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Prevention of Perinatal HIV Transmission

Current Status and Future Developments in Anti-Retroviral Therapy

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Contents

Abstract

Significant progress has been made in the battle against transmission of HIV-1 from mother to infant. Antiretroviral regimens covering the later part of gestation, labour and the first few weeks of neonatal life have shown great efficacy in reducing such transmission. With the advent of combination antiretroviral therapies, transmission rates lower than 2% have been achieved in clinical studies. Elective caesarean delivery has been shown to enhance the benefit of antiretroviral regimens; however, the risks associated with this approach in many resource-poor settings in developing countries limit its role worldwide. Abbreviated antiretroviral regimens covering labour and the first few days of neonatal life have shown considerable promise in the developing world, resulting in 50% reduction in transmission.

Several questions and challenges remain, however. Amongst them, choice of the optimal antiretroviral agent(s), evaluation of purely post-exposure neonatal prophylaxis, availability of antiretroviral agents in developing countries, long-term safety of antiretroviral therapy during pregnancy and early neonatal life, and the problem of breastfeeding transmission in the developing world are some issues that need urgent attention.

One of the greatest public health achievements in the war against AIDS is undoubtedly the significant reduction in mother-to-infant transmission of HIV in the developed world. Transmission rates lower than 2% have been achieved in clinical trial settings,[1-3] as compared with transmission rates of 14 to 42% without any intervention.[4,5] Despite this, there is ongoing mother-to-infant transmission of HIV in the US today,[6] since not all mothers receive prenatal care or know of their HIV sta-

tus when they deliver. Furthermore, the situation in the developing world, which experiences the greatest proportion of the HIV/AIDS burden, is much more sobering. In a single maternity hospital in Nairobi, Kenya, approximately 1000 perinatal HIV infections occur annually, a number several times higher than the annual number of perinatal infections in the entire US.[7] However, both lengthy pharmacological regimens and operative delivery, the cornerstones in the effort to prevent perinatal HIV transmission in the developed world, are far from feasible or affordable in the developing world. Consequently, the advent of newer single dose pharmacological approaches with substantial impact in reducing mother-to-infant transmission of HIV is very promising.

Determining the timing of HIV transmission from mother to infant is of great clinical relevance for implementing cost-effective prophylactic regimens.[8,9] On the basis of virological detection of HIV during the infant's first 2 days of life, it is generally accepted that approximately one third of transmission in non-breast-feeding women occurs during gestation and the remaining two thirds either very late in gestation (in the days before active onset of labour, when uterine contractions may occur irregularly), or during labour.[10-15] Further arguments supporting the notion that most HIV transmission occurs near the time of delivery include the association of transmission with prolonged duration of membrane rupture,[16-18] the protective effect of elective caesarean delivery,[1,3,19,20] and a virological and immunological pattern of acute primary HIV infection in a majority of infants.[21] The risk of perinatal HIV transmission is higher for mothers with immunological and clinical indicators of advanced disease, and with increased viral load.[22,23] Breastfeeding accounts for an additional 7 to 22% of transmission in countries where it is practised among HIV-infected women.[9] We have recently argued, based on synthesising the results of prevention studies, that approximately one half of mother-to-infant HIV transmission occurs in the days before delivery, as the placenta begins to separate from the uterine wall; another third occurs during active labour and delivery, presumably through exposure of the infant to maternal blood and genital tract secretions. Only a very small proportion of mother-to-infant transmission of HIV (<4%) seems to occur in the first trimester and <20% by 36 weeks of gestation.[15]

This commentary presents an overview of the current status and future direction of the perinatal HIV prevention efforts. Antiretroviral-based regimens have shown the highest efficacy in reducing such transmission and are the subject of this review. Elective caesarean delivery and avoidance of breastfeeding are other effective interventions for preventing perinatal HIV transmission, but are not addressed here. Other approaches, such as birth canal cleansing, prevention of chorioamnionitis, nutritional supplementation and immune-based approaches, need further evaluation and are not included. For this paper, a comprehensive literature review was performed; all clinical trials and meta-analyses published up until July 2002 have been referenced.

1. Antiviral Regimens

1.1 Zidovudine

In the AIDS Clinical Trials Group 076 protocol, administration of zidovudine, a nucleoside reverse transcriptase inhibitor, to the pregnant mother starting at 14 to 34 weeks of gestation (median 26 weeks) and continuing through delivery and to the infant for 6 weeks decreased HIV transmission by approximately 66%, from 25.5 to 8.3%.[24] The zidovudine dose used was 100mg orally five times daily during pregnancy, and 2 mg/kg bodyweight intravenously over a 1-hour period, followed by a continuous infusion of 1 mg/kg/hour intravenously during labour until delivery. The infants received oral zidovudine 2mg/kg four times daily for 6 weeks, beginning 8 to 12 hours after birth. All women in this study had CD4+ counts >200/mm^2,[24] were asymptomatic and had not received antiretroviral therapy during the pregnancy before zidovudine was started; none of them breastfed. The mechanism by which zidovudine achieved the reduction

in HIV transmission is not fully understood; however, the efficacy achieved is greater than what would have been expected based on the effect of zidovudine on maternal viral load.[25] Transient anaemia was the most common adverse effect observed in the infants receiving zidovudine. There was no difference in the incidence of major or minor congenital anomalies among infants receiving zidovudine compared with those receiving placebo.

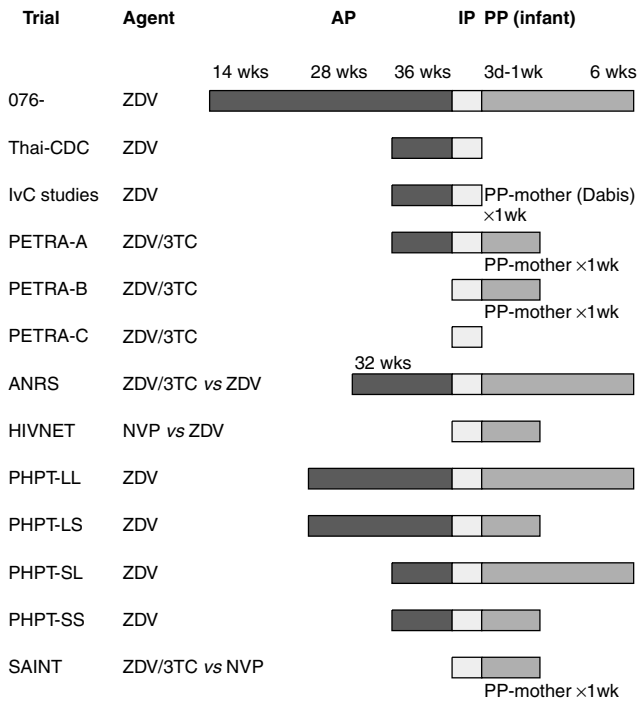
More recently, a study from France reported eight cases of mitochondrial dysfunction in infants not infected with HIV but exposed to zidovudine;[26] two of these infants died of severe neurological disease, three had mild to moderate disease, and three had no disease but transient laboratory abnormalities. Since this report, an extensive review of data accumulated from over 20 000 children exposed to zidovudine in the US is reassuring, as it identified no deaths that could have been due to mitochondrial dysfunction.[27]

Development of genotypic resistance to zidovudine by the time of delivery was unusual in the pregnant women of the 076 study who had CD4+ counts >200/mm^2 and were antiretrovirally naïve; when it appeared, it did not seem to correlate strongly with transmission of virus to the infant.[28] Similar results were recently reported from the Perinatal AIDS Collaborative Transmission (PACTS) study, where a 17.3% rate of genotypic resistance to zidovudine was found in mothers who received zidovudine at the time of delivery and no significant association with perinatal transmission was documented.[29]

The 076 regimen seemed to retain much of its efficacy when administered in clinical practice; in the Women and Infants Transmission Study, perinatal transmission rates dropped from 19 to 8% after its implementation,[30] and in the PACTS study rates declined from 21 to 11%.[31] Similar results have been reported from surveillance studies in the US and in Europe.[32] This protocol is still considered the standard of care in the US and Europe, although, in practice, many HIV-infected pregnant women these days have already been on different combination antiretroviral regimens before their pregnancy, to treat their own infections. They usually continue such regimens during their pregnancies. Furthermore, the high complexity and costs of the 076 protocol have severely limited its adoption and widespread implementation in the developed world.

When a shortened version of the 076 regimen was started at 36 weeks of gestation in non-breastfeeding Thai women (figure 1), transmission decreased by 50%, from 18.9 to 9.4%.[33] This study did not include a neonatal zidovudine component and the zidovudine was administered orally rather than intravenously during labour. The dose of zidovudine used was 300mg orally twice daily starting at 36 weeks of gestation and every 3 hours from the onset of labour until delivery. This regimen has since been recommended for the developing countries that can adopt it. Slightly lower efficacy rates were demonstrated with shortened zidovudine regimens among breastfeeding women in Côte d'Ivoire and in Burkina Faso.[34,35] One of these studies used the Thai zidovudine regimen,[34] while the other added a 7-day 300mg oral twice daily postnatal course of zidovudine in the mother.[35] In the Perinatal HIV Prevention Trial (PHPT) from Thailand,[2] modifications of the 076 protocol with different times of initiation during gestation and different postnatal lengths of prophylaxis in the infant, resulted in transmission rates of 8.6 to 10.5% when zidovudine was initiated at 36 weeks and 4.7 to 6.5% when it was initiated at 28 weeks, depending on the length of the neonatal component.

With regard to the efficacy of neonatal zidovudine use alone, data are conflicting. In an observational study from North Carolina, USA, use of only postpartum zidovudine to the infant did not appear to protect against HIV transmission.[36] However, data from New York, USA,[37,38] and the PACTS cohort[39] indicate a substantial benefit of neonatal postexposure prophylaxis if zidovudine is started within 12 to 24 hours after birth.



Trial	Agent	AP	IP	PP (infant)	Transmission rates (%) Intervention	Placebo	% Reduction	p Value
076-	ZDV				8.3	25.5	68	0.001
Thai-CDC	ZDV				9.4	18.9	50	0.008
IvC studies	ZDV				12.2/16.8	21.7/25.1	44/37[a]	0.05/0.04
PETRA-A	ZDV/3TC				5.7	15.3	63 (at 6wk)	0.001
PETRA-B	ZDV/3TC				8.9	15.3	42 (at 6wk)	0.025
PETRA-C	ZDV/3TC				14.2	15.3	7 (at 6wk)	NS
ANRS	ZDV/3TC *vs* ZDV				1.6	6.8[b]	78	<0.001
HIVNET	NVP *vs* ZDV				11.9	21.3[c]	44 (at 2mo)[c]	0.003
PHPT-LL	ZDV				6.5		RR	
PHPT-LS	ZDV				4.7		28[d]	NS
PHPT-SL	ZDV				8.6		0[d]	NS
PHPT-SS	ZDV				10.5		0[e]	
SAINT	ZDV/3TC *vs* NVP				10.2	13.3[f]	23 (at 8 wk)[f]	NS

Fig. 1. Summary of clinical trials of antiretroviral regimens to reduce mother-to-infant transmission of HIV. The 076, Thai-CDC, PHPT and ANRS studies were of non-breast-feeding populations; the Ivory Coast, PETRA, HIVNET 012 and SAINT studies were of breast-feeding populations. **a** Results refer to two different studies: Wiktor et al. (efficacy at 1 month) and Dabis et al. (efficacy at 3 months). **b** Comparison group rate refers to historical control cohort receiving the zidovudine 076 regimen. **c** In the HIVNET 012 trial, the comparison group received intrapartum oral zidovudine and 1 week of zidovudine was given to the neonate. **d** In the PHPT trial comparisons are to the long-long regimen (reference regimen). **e** The short-short arm of the PHPT study was found in an interim analysis to result in higher transmission rates compared to the long-long regimen and was subsequently dropped from the study. **f** In the SAINT trial, the two arms were equivalent in transmission rates-there was no placebo arm. **076** = the Pediatric AIDS Clinical Trials Group (PACTG) 076 protocol; **3TC** = lamivudine; **ANRS** = Agence Nationale de Recherches sur le SIDA 075 study; **AP** = antepartum; **CDC** = Centers for Diseases Control and Prevention; **HIVNET** = HIV Network, National Institutes of Health; **IP** = intrapartum; **IvC** = Ivory Coast; **LL** = long-long; **LS** = long-short; **NS** = non-significant (p>0.05); **NVP** = nevirapine; **PETRA** = Perinatal Transmission Study - A, B and C refer to the respective arms of the trial; **PHPT** = Perinatal HIV Prevention Trial; **PP** = postpartum; **RR** = reference regimen; **SAINT** = South African Intrapartum Nevirapine Trial; **SL** = short-long; **SS** = short-short; **Thai** = Thailand; **ZDV** = zidovudine.

1.2 Nevirapine

Considering the complexities and costs of zidovudine-based regimens, which make their implementation in the developing world problematic, the advent of nevirapine-based regimens was an important step. Nevirapine, a non-nucleoside reverse transcriptase inhibitor, is an excellent candidate for prevention of perinatal HIV transmission as a single dose therapy,[40] because of its pharmacokinetic profile and long half-life in pregnant women during labour (61.3 to 65.7 hours) and in the neonate (45.4 to 72.1 hours for elimination after a single 200mg maternal dose).

In a Ugandan trial (HIVNET 012) of a predominantly (98.8%) breastfed population, a single oral dose of nevirapine 200mg given to the mother at onset of labour and to the neonate (2 mg/kg single oral dose of nevirapine suspension) prior to discharge from the hospital and within 72 hours of birth (median 24 to 30 hours), reduced HIV trans-

mission or death in the first 4 months by 47% compared with a short regimen of zidovudine given to the mother during labour (600mg orally at the onset of labour, followed by 300mg every 3 hours during labour) and for 1 week to the neonate (oral zidovudine syrup 4 mg/kg twice daily).[41] This difference decreased with longer time of follow-up in the infants because of continued breastfeeding. At 12 months, 16% of infants in the nevirapine group and 24% of infants in the zidovudine group were infected. No serious drug-related adverse events were reported among women and infants receiving nevirapine in this study; rash was observed with a frequency of less than 2% and in none of the participants was it severe.

A second short-course nevirapine regimen (as in HIVNET 012 but with the addition of a 200mg dose to the mother 24 to 48 hours after delivery), has since been compared with the zidovudine/lamivudine regimen used in the Perinatal Transmission (PETRA) trial in the South African Intrapartum Nevirapine Trial (SAINT) [see section 1.3].[42] The two regimens had similar efficacy regarding HIV transmission to the infant and good tolerability; however, the additional nevirapine dose did not seem to confer benefit compared with the original HIVNET 012 regimen.

Cost-benefit modelling showed the HIVNET 012 nevirapine regimen to be more cost-effective than zidovudine-based regimens (Thai, PETRA and SAINT protocols) in reducing mother-to-infant HIV transmission in sub-Saharan Africa.[40] A concern that has emerged is that 19% of the HIVNET 012 mothers (21 of 111) had evidence of nevirapine resistance mutations 6 to 8 weeks after receiving the single dose of nevirapine; the mutation was no longer found within 12 to 24 months in all 11 women studied.[43] Furthermore, the rate of nevirapine resistance was similar among women whose infants did or did not become HIV infected. Interestingly, nevirapine resistance (although a different mutation) was found more frequently among infants than women (11 of 24 infected infants at 6 to 8 weeks of age), but none of 7 infants at 12 months of age.[43] These findings indicate that in the absence of selective pressure posed by the drug, nevirapine-sensitive virus would be expected to become predominant again, hence preserving the effectiveness of nevirapine-based prophylactic regimens for future pregnancies. Nevertheless, they also raise concerns regarding potential loss of nevirapine effectiveness for interruption of HIV transmission through breastfeeding, as well as about future optimal maternal treatment regimens. Universal administration of nevirapine to all women presenting in labour has been suggested as an approach for countries where HIV prevalence is very high, and routine HIV counselling and testing not widely available. However, the potential long-term risk of exposing large numbers of infants to nevirapine at birth has not yet been studied.

1.3 Antiretroviral Combinations

In the multicentre PETRA study in Africa, a combination of zidovudine with lamivudine starting at 36 weeks of gestation, through delivery and to the neonate for 1 week, resulted in a 63% reduction in transmission compared with placebo (from 35 to 79%, $p = 0.001$); a similar regimen starting during delivery decreased transmission by 42% (to 8.9%, $p = 0.025$), whereas the intrapartum-only regimen had no efficacy.[44] Dosages used in this study were oral zidovudine 300 to 600mg at the onset of labour, then 300mg every 3 hours until delivery and 300mg twice daily for 1 week to the mother, and 4 mg/kg every 12 hours for 1 week to the neonate. The dosage of oral lamivudine used was 150mg twice daily during labour and for 1 week after delivery for the mother, and 2 mg/kg every 12 hours for 1 week for the neonates. The benefit of this intervention was diminished considerably after 18 months of follow-up in the breastfed infants.[44]

In the ANRS (Agence Nationale sur le SIDA) 075 study, the results of which were published recently,[45] the addition of lamivudine to the 076 zidovudine regimen started at 32 weeks of gestation (150mg twice per day orally to the mother until delivery and then to the neonate 2 mg/kg

twice per day for 6 weeks), resulted in a transmission rate of 1.6% (or approximately 5-fold lower than an historical control cohort receiving the 076 regimen). This population was a non-breastfeeding population in Europe, and the mother-to-infant transmission rate of HIV is one of the lowest so far achieved by any large prospective antiretroviral study. Cases of moderate to severe anaemia (9%), neutropenia (6%), liver abnormalities (6 of 452 children) and mitochondrial dysfunction (2 of 452 children) were seen in the exposed children; however, the frequency was similar to that observed in the comparison zidovudine cohort. Almost all of the haematological and liver function test abnormalities resolved after discontinuation of the drugs.

An additional concern with the use of lamivudine is the frequency of development of resistance among treated women and the potential untoward effects for future treatment of the mother or the child, or for future perinatal prophylaxis regimens. Resistance to lamivudine developed in approximately one third of women;[45,46] two children were infected with lamivudine-resistant virus.

Currently, many HIV-infected pregnant women in the developed world are on combination antiretroviral regimens to treat their own infection, as a result of evolving clinical practice guidelines. Observational and clinical trial data thus far indicate that the transmission rate while on combination regimens is very small;[45,47-50] this is most probably related to the highly significant effect of these regimens in reducing viral load. Furthermore, there appears to be no additional advantage of single-dose nevirapine when given to mothers already receiving standard antiretroviral therapy.[49] However, it should be kept in mind that most of the antiretroviral agents have been introduced relatively recently and long-term follow up is not available. Thus, great care should be taken when using these agents during pregnancy, particularly in the first trimester.

A high prematurity rate was reported from a Swiss cohort of 20 women receiving combination therapy with or without protease inhibitors;[51] these data however were not confirmed in a larger study.[52] A recent study has indicated that exposure to the combination of antiretroviral agents and folic acid antagonists (which include trimethoprim, pyrimethamine or dapsone) during the first trimester of pregnancy may increase the risk for congenital anomalies in the fetus.[53] Folic acid supplements may thus be particularly important for these women.

Finally, promising results have been shown with tenofovir (PMPA) in preventing infection or ameliorating the clinical course of simian immunodeficiency virus disease in newborn macaques,[54] which may be applied in human studies of postexposure prophylaxis and in human newborns.

2. Conclusions and Future Directions

The accumulated evidence so far suggests that the most comprehensive antiretroviral regimens for preventing perinatal transmission of HIV are those initiated early in the third trimester of pregnancy and continued throughout the first week(s) of neonatal life.[15] However, in many disadvantaged communities whether in the US or in the developing world, HIV-infected women will continue to present in labour without any prior antiretroviral therapy.[55] Studies are urgently needed to evaluate the use of immediate postpartum antiretroviral prophylaxis in the neonate when neither the antenatal nor intrapartum regimen was received by the mother.[56] When initiated within hours after birth, postexposure prophylaxis, similar to the hepatitis B model of perinatal prevention, may still be effective in preventing HIV infection, even in situations where prior opportunities for intervention have been missed.

Routine offering of HIV counselling and testing to pregnant women should be one of the priorities of any program aimed to reduce perinatal HIV transmission.[5] Evaluation and implementation of rapid testing during labour for women who do not know their HIV status will be an important step in this direction. Very short antiretroviral regimens given universally to mothers during labour or in the

newborn in areas of high HIV prevalence may be an alternative approach, provided the long-term safety of the medications is assured. Development of safer infant feeding alternatives to breastmilk or of prophylactic regimens during breastfeeding are necessary, since blocking transmission during breastfeeding remains one of the greatest challenges in the battle against perinatal HIV transmission worldwide. A preliminary report describing breastmilk accumulation of the antimalarial agent chloroquine, which has anti-HIV activity, was recently published and may be a promising alternative approach.[57] Finally, reduction of HIV transmission is only one of multiple factors contributing to high rates of morbidity and mortality in children in developing countries; further research should focus on factors contributing to persistently high rates of child mortality despite recent advances in reducing HIV infection in the infants.

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