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Options for Prevention of HIV Transmission from Mother to Child, with a Focus on Developing Countries

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Abstract

Use of antiretroviral drugs among HIV-infected pregnant women in many developed countries has significantly reduced rates of mother-to-child HIV transmission, demonstrating that this route of transmission is amenable to intervention. Prevention of transmission in developing countries has proved to be more difficult, although recent advances in short-course antiretroviral drug interventions have made it an immediate possibility, rather than a distant hope as it was seen to be in the recent past. Non-antiretroviral drug interventions, including washing of the birth canal with antiseptic solution and micronutrient supplementation, have not been found to be effective at interrupting mother-to-child HIV transmission, but may have other benefits for maternal and child health. An important issue for developing countries is prevention of postnatal HIV transmission through breast feeding. In most developing countries, formula feeding is not a reasonable option, given the higher rates of mortality from diarrheal and respiratory disease associated with avoidance of all breast feeding. A promising new line of research has recently been broached with the findings from a study in South Africa, which demonstrated that exclusive breast feeding is associated with a significant reduction in postnatal transmission of HIV.

Mother-to-child transmission of HIV is an important aspect of the AIDS pandemic and has rightly been the focus of much preventive research. In the absence of interventions, an estimated 20 to 30% of infants born to HIV-infected mothers will also become infected.[1] In the US and Europe, widespread use of antiretroviral drugs among HIV-infected pregnant women has reduced rates of mother-to-child HIV transmission to as low as 2%, demonstrating that this route of transmission is amenable to intervention.[2] Much recent research, therefore, has focused on the reduction of mother-to-child HIV transmission in developing countries, where perinatal HIV infection contributes significantly to infant mortality. Data from southern and eastern Africa, for example, suggest infant and child mortality is now almost two-thirds higher than it would have been in the absence of HIV/AIDS.[3]

Several factors amplify mother-to-child HIV transmission in developing countries. Women in developing countries have little access to HIV testing and treatment or prenatal care, which were necessary elements involved in the substantial reduction of mother-to-child transmission in developed countries. HIV sero-

prevalence among women of childbearing age (15 to 49 years) is significantly higher in many developing countries than in the US and Europe. In sub-Saharan Africa, it is estimated to be about 8% overall, and as high as 36% in some areas, compared with 0.25% in the US.[4] Furthermore, seroprevalence data indicate that HIV infection is increasing most in women in their twenties, the population segment with the highest fertility. Finally, breast feeding is nearly universal in almost all developing countries. While it provides many health benefits, it also entails potential exposure of infants to HIV.

The factors listed above should not be interpreted as immutable or unsurpassable barriers to the control of mother-to-child transmission of HIV in developing countries. Recent advances in short-course antiretroviral drug interventions have made prevention an immediate possibility, rather than a distant hope as it was seen to be in the recent past. Nor, for that matter, should it be assumed that control of perinatal HIV infection is uniformly satisfactory in developed countries. Surveillance data in the US, for example, show that mother-to-child transmission is significantly higher among young minority women in inner-city areas.[2] These diverse situations underscore the need for creative, forward-looking and situationally relevant epidemiologic research into the prevention of mother-to-child transmission.

From this perspective, this paper provides an overview of the current avenues of epidemiologic research related to the prevention of mother-to-child HIV transmission, with an emphasis on developing countries. Issues regarding the timing and biological mechanisms underlying mother-to-child transmission are briefly reviewed, followed by a discussion of specific interventions.

1. Timing and Mechanisms of Mother-to-Child HIV Transmission

The timing of mother-to-child HIV transmission has important implications for the development of interventions aimed at disrupting transmission occurring *in utero*, intrapartum and postnatally. Diagnostic, clinical and epidemiologic data have provided the basis of current knowledge about the timing and specific etiological mechanisms of transmission. A brief review of these data will establish a framework for the discussion of preventive interventions, which follows later in the paper.

1.1 *In Utero* and Intrapartum Transmission

The timing of mother-to-child HIV transmission has been the subject of some controversy. In particular, it has been difficult to determine the relative contributions of *in utero* and intrapartum transmission to the overall rate of transmission.[5] Clinical signs of HIV disease do not clearly distinguish intrauterine from intrapartum transmission. *In utero* HIV infection does not appear to have unique clinical manifestations, clinical signs of HIV in neonates are rare, and there is a wide variation in the natural history of HIV-associated disease among infected infants, with some showing rapid progress of disease in the first year of life and others surviving into childhood and adolescence.[6]

The best available data on the timing of transmission have come from virologic methods of diagnosing HIV infection, specifically viral culture, and amplification of HIV DNA by polymerase chain reaction (PCR). These tests detect the presence of circulating virus in the blood and, therefore, are not influenced by passive transfer of maternal antibodies, which limits the use of standard antibody assays in infants. Viral culture and PCR when used in neonates within a day or two of birth have sensitivities of only about 30%.[7-10] It has been inferred from these results that in non-breast-feeding infants who have no detectable virus at birth but who are later determined to be HIV-infected, the lack of detectable virus near birth is indicative of recent infection (i.e. very late *in utero*, or during birth). Given this, *in utero* infection is typically defined by the detection of virus in the infant's peripheral blood through virologic methods within 48 hours of birth, while intrapartum infection is defined by a negative finding within 48 hours of birth with positive findings occurring only later within 1 week to 90 days of birth.[11] This classification system is clearly imperfect, and factors other than the timing of transmission may influence whether early diagnostic tests are positive or negative. For example, among infants infected *in utero*, HIV may remain sequestered in noncirculating tissues before activation of the infant's immune system. In this instance, HIV will not be found circulating in the infant's peripheral blood within 48 hours of birth.

Other epidemiologic data, however, tend to support the notion that most mother-to-child transmission among non-breast-fed infants occurs during birth. One line of evidence to support the importance of intrapartum transmission comes from findings that in HIV-exposed vaginally delivered twins, first-born twins have significantly higher rates of HIV infection than second-born twins.[12,13] Higher rates of infection observed among HIV-exposed infants after prolonged rupture of membranes prior to delivery[14] and lower rates of infection observed among those delivered by elective cesarean section[15] also support the importance of this route of transmission. Intrapartum HIV transmission may occur in labor through maternal-fetal microtransfusions of blood and through direct mucosal contact of the infant with infected fluids and blood in the birth canal.[16]

The presumed rarity of *in utero* HIV transmission conforms to what is known about the effectiveness of the placental barrier in preventing maternal pathogens from reaching fetal circulation. *In utero* infection is thought to occur either through breaks in the placental barrier or through direct infection of the cells in the trophoblastic layer of the placenta. Evidence of the latter comes from identification of HIV in trophoblasts of some HIV-exposed placentas[17,18] and the observation that trophoblasts can be infected with HIV *in vitro*.[19,20] Other researchers, however, have found placental infection to be rare,[21] leading to the conclusion that *in utero* transmission occurs primarily through breaks in the placental barrier. Despite the likely preponderance of HIV transmission near birth, studies of electively aborted fetuses of HIV-infected women suggest that early *in utero* HIV infection can occur.[22-25]

1.2 Postnatal Transmission

It is well established that HIV can be transmitted during the postnatal period through breast feeding, although the frequency of transmission via this route is not accurately quantified. The widely quoted estimate of 14% [95% confidence interval (CI) 7 to 22%] as the excess risk of HIV infection associated with postnatal exposure to breast milk from women with prevalent HIV infection is based on a meta-analysis with serious methodological flaws.[26] In the meta-analysis, the excess risk was calculated by subtracting the overall transmission rate observed among HIV-infected women who had never breast fed their infants from the rate among women who had breast fed; however, none of the individual studies included in the meta-analysis had recruited substantial numbers of ever and never breast-fed infants: in studies conducted in Africa, most infants were breast fed; in studies conducted in the US and Europe, most were not. Furthermore, other factors associated with the decision to breast feed were not taken into account. Despite the methodologic limitations of the meta-analysis, its estimate of the excess risk associated with breast feeding has largely been supported. Notably, a randomized clinical trial conducted in Nairobi, Kenya, generated a similar estimate for the excess risk of postnatal transmission of 16% (95% CI 7 to 26%).[27]

Breast feeding cannot simply be considered as a homogeneous, all-or-nothing exposure. Some epidemiologic data suggest that the risk of postnatal HIV-1 infection is greatest early on. In the Nairobi trial, 63% of the excess risk associated with breast feeding had occurred in infants by age 6 weeks.[27] A cohort study conducted in Malawi of infants breast fed by their HIV-infected mothers also observed a trend for decreasing incidence of postnatally acquired HIV infection as children aged.[28] An important question requiring further study is whether the observed predominance of early postnatal transmission is due primarily to age-specific risk mechanisms (such as infant immune immaturity), variations in breast milk infectivity over time, or other factors.[29] Despite the apparent declining risk over time, several studies support the notion that breast feeding poses a detectable risk of HIV infection transmission throughout the duration of breast feeding.[30-34] In almost all the observational cohort studies that investigated this, new infections continued to be observed while breast feeding continued, although the risk of such 'late postnatal' infection may have been as low as 3 per 100 child-years of breast-feeding follow-up.[35]

Largely overlooked in research into postnatal HIV transmission has been the important distinction made by nutritionists between exclusive and partial or predominant breast feeding. Exclusive breast feeding is defined as breast feeding in the complete absence of all other fluids and solids and is recommended for up to 6 months of age, during which time breast milk alone can satisfy all the infant's nutritional and fluid needs.[36] Though rarely practiced, exclusive breast feeding has long been known to be superior to partial and predominant breast feeding as a way of reducing non-HIV-related infant morbidity and mortality in the first 6 months of life.[37-39] A recent observational study conducted in Durban, South Africa, observed no increased risk in infants being exclusively breast fed compared with never breast-fed infants. Postnatal transmission rates at comparable ages were significantly higher among predominantly and partially breast-fed infants than among their exclusively breast-fed counterparts.[40] While these findings require confirmation, they highlight the importance of clarifying not only the duration, but also the quality of breast feeding when discussing rates of postnatal HIV transmission.

Another aspect of postnatal HIV transmission is highlighted in findings that mothers infected postnatally with HIV are at higher risk of transmitting the virus to their infants, probably because of peak viremia associated with initial infection.[41] Approximately 30% of women with primary HIV infection while breast feeding are thought to transmit HIV to their infants via breast milk.[26] In areas where the incidence of adult HIV infection is high, this issue has important public health implications. All in all, these data underscore the importance of breast feeding as a potential source of HIV infection in infants.

2. Interventions to Reduce Mother-to-Child HIV Transmission

Having reviewed the salient aspects of the timing and mechanisms of mother-to-child HIV transmission, we now turn to an

examination of the major areas of research related to interrupting transmission, including antiretroviral drug prophylaxis, preventive cesarean section and vaginal lavage, prenatal use of vitamins, and exclusive breast feeding. Research into these interventions has led to new questions about hypothesized mechanisms of transmission and has brought forth debates about the ethics, feasibility and standards relating to public health policy and research in developing countries. The following discussion outlines the central findings of such research trajectories, while highlighting areas that will be of concern in future research.

2.1 Antiretroviral Drugs

A major breakthrough in the study of prevention of mother-to-child HIV transmission was provided in 1994 by the Pediatric AIDS Clinical Trial Group (PACTG) protocol number 076 clinical trial of the three-part prophylactic regimen of zidovudine (ZDV).[42] Carried out in a ZDV-naïve, relatively asymptomatic, and non-breast-feeding population in the US and France, the PACTG 076 clinical trial showed a 67.5% reduction in mother-to-child HIV transmission in treated individuals compared with controls, thus demonstrating the principle that antiretroviral drug prophylaxis substantially reduces the risk of mother-to-child HIV transmission. Subsequent observational studies suggested that the PACTG 076 regimen was effective in individuals previously treated with ZDV as well as in those with more advanced HIV-1 disease.[43-47] Furthermore, an observational study of pregnant women in the US found that even abbreviated periods of ZDV use were associated with some reduction of HIV transmission.[48] Data from various study populations suggest that the overall effectiveness of the PACTG 076 regimen in clinical practice is exceptionally good. Some studies of HIV-infected women in the US have reported transmission rates as low as 3 to 6%,[2] but whether these low rates are solely attributable to implementation of the PACTG 076 prophylactic protocol or to more widespread treatment of HIV-infected women with highly active combinations of antiretroviral drugs is unclear.

Since rapidly becoming the standard of care in the US in 1994, uptake of the PACTG 076 regimen in clinical practice has been remarkable, and has been largely credited with the observed 67% decline in perinatal AIDS in the US from 1992 to 1997.[49-51] Observational studies and surveillance data have shown that the percentage of HIV-infected pregnant women identified in the prenatal period who are offered and given ZDV has increased substantially from just 7% in 1993 to 91% in 1997;[50] however, while the PACTG 076 regimen has had a substantial effect on mother-to-child transmission of HIV in the US population overall, access to the intervention is significantly lower in population subgroups such as adolescents, socioeconomically disadvantaged groups, and illicit drug users.[2,52] A major barrier to ZDV prophylaxis in these groups is the persistence of inadequate, late or nonexistent prenatal care, as well as low rates of early identification of maternal HIV status.[2]

Despite its public health impact in the US and Europe, the PACTG 076 regimen was never seriously considered as an option for developing countries, largely because of drug costs and the inadequacy of health infrastructure in many countries. The urgency of developing and testing more appropriate short-course antiretroviral drug regimens for use in developing countries with high maternal HIV seroprevalence was acutely felt after the success of PACTG 076. To this end, several placebo-controlled clinical trials were carried out in Africa and Asia to determine the efficacy of various short-course antiretroviral regimens. These trials were sharply criticized for using placebo controls when an existing therapy, namely the PACTG 076 regimen, was known to be efficacious. Further discussion about this important issue can be found elsewhere.[53]

The efficacy of short-course regimens can be most directly compared with that of the PACTG 076 protocol, either in non-breast-feeding or breast-feeding populations, by considering the regimens' short-term effects on HIV transmission attributable to intrauterine and intrapartum routes only. Overall, results of these clinical trials indicate significant reductions (~34 to 50%) in intrauterine and intrapartum HIV transmission associated with short-course antiretroviral drug interventions (table I).[54-58] Although possibly less efficacious than the PACTG 076 regimen, these regimens offer potentially feasible options for settings where the HIV pandemic predominates. In addition, studies that examined the use of short-course antiretroviral drug regimens over the longer term in breast-feeding populations demonstrate that although breast feeding reduces the efficacy of antiretroviral drug prophylaxis, there remains significant benefit in the use of these therapies in nursing populations (figure 1).[59] Studies are under way to test whether continued use of antiretroviral drugs during the postnatal period can reduce breast feeding-associated transmission.

Areas of continued interest to researchers are determination of the following: the part of an antiretroviral regimen most essential to preventing mother-to-child HIV transmission; and the duration of treatment needed for efficacy. Data from the clinical trials reviewed above provide some evidence with regard to these questions. Firstly, the observed efficacy of short-course regimens, which are started in the late prenatal period or intrapartum, suggests that most of the preventive effect of the PACTG 076 regimen is not due to initiation early in gestation; however, data from

Table I. Randomized clinical trials to evaluate the efficacy of antiretroviral drugs in reducing mother-to-child transmission of HIV in non-breast-feeding populations and over the short term in breast-feeding populations

Study, site, date	Sample size	Intervention	Outcome [efficacy[a] or transmission[b] % (95% CI)]	Breast fed
PACTG 076,[42] United States, 1994	363	*Mother:* 100mg ZDV 5 times daily upon ≥14wk gestation, intravenous ZDV at delivery. *Neonate:* ZDV for 6wk	Efficacy at 18mo compared with placebo: 67.5 (40.7, 82.1) p < 0.0001	No
PETRA,[57] South Africa, Tanzania, Uganda, 1997	1326	*Intensive mother:* ZDV-3TC from 36wk, during labor, to 1wk past delivery. *Neonate*: ZDV-3TC for 1wk *Labor/postpartum mother:* ZDV and 3TC from labor to 1wk past delivery. *Neonate*: no treatment *Labor-only mother:* ZDV and 3TC at onset of labor. *Neonate:* no treatment	Efficacy at 6wk compared with placebo (no CI available): intensive 50; labor/postpartum 37; labor only 0	Yes
CDC,[56] Thailand, 1999	393	*Mother:* 300mg ZDV twice daily from 36wk gestation, oral dose at onset of labor, then every 3h. *Neonate:* no treatment	Efficacy at 6mo compared with placebo: 50.1 (15.4, 70.6) p = 0.006	No
CDC,[54] Côte d'Ivoire, 1999	280	*Mother:* 300mg ZDV twice daily from 36wk gestation, oral dose at onset of labor, then every 3h. *Neonate:* no treatment	Efficacy at 4wk compared with placebo: 44 (–1.0, 69.0) p = 0.05	Yes
Ditrame,[55] Côte d'Ivoire, Burkina Faso, 1999	431	*Mother:* 300mg ZDV twice daily from 36wk gestation, oral dose at onset of labor, then every 3h, 1wk of ZDV postpartum. *Neonate:* no treatment	Efficacy at 45 days compared with placebo: 34 (0.0, 66.0)	Yes
HIVNET,[58] Uganda, 1999	609	*Nevirapine mother:* 200mg at onset of labor. *Neonate:* single dose 2 mg/kg within 72h of birth *ZDV mother:* 600mg orally at onset of labor, and 300mg every 3 hours. *Neonate:* 1 week of ZDV	Efficacy at 6-8wk nevirapine *vs* ZDV: 44 (24.0, 64.0) p < 0.0001	Yes
Lallemant et al.,[60] Thailand, 2000	1409	*Short-short (s-s) mother*: ZDV from 35wk gestation through delivery. *Neonate:* 3 days of ZDV	Actual HIV transmission rate at 6mo s-s: 10.5 (6.4, 14.4) p = 0.004 *vs* l-l	No
		Short-long (s-l) mother: ZDV from 35wk gestation through delivery. *Neonate:* 6wk of ZDV	s-l: 8.6 (5.6, 11.6) NS *vs* l-l	
		Long-short (l-s) mother: ZDV from 28wk gestation through delivery. *Neonate:* 3 days of ZDV	l-s: 4.7 (2.4, 7.0) NS *vs* l-l	
		Long-long (l-l) mother: ZDV from 28wk gestation through delivery. *Neonate:* 6wk of ZDV	l-1: 6.5 (4.1, 8.9)	

a Efficacy is defined as the percentage reduction in HIV transmission.

b Transmission is defined as the percentage infected.

3TC = lamivudine; **CI** = confidence interval; **mo** = months; **NS** = not significant; **wk** = weeks; **ZDV** = zidovudine.

an equivalence trial comparing various short-course ZDV regimens with a regimen similar to the full-length PACTG 076 regimen show that starting prophylaxis earlier (i.e. 28 weeks versus 35 weeks) increases effectiveness of the regimen.[60] Interestingly, lengthening the postnatal component from 3 days to 6 weeks could also increase effectiveness of the regimen and could counteract the reduced effectiveness of starting the regimen relatively late during the postnatal period. Specifically, the study showed

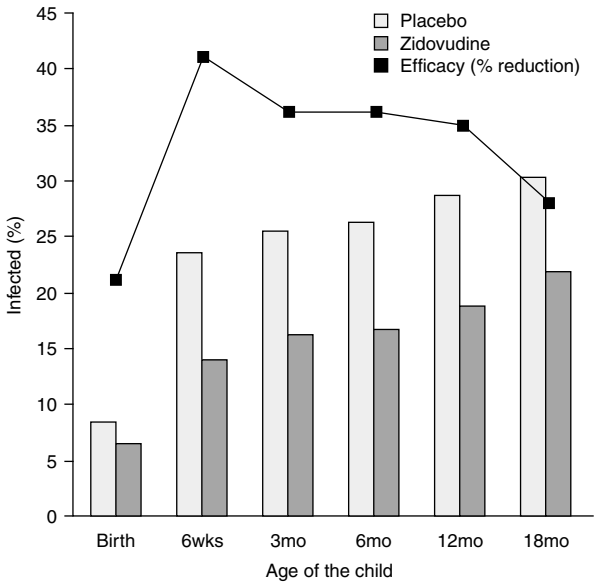

Fig. 1. Longer-term efficacy of short-course zidovudine to prevent mother-to-child HIV transmission.[59] **mo** = months; **wks** = weeks.

no statistical difference in HIV incidence in infants exposed to ZDV from 35 weeks' gestation to 6 weeks postnatally compared with infants who received essentially the full-length PACTG 076 regimen.[60] The labor-only use of antiretroviral drugs appears to be ineffective for reducing transmission.[57]

Another area of active research is the role of maternal viral load in accounting for the efficacy of antiretroviral drug prophylaxis. Since maternal viral load, as measured by HIV RNA quantities in maternal plasma, is one of the strongest correlates of mother-to-child HIV transmission,[61-63] it was assumed that the benefits of antiretroviral drug prophylaxis would be explained by viral reductions; however, this was not borne out by analysis of data from the PACTG 076 trial. After initiation of ZDV, small reductions were observed in HIV RNA copy numbers in maternal plasma by the time of delivery, but these decreases could account for only a small fraction of the reduction observed in HIV transmission.[64] Other mechanisms are thus likely to account for the benefit of antiretroviral drug interventions. The observed effectiveness of postexposure prophylaxis in healthcare workers,[65] and some non-clinical trial data attesting to the same in infants,[48] point to the existence of other mechanisms through which ZDV may act to prevent transmission. Further research is needed to elucidate how ZDV prophylaxis may affect these other factors and thus reduce the risk of mother-to-child HIV transmission. Nevertheless, reduction of maternal viral load may be an effective intervention. Evidence to date suggests that women treated with effective drug cocktails potent enough to suppress viremia during pregnancy have very low rates of HIV transmission.[66,67]

An important topic to be considered in future research into antiretroviral drugs is the potential for long-term adverse effects of antiretroviral drug prophylaxis in mothers and children. Thus far, analysis of PACTG 076 data has shown no difference in immunologic function, cognitive development, growth, or mortality in the first years of life among infants whose mothers used ZDV in pregnancy compared with infants whose mothers did not.[68] Data about short-course ZDV use in Thailand also showed no significant adverse events within 18 months of follow-up.[69] Although these findings are encouraging, rarer and longer-term adverse outcomes require further investigation. Indications of the potential for rare adverse outcomes associated with ZDV prophylaxis come from a registry of clinical and observational data of mother-to-child HIV transmission in France, which reveals an abnormally high, though still rare, occurrence of mitochondrial abnormalities in infants exposed to ZDV.[70,71] It has not been possible to replicate these observations in the US.[72] Further evidence of possible ZDV toxicity has been shown in animal studies, as well as in findings that exposed women and their infants had ZDV incorporated in their DNA, suggesting the tumorigenic potential of ZDV in humans.[73] At present, however, it is clear that the health benefits of antiretroviral drug prophylaxis in HIV-infected pregnant women far outweigh the theoretical risks, and women should continue to be offered these therapies while being fully informed of the issues of possible toxicity.

Perhaps of more immediate concern than toxicity is the obstacle that drug resistance may pose to the effectiveness of ZDV prophylactic monotherapy in preventing transmission. Studies have demonstrated that, although rare, development of ZDV-resistant strains can occur among women taking ZDV during pregnancy;[74,75] however, this is more common among women with prior exposure to ZDV or with more advanced clinical disease.[76] Viral resistance to ZDV in the presence of ZDV prophylaxis appears to increase the risk of mother-to-child HIV transmission in some,[77] but not all reports.[78] In the report that observed an increase in HIV transmission associated with resistance to ZDV, resistance was associated with a higher viral load but predicted HIV transmission independent of viral load.[77] It is not clear what accounts for the contradictory findings, and there is evidence to suggest that wild strains are more efficiently transmitted than mutant strains, independent of their abundance in maternal plasma.[74] Resistance to nevirapine is common, even after the single dose used for prophylaxis.[79] The clinical significance of resistance to nevirapine in subsequent pregnancies needs to be investigated, and ongoing monitoring of viral sensi-

tivity to the drugs most commonly used for prophylaxis will be necessary in the long term as these drugs become more widely used in developing countries.

The critical research question now for prevention of mother-to-child HIV transmission in developing countries is how to implement programs to make antiretroviral drug interventions available to the many HIV-infected pregnant women who need them. Moving from clinical trial results, which demonstrated unambiguous benefit for these relatively simple and inexpensive (in terms of drug costs) interventions, to public programs has proved especially difficult. Obstacles have emerged from several sources within international agencies, private enterprise and national governments, and individual resistance to HIV testing and interventions is widespread. Continued support is needed for researchers and service providers in their efforts to understand situation-specific impediments to implementation and to find creative ways to overcome them.

2.2 Obstetric Interventions: Cesarean Sections and Vaginal Lavage

Antiretroviral drugs are likely to remain the cornerstone of interventions to interrupt mother-to-child HIV transmission and are the interventions most strongly supported by research; however, other interventions, particularly those focused on the intrapartum period, may be useful to supplement drug interventions or in special circumstances in which antiretroviral drugs cannot be, or have not been, used.

One such obstetric intervention is elective cesarean delivery. The idea that cesarean delivery may be effective to reduce HIV transmission hinges, in part, on the concept that most mother-to-child HIV transmission probably occurs during labor and delivery. Initial studies, many of which predated the antiretroviral drug era, were inconsistent and ambiguous regarding whether or not mode of delivery was associated with transmission.[80,81] In part, the lack of clarity was due to small sample sizes, but primarily to a failure to distinguish correctly between elective and emergency procedures. When elective procedures were rigorously defined, based on their use prior to membrane rupture, cesarean delivery reduced the risk of infant HIV infection by more than 50%, after adjusting for several potential confounders including maternal disease stage, antiretroviral drug use, and birth weight.[15] A small, multisite clinical trial in Europe confirmed the benefit of elective cesarean delivery to reduce HIV transmission, reporting an 80% lower risk of HIV infection with cesarean compared with vaginal delivery (table II).[82] Of note, the benefits of elective cesarean delivery and ZDV monotherapy appear to be additive, with reductions in mother-to-child HIV transmission observed to

Table II. Randomized clinical trials to evaluate the efficacy of other interventions in reducing mother-to-child transmission of HIV

Study, site, date	Sample size	Intervention	Efficacy	Breast fed
Biggar et al.,[84] Malawi, 1996	982	*Mother:* manual cleansing of birth canal with chlorhexidine prior to delivery *Neonate:* washing after birth with chlorhexidine	No difference in percentage of infants HIV infected at 12wk (27% infected in intervention *vs* 28% in placebo group) Subgroup effect in those with ROM >4h (% reduction): 36.5 (95% CI 25.6,47.5) p = 0.02	Yes
European Mode of Delivery,[80] Europe, 1999	370	Elective cesarean section at 38wk gestation	Percentage reduction by intent-to-treat, elective cesarean section *vs* vaginal in multivariate analysis: 80% (95% CI 40.0, 90.0) p < 0.001	No
Coutsoudis et al.,[85] South Africa, 1999	728	Daily supplement of 5000IU retinyl palmitate and 30mg β-carotene from 28 to 32wk. 200 000IU megadose of retinyl palmitate at delivery	Percentage of infants HIV infected by 3mo: Vitamin A: 20.3% (95% CI 15.7, 24.9) Placebo: 22.3% (95% CI 17.5, 27.1)	Yes
Fawzi et al.[86] Tanzania, 2000	962	Factorial design: Factor 1: Vitamin A (30mg β-carotene plus 5000IU preformed vitamin A, oral vitamin A delivery) Factor 2: Multivitamins excluding vitamin A (20mg B1, 20mg B2, 25mg B6, 100mg niacin, 50μg B12, 500mg C, 30mg vitamin E and 0.8mg folic acid)	Risk of HIV at 6wk among infants HIV-negative at birth in experimental groups compared with placebo Vitamin A: RR = 1.04 (95% CI 0.65,1.66) Multivitamin: RR = 1.30 (95% CI 0.80, 2.09)	Yes
Gaillard et al.,[87] Kenya, 2001	606	*Mother:* Flushing of cervical area with 60ml chlorhexidine solution during labor every 3h until delivery	Risk of infant HIV infection by 14wk: OR of intervention *vs* placebo 0.9 (95% CI 0.6, 1.4)	Yes

CI = confidence intervals; **mo** = months; **OR** = odds ratio; **ROM** = duration of membrane rupture prior to delivery; **RR** = relative risk; **wk** = weeks.

be between 0 and 2% in some populations if both interventions are implemented.[15,83]

Despite these encouraging findings, the benefit associated with cesarean sections in preventing vertical HIV transmission should be balanced against the potential surgical risks to the mother.[88,89] Postoperative morbidity and mortality are greater among immunocompromised people and are also considerably higher in developing countries. Significantly increased postdelivery complications have been observed among HIV-infected women undergoing cesarean compared with non-cesarean delivery.[82,88,89] Under current conditions, elective cesarean section is not a feasible preventive strategy against HIV transmission in developing countries. In developed countries, the added benefits of elective cesarean section should be considered in relation to the apparently high efficacy of combination therapy with antiretroviral drugs. Although not without side effects and toxicities, combination therapy may be safer than surgical delivery.

A simpler and safer obstetric intervention proposed to prevent intrapartum HIV transmission is the use of vaginal lavage, which entails washing the birth canal with an antiseptic during labor. An advantage of vaginal lavage is that it can safely be conducted on all women giving birth, which is particularly beneficial in settings with low levels of HIV testing. The potential efficacy of vaginal lavage to prevent HIV transmission is based on the assumption that antiseptic washes can successfully reduce neonatal exposure to maternal blood and genital secretions in the birth canal. Vaginal lavage may also be effective in preventing ascending HIV infection, since it has been shown to reduce vertical transmission of other infections, such as group B streptococci, which are known to infect neonates by ascending through the birth canal prior to delivery.[90]

Unfortunately, data now available from two separate clinical trials, one carried out in Malawi and the other in Kenya, do not support the use of chlorhexidine vaginal lavage as an effective means of preventing perinatal HIV transmission (table II).[84,87] In the Malawian trial, vaginal lavage had no effect on HIV transmission rates overall, but was associated with a reduction in transmission among women who experienced ruptured membranes for more than 4 hours prior to delivery;[84] however, this subgroup finding was not replicated in the Kenyan trial.[87] Factors that may account for the null effects include the type or concentration of solution used, the effectiveness of the solution in reducing viral exposures, or an overestimation of the importance of birth canal exposure in HIV transmission. Importantly, reductions were observed in severe maternal and neonatal morbidity and in neonatal mortality due to infectious causes,[91] suggesting that chlorhexidine vaginal lavage may have more general health benefits in populations in developing countries, despite its apparent lack of effect in reducing mother-to-child HIV transmission.

2.3 Vitamin A and Other Micronutrients

Interest in vitamin A as a potential preventive measure against mother-to-child HIV transmission was piqued by a study in Malawi that observed a strong dose-response relationship between serum levels of retinol in HIV-infected women and the risk of HIV transmission, even after adjusting for other factors associated with transmission including maternal CD4+ T lymphocyte counts, clinical symptoms, and body mass index.[92] Based on these data, as well as on studies of the association between serum retinol and disease progression among HIV-infected adults,[93] and on studies showing some benefits of vitamin A supplementation in reducing morbidity in HIV-infected children,[94] clinical trials were set up to test whether supplementation of pregnant HIV-infected women with vitamin A could reduce the risk of mother-to-child HIV transmission. The hypothesized mechanisms underlying putative vitamin A benefit were stimulation of the immune system and/or maintenance of the integrity of mucosal surfaces.

The results of two trials, one conducted in South Africa and one in Tanzania, have now been published: neither trial reported significant reductions in HIV transmission among women receiving vitamin A rather than placebo (table II).[85,86] The contradictory findings between clinical trials and the nonexperimental observational study in Malawi may be explained as follows: low serum vitamin A may only be a marker of advanced disease (not reflected in CD4 counts) or other nutritional deficiencies, which in turn are the true factors influencing HIV transmission. Although vitamin supplementation has not been shown to reduce rates of HIV transmission, findings from the South African and Tanzanian trials suggested other benefits of micronutrient supplementation. For example, in the Tanzanian trial, which also included a multivitamin arm, significant benefits were observed for multivitamin supplementation on maternal CD4+ T lymphocyte counts and on adverse pregnancy outcomes, including perinatal mortality.[95] Although apparently without demonstrable benefit regarding mother-to-child HIV transmission, nutritional interventions, similarly to vaginal lavage, may have other health benefits among populations in developing countries with a high seroprevalence of HIV.

2.4 Exclusive Breast Feeding and Early Cessation of Breast Feeding

Assuming the successful implementation of programs to ensure access of HIV-infected women to short-course antiretroviral

drug interventions, postnatal HIV transmission will become the predominant route of mother-to-child HIV transmission in developing countries. In developed countries, it is universally recommended that HIV-infected women formula feed their infants to avoid any risk of HIV infection through breast feeding; however, in resource-poor areas in developing countries, formula feeding is not a reasonable option for many women, primarily because formula-fed infants experience higher rates of mortality from diarrheal and respiratory disease than breast-fed infants.[96-102] An important issue, then, is to establish infant feeding recommendations for HIV-infected women in resource-poor settings that balance the risk of postnatal HIV transmission against the risk of non-HIV infant mortality.

To address the question of competing risks, several researchers have used mathematical modeling to quantify adverse outcomes (mortality or HIV infection) associated with infant-feeding options under various conditions.[103-108] Results of these models have shown that optimal strategies, in terms of reducing the overall number of adverse events, are highly sensitive to background infant mortality rates and to the expected risks associated with avoidance of breast feeding.[105,107,108] The latter, particularly, is seldom known with any precision. In populations with high background infant mortality rates, even small to moderately increased risks associated with an avoidance of breast feeding can wipe out gains achieved by avoiding breast feeding-associated HIV transmission.[105,107,108] Another unequivocal finding from mathematical models is that shifts away from breast feeding, if not confined to HIV-infected women, always have the worst outcome.[103-108] This underscores the need to protect and support breast feeding in uninfected women and also the importance of HIV testing. Unfortunately, tailoring infant-feeding advice specifically to a woman's sero-status may contribute to stigma and unintended disclosure of HIV status.

A promising new line of research has recently been broached with findings from a nonexperimental, prospective study carried out in Durban, South Africa, which demonstrated that exclusive breast feeding was associated with a significant reduction in postnatal transmission of HIV.[40] Among infants who were HIV RNA negative by PCR at birth, 8% had detectable HIV RNA in peripheral blood by 3 months of age, if exclusively breast fed to this age. This proportion was similar to that observed in never breast-fed infants (13%) and hence presumably attributable to intrapartum transmission. In contrast, a higher proportion of infants negative by PCR at birth (20%) had HIV RNA detected by 3 months of age if breast fed partially or predominantly (i.e. other foods and drinks supplemented breast feeding). This proportion presumably included intrapartum plus postnatal transmission.[40] Longer follow-up of these infants supported the protective benefits of exclusive breast feeding throughout the period that breast feeding continued to be exclusive (the maximum duration of exclusive breast feeding was 6 months).[109] Further studies are needed to exclude the possibility that self-selection and other methodologic issues account for the apparent protective effect of exclusive breast feeding found in this observational study; however, if supported with further evidence, exclusive breast feeding may represent an effective way to reduce mother-to-child HIV transmission, while maintaining the benefits of breast-milk nutrition for infants in resource-poor settings. Exclusive breast feeding is, unequivocally, the healthiest option for infants during their first 6 months of life, in the absence of HIV infection.

Exclusive breast feeding is a novel concept for reducing the risk of HIV transmission; however, its protective effects against morbidity associated with gastrointestinal and respiratory disease are well established, and several biological mechanisms have been investigated to account for these effects.[110] The relevance of these mechanisms to reduced HIV transmission is as yet unknown, but they provide biological plausibility for the observed association. For example, exclusive breast feeding exposes the child to fewer bacterial contaminants and to a restricted range of food antigens. This may reduce immune activation in the gastrointestinal tract. Exclusive breast feeding also facilitates maturation of the infant's gut and may assist in maintaining the integrity of the intestinal mucosal barrier.[110]

In the Durban study, after 6 months of age, new infections were detected among previously exclusively breast-fed infants, if breast feeding continued supplemented with other foods and liquids.[109] One way to avoid such late postnatal infections, after breast feeding can no longer be exclusive, is abrupt cessation of all breast feeding. Early cessation of breast feeding has been floated as an option to reduce postnatal HIV transmission but it has not yet garnered sufficient enthusiasm to spur an evaluation of its capacity to reduce mother-to-child HIV transmission. Although there are continuing benefits of longer duration of breast feeding (>6 months) on infectious disease morbidity and mortality, on child cognitive development, and on extending postpartum amenorrhea, protection accorded by breast feeding from severe and life-threatening conditions is greatest in the first few months of life.[111-113] In part, the lack of enthusiasm for early cessation of breast feeding may be because, on its own, it provides no means to reduce early postnatal HIV transmission. If, however, the protective benefits of exclusive breast feeding on postnatal transmission during the first few months of life are supported by further studies, short exclusive breast feeding may be the optimal infant feeding practice. Empiric testing of the safety and efficacy of

the concept is of course essential. A concern was raised that breast feeding may have a detrimental effect on the health of HIV-infected mothers.[114] This was not confirmed in another study;[115] however, it is important that studies of interventions to reduce HIV transmission to the infant also include careful evaluation of the effect of these interventions on maternal health.

The practicality of achieving exclusive breast feeding among a large proportion of women should not be underestimated. Many barriers to exclusive breast feeding outside the HIV context have been identified, including cultural traditions, work outside the home, maternal health, and perceptions of insufficient milk production.[110] HIV-infected women may be more receptive to modification of infant-feeding practices (given the emotional salience of HIV infection), but additional social, psychological and material barriers may reduce the impact of educational interventions. Food insecurity may contribute as a major impediment to shortening the duration of breast feeding, since in many developing countries, breast feeding continues to provide many children older than 6 months with substantial proportions of their nutrition. Independent of HIV prevention, several studies have demonstrated that it is possible to achieve significant improvements in the uptake and duration of exclusive breast feeding with modest educational interventions.[116-118]

3. Conclusions

Several interventions have been shown to be beneficial in reducing mother-to-child HIV transmission *in utero*, intrapartum and postnatally. Establishing high-quality programs to implement these effective interventions is now the challenge for years to come.

Prevention of mother-to-child HIV infection also cannot be separated from efforts to prevent HIV infection in adults. Prevention of HIV infection in the mothers and fathers of future generations remains the best means of preventing HIV infection in children.

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