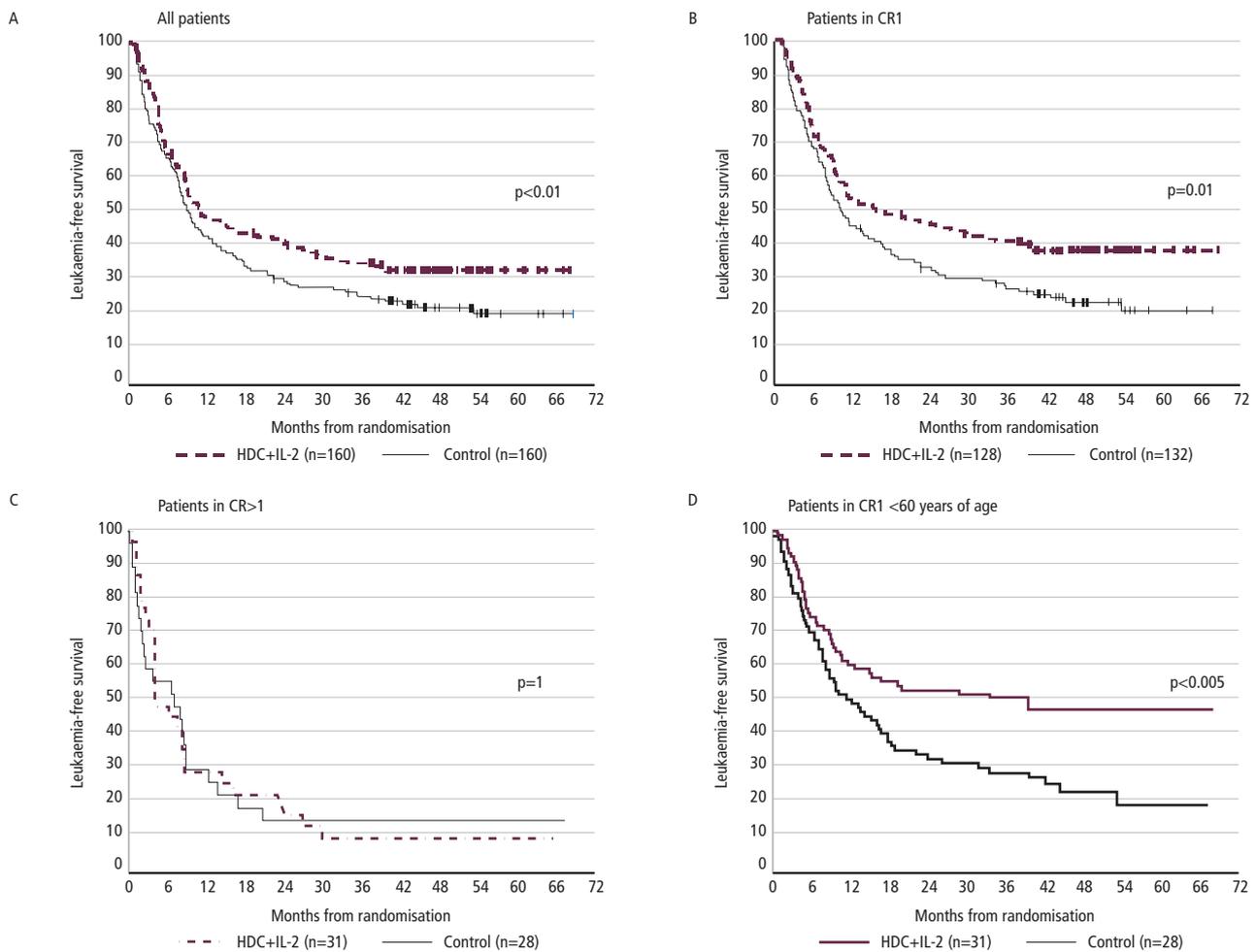
avoidance of breastfeeding is often not possible or acceptable, and Caesarean delivery for the prevention of MTCT of HIV is generally not feasible due to lack of clinical infrastructure and staffing. In these settings, developing new interventions, or adapting existing interventions so that they are feasible and affordable, remains an urgent priority.

In summary, without interventions to prevent transmission, the risk of MTCT generally is in the range of 25–30%. Transmission can occur

during pregnancy, around the time of labour and delivery or post-natally through breast milk, and, in general, most transmission occurs during the intrapartum period. Primary prevention is essential in order to eradicate MTCT of HIV, and different efficacious interventions have been developed and implemented for secondary prevention (transmission from an HIV-infected woman to her infant). Additional basic science, clinical and public health research is essential in order to enable more widespread prevention, and ultimately eradication, of MTCT of HIV. ■

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Figure 1: Kaplan-Meier Plots of Leukaemia-free Survival in Acute Myeloid Leukaemia Patients Receiving Post-consolidation Therapy with Histamine Dihydrochloride/Interleukin-2 or No Treatment in a Phase III Trial



Leukaemia-free survival (LFS) defined as the time from complete remission (CR) to relapse or death from any cause.

Panel A: shows LFS of all patients randomised primary trial end-point (n=320).

Panel B: shows LFS of patients in first CR (CR1; n=261).

Panel C: shows LFS of patients in second or subsequent CR (CR>1).

Panel D: shows LFS of CR1 patients below 60 years of age.

All analyses were performed according to intent-to-treat. The log-rank test (after stratification for CR and country) was used for statistical analysis.¹⁷

Clinical Results of Combination Immunotherapy with Histamine Dihydrochloride and Interleukin-2

A recent phase III trial has demonstrated that treatment with histamine dihydrochloride (HDC, 0.5mg sq bid) in conjunction with low-dose IL-2 (14MIU/month sq bid) significantly prevented relapse in non-transplanted AML patients. The trial was performed in 10 countries with 320 participating CR patients. HDC/IL-2 was administered by the patients at home in a total of 10 three-week courses followed by three- to six-week rest periods for a total of 18 months. The therapy intended to coincide with the period of highest relapse risk after achieving CR. HDC/IL-2 therapy was acceptably well tolerated with no major impact on quality of life.¹⁷ The benefit of HDC/IL-2 appeared to be the result of the prevention of leukaemic recurrence in patients in first CR (CR1), in particular in those below 60 years of age (see Figures 1 and 2).

HDC/IL-2 therapy has been developed on the basis of pre-clinical studies suggesting that HDC improves the immuno-activating properties of IL-2.¹⁸ HDC promotes IL-2 activity by reducing or inhibiting suppressive signals from adjacent myeloid cells.

Pre-clinical Pharmacodynamics of Histamine Dihydrochloride

Studies in pre-clinical models imply that the principal action of HDC is to protect T cells and NK cells from inhibition and apoptosis induced by myeloid cells such as mononuclear or polymorphonuclear phagocytes. These myeloid cells confer inhibition of T- and NK-cell function and also trigger cell death by apoptosis in cytotoxic lymphocytes.¹⁹ HDC counters myeloid-cell-induced inhibition of T and NK cells by reducing or inhibiting the formation of reactive oxygen species (oxygen radicals) in several types of myeloid cells.²⁰ The T and NK cells will remain viable, functional and reactive to IL-2 in the presence of myeloid cells.²⁰ For example, the combination of HDC/IL-2, neither compound used alone, activates cytotoxic lymphocytes to efficiently lyse AML blasts in the presence of mononuclear phagocytes.^{21,22} In addition, HDC improves the IFN- γ -producing capacity of T and NK cells and efficiently improves the IL-2-induced appearance of activation antigens such as CD69 on the surface of these cells.²³ Figures 2 and 3 depict these immunostimulatory properties of HDC, and Table 1 summarises the effects of HDC on T- and NK-cell function *in vitro* along with studies suggesting that the addition of HDC improves the antitumour activity of IL-2 in tumour-bearing rodents *in vivo*.