Advances in the Prevention of Perinatal HIV-1 Transmission
Avinash K. Shetty and Yvonne Maldonado

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Objectives After completing this article, readers should be able to:

1. Describe the impact of antiretroviral prophylactic regimens on mother-to-child transmission of HIV-1.
3. Describe efforts being taken to prevent the transmission of HIV-1 in human milk.

Introduction
Significant advances have occurred in the prevention of perinatal transmission of human immunodeficiency virus type 1 (HIV-1) during the last decade in the United States and Europe. (1) In 1994, the Pediatric AIDS Clinical Trials Group (PACTG) 076 published data showing that a long course of zidovudine (ZDV) prophylaxis given to HIV-1 infected mothers during the antepartum and intrapartum periods and postnatally to the baby significantly reduced perinatal HIV-1 transmission. (2) Since then, rates of perinatal HIV-1 transmission have decreased to less than 2% in resource-rich countries due to widespread implementation of universal prenatal HIV-1 testing, antiretroviral prophylaxis, elective cesarean section, and avoidance of breastfeeding. (1)(3) Currently, fewer than 400 infants acquire HIV-1 from their mothers in the United States. (1)(3)

In contrast, prevention of perinatal transmission of HIV-1 is a major public health challenge in many resource-limited countries. (4) Each day, more than 2,000 infants are born infected with HIV-1 globally, and by the end of 2002, approximately 3.2 million children were living with HIV-1. (5) More than 90% of affected children reside in resource-limited countries. (1) Although many effective, simple, and less expensive antiretroviral prophylaxis regimens are available to prevent mother-to-child HIV-1 transmission, these interventions have not been implemented on a large scale in resource-limited settings. (1) This article reviews advances in the prevention of perinatal HIV-1 transmission, highlights progress made in resource-rich countries, and discusses challenges faced by resource-limited countries.

Perinatal HIV-1 Transmission: Timing, Rates, and Risk Factors
Mother-to-child transmission (MTCT) of HIV-1 can take place in utero, during labor and delivery, or postnatally via breastfeeding. (6)(7) Knowledge about the precise timing of transmission is critical for the design of potential prevention strategies. In the nonbreastfed infant, about one third of transmissions occur during gestation; the remaining two thirds occur during delivery. (6) In the breastfed infant, however, as much as one third to one half of overall transmission may occur after delivery during lactation. (7) Transmission rates of MTCT vary from about 10% to 30% among nonbreastfeeding HIV-1-infected women in more developed countries to 25% to 45% among breastfeeding populations in Africa. (4)

The level of maternal serum HIV-1 RNA is a critical determinant of both intrapartum and intrapartum MTCT of HIV-1, although transmission can occur rarely even at low or undetectable viral loads. (8)(9)(10) Other important factors known to increase the risk of transmission include advanced maternal disease, low CD4 count, primary HIV-1 infection, rupture of membranes more than 4 hours prior to delivery, vaginal delivery, invasive obstetric procedures, and prematurity. (6)
Antiretroviral Prophylactic Regimens

Long-course ZDV Prophylaxis

In 1994, the PACTG 076 trial showed that, in non-breastfed infants, a three-part complex regimen of ZDV given orally to pregnant HIV-1-infected women starting between 14 and 34 weeks’ gestation, intravenously during labor, and orally to the infant for the first 6 weeks after birth dramatically reduced the risk of transmission by 68% (Table 1). (2) All women had CD4 counts higher than 200, were symptom-free, and had not received ZDV previously.

The mechanism of ZDV action is not understood fully. In the PACTG 076 study, ZDV only modestly reduced maternal HIV-1 RNA, and change in maternal viral load accounted for only 17% of the reported efficacy of the drug. (14) In addition, ZDV reduced transmission at all levels of maternal HIV-1 RNA. These findings indicate that the ZDV effect was partly through the reduction of maternal viral load.

The continued efficacy of ZDV in reducing transmission even in women who have low viral loads suggests that pre- and postexposure prophylaxis of the infant during labor and delivery may have been a substantial component of protection. (1) In a meta-analysis of seven European and United States prospective studies that investigated risk factors for perinatal HIV-1 transmission in 1,202 HIV-infected women who had RNA virus loads of less than 1,000 copies/mL at delivery, transmission was significantly lower in treated than untreated mothers (1% versus 9.8%); multivariate analysis showed that transmission even in women with very low or undetectable viral load levels.

A number of studies suggest that infant postexposure prophylaxis may contribute to ZDV efficacy. (15)(16)(17) Quantitative HIV-1 by cervicovaginal lavage (CVL) is an independent risk factor for perinatal HIV-1 transmission. In a randomized, placebo-controlled trial of brief antepartum ZDV treatment, HIV-1 levels in CVL and plasma samples were evaluated in relation to perinatal transmission. (15) At 38 weeks, after a 2-week treatment period, CVL HIV-1 was quantifiable in 23% and 52% of samples in the ZDV and placebo groups, respectively (P<0.001). The perinatal transmission rate was 28.7% among women who had quantifiable CVL HIV-1 and high plasma virus levels (>10,000 copies/mL) and 1% among women who did not have quantifiable CVL HIV-1 and had low plasma virus levels (P<0.001). A case-control substudy to determine the association between genital tract shedding of HIV-1 and perinatal transmission also showed a significantly higher risk of transmission (OR, 2.28; 95% confidence interval [CI], 1.09 to 4.78; P=0.03) in women receiving antiretroviral therapy (67% ZDV alone) for each one-log increase in mean titer of CVL HIV-1 DNA. (16) An observational study from New York suggested that administration of oral ZDV for 6 weeks, when started within 24 hours after birth, was beneficial in infants whose mothers had not received ZDV before or during delivery. (17)

In the United States, most pregnant women receive combination antiretroviral therapy during pregnancy, and transmission rates of 2% or less have been reported with the advent of highly active antiretroviral therapy, widespread implementation of the PACTG 076 regimen, elective cesarean section, and use of formula milk. (1)(3) Thus, elimination of perinatal HIV-1 transmission in the United States could become a reality in the future.

Short-course ZDV Prophylaxis

Although the three-part PACTG 076 regimen is most effective, it is not feasible to implement this regimen in resource-limited countries because of the complexity and prohibitive cost. In addition, most transmission occurs late in pregnancy or at the time of delivery. (18) Therefore, there was an urgent need to develop shorter, less expensive regimens more applicable to resource-limited countries. Initial studies focused on modifications of prophylactic regimens using ZDV alone.

The efficacy of short-course prophylaxis regimens of ZDV in reducing perinatal HIV-1 transmission was studied among nonbreastfeeding populations in Thailand (Table 1). (11)(12) In 1998, a placebo-controlled, randomized trial in Thailand demonstrated that a short course of oral ZDV starting at 36 weeks’ gestation, oral ZDV intrapartum, and no neonatal therapy reduced MTCT by 50% at age 6 months in nonbreastfed infants. (11)

A recent trial of a shortened ZDV regimen in Thailand showed that longer (28 wk) antepartum prophylaxis was more effective than shorter (36 wk) antepartum prophylaxis, suggesting that a significant proportion of in utero infection occurs between 28 and 36 weeks of gestation (Table 1). (12) Also, when women received the longer three-part ZDV prophylaxis during pregnancy, prolonged treatment of the infant did not provide additional benefit. However, when the antenatal regimen was shortened, longer treatment of the infant was found to be beneficial.
Table 1. Antiretroviral Intervention Trials for Reducing Perinatal HIV-1 Transmission In Nonbreastfeeding Populations

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sample Size</th>
<th>Timing and Dosing Regimen of ART Prophylaxis</th>
<th>Transmission Rate/Relative Efficacy</th>
</tr>
</thead>
</table>
| ZDV/Placebo PACTG 076 United States, France (2) | N=477 | AP+IP+PP  
AP=oral ZDV 100 mg 5 times/d starting at 14 weeks' gestation  
IP=2 mg/kg, then 1 mg/kg per hour IV  
PP (mother)=none  
PP (infant)=oral ZDV 2 mg/kg q 6 h for 6 wk | At 18 months:  
8.3% ZDV versus 25.5% Placebo  
68% efficacy |
| ZDV/Placebo Bangkok Trial Thailand (11) | N=392 | AP+IP  
AP=oral ZDV 300 mg q 12 h starting at 36 weeks' gestation  
IP=oral ZDV 300 mg q 3 h  
PP=none | At 6 months:  
9.4% ZDV versus 18.9% Placebo  
50% efficacy |
| ZDV/Comparative PHPT, Thailand (12) | N=1,437 | AP+IP+PP  
ZDV (long-long) [LL]:  
AP=oral ZDV 300 mg q 12 h starting at 28 weeks' gestation  
IP=oral ZDV 300 mg q 3 h  
PP (mother)=none  
PP (infant)=oral ZDV 2 mg/kg q 6 h for 6 wk  
ZDV (long-short) [LS]:  
AP=oral ZDV 300 mg q 12 h starting at 28 weeks' gestation  
IP=oral ZDV 300 mg q 3 h  
PP (mother)=none  
PP (infant)=oral ZDV 2 mg/kg q 6 h for 3 d  
ZDV (short-long) [SL]:  
AP=oral ZDV 300 mg q 12 h starting at 36 weeks' gestation  
IP=oral ZDV 300 mg q 3 h  
PP (mother)=none  
PP (infant)=oral ZDV 2 mg/kg q 6 h for 6 wk  
ZDV (short-short) [SS]:  
AP=oral ZDV 300 mg q 12 h starting at 36 weeks' gestation  
IP=oral ZDV 300 mg q 3 h  
PP (mother)=none  
PP (infant)=oral ZDV 2 mg/kg q 6 h for 6 wk | At 6 months final analysis:  
6.5% (LL) versus 4.7% (LS) versus 8.6% (SL)  
In utero transmission:  
1.6% (LL+LS) versus 5.1% (SL+SS)  
At 6 months interim analysis:  
4.1% (LL) versus 10.5% (SS) (SS arm stopped) |
| NVP/Placebo PACTG 316 United States, Europe, Brazil, and Bahamas (13) | N=1,248 | AP+IP+PP  
NVP arm:  
AP=Standard ART starting from 14 weeks' gestation (77% combination, 23% ZDV alone)  
IP=ZDV 2 mg/kg, then 1 mg/kg per hour IV plus NVP  
200 mg × 1  
PP (mother)=ART if needed  
PP (infant)=ZDV 2 mg/kg for 6 wk plus NVP 2 mg/kg × 1 at birth  
Placebo arm:  
AP=Standard ART starting from 14 weeks' gestation (77% combination, 23% ZDV alone)  
IP=ZDV 2 mg/kg, then 1 mg/kg per hour IV plus NVP placebo  
PP (mother)=ART if needed  
PP (infant)=ZDV 2 mg/kg q 6 h for 6 wk plus NVP placebo at birth | At 6 months:  
1.4% NVP versus 1.6% NVP Placebo |

ART=antiretroviral therapy, ZDV=zidovudine, AP=antepartum, IP=intrapartum, PP=postpartum, NVP=nevirapine, PACTG=Pediatric AIDS Clinical Trials Group, IV=intravenous.
The identical short-course ZDV antepartum/intrapartum regimen used in Thailand, (11) when evaluated in a placebo-controlled trial in Abidjan, Cote d'Ivoire involving breastfeeding populations, showed a 37% reduction in transmission compared with placebo at 3 months of age (Table 2). (19) Another placebo-controlled trial in West Africa (DITRAME trial) studied a similar antepartum/intrapartum short-course ZDV prophylaxis regimen with the addition of a 1-week course of ZDV to mothers during the postpartum period and reported an efficacy of 38% at 6 months of age in predominantly breastfed infants (Table 2). (20) Thus, an additional week of postpartum maternal ZDV therapy did not confer any additional benefit over the antepartum/intrapartum ZDV alone prophylaxis regimen.

Long-term pooled analysis showed an efficacy of 26% by 24 months of age compared with 37% to 38% efficacy noted in infants at 3 and 6 months of age, despite long-term breastfeeding. (25) Thus, the overall efficacy of short-course ZDV is less in breastfeeding populations in sub-Saharan Africa than in formula-fed populations, (19)(20) and the early efficacy seems to diminish with prolonged periods of breastfeeding. (25)

**ZDV/Lamivudine (3TC) Prophylaxis**

Once the efficacy of short-course ZDV was established, studies explored whether short-course combination regimens might improve efficacy. Investigators from the United States, France, and Thailand evaluated whether combining a second antiretroviral agent such as 3TC would enhance the efficacy of short-course ZDV further in reducing transmission in nonbreastfeeding populations. (26)(27) The French open-label, nonrandomized study assessed the safety of perinatal 3TC-ZDV combination prophylaxis in infants and its effects on perinatal transmission of HIV-1 in a nonbreastfeeding population. (26) A total of 445 HIV-1-infected pregnant women were enrolled and received lamivudine at 32 weeks' gestation through delivery in addition to the standard PACTG 076 Study ZDV prophylaxis regimen. Infants received 3TC for 6 weeks in addition to the standard 6-week course of ZDV. The transmission rate in the study group was 1.6% compared with 6.8% in a historical control group of HIV-infected mother-infant pairs in France who had received only ZDV prophylaxis. This represents a five-fold reduction from controls when adjusted for mode of delivery, history of antiretroviral therapy, and CD4 cell count. The Thailand open-label, nonrandomized trial studied the efficacy of 3TC added to short-course ZDV prophylaxis. A total of 106 HIV-1-infected pregnant women were enrolled, and 3TC and ZDV were begun at 34 weeks' gestation and given orally during labor. Control infants received a 4-week course of ZDV alone. The transmission rate in the study group was 2.8% compared with 11.7% in a historical control group of HIV-infected women in Thailand who had received only short-course ZDV. (27)

A multicenter, placebo-controlled trial conducted among breastfeeding populations in Africa (PETRA trial) showed an efficacy of 63% at 6 weeks for ZDV/3TC given from 36 weeks' gestation, intrapartum, and for 1 week postpartum to mothers and infants; 42% efficacy for intrapartum-postpartum ZDV/3TC; and no efficacy for intrapartum treatment only (Table 2). (21)

**Single-dose Nevirapine (NVP) Prophylaxis**

NVP is a very potent nonnucleoside analog that has a long half-life and excellent penetration across the placenta. (28) In Uganda (HIVNET 012 trial), a single dose of NVP given to the mother at onset of labor and a single 2-mg/kg oral dose given to the infant at 48 to 72 hours after birth was safe and reduced MTCT by 47% at 14 to 16 weeks of age and by 41% at 18 months in breastfeeding infants (Table 2). (22)(23) This ultra-short NVP prophylaxis is simple to administer, less expensive (costing around $US4.00 per mother-infant pair), and is being used increasingly for prevention of MTCT in resource-limited settings. (23)

Another trial conducted in South Africa (SAINT trial) comparing the efficacy of NVP (intrapartum and a single dose postpartum to mothers and to infants) versus ZDV/3TC (intrapartum and for 1 week postpartum to mothers and infants) showed that the risk of infant HIV-1 infection at 8 weeks of age was similar in the two groups (Table 2). (24) Data from the SAINT study, which enrolled more than 1,300 mother-infant pairs, showed that single-dose NVP and short-course ZDV/3TC prophylaxis regimens are safe and well tolerated. (24) Thus, although the three-part antepartum, intrapartum, postpartum prophylaxis is most effective, both antepartum/intrapartum and intrapartum/postpartum antiretroviral prophylaxis regimens can reduce perinatal HIV-1 transmission significantly. (11)(12)(21)(22) ZDV/3TC prophylaxis was more effective than ZDV alone in short-course regimens, (25) but the intrapartum/postpartum ZDV/3TC regimen had similar efficacy to single-dose NVP. (24) Data from these trials indicate the utility of both maternal viral load reduction at labor and delivery and of postexposure neonatal prophylaxis. (1)
Table 2. Antiretroviral Intervention Trials for Reducing Perinatal HIV-1 Transmission in Breastfeeding Populations

<table>
<thead>
<tr>
<th>Trial</th>
<th>Country</th>
<th>Timing of Prophylaxis</th>
<th>Transmission Rate/ Relative Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZDV/Placebo (19) N=280</td>
<td>Ivory Coast</td>
<td>AP+IP</td>
<td>At 3 months:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IP=oral ZDV 300 mg q 12 h starting at 36 weeks' gestation</td>
<td>16.5% ZDV versus 26.1% Placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PP (mother)=none</td>
<td>37% efficacy at 3 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PP (infant)=none</td>
<td></td>
</tr>
<tr>
<td>ZDV/Placebo (20) DITRAME N=400</td>
<td>Ivory Coast</td>
<td>AP+IP+PP</td>
<td>At 6 months:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IP=oral ZDV 600 mg × 1</td>
<td>18% ZDV versus 27.5% Placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PP (mother)=oral ZDV 300 mg q 12 h for 1 wk</td>
<td>38% efficacy at 6 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PP (infant)=oral ZDV 4 mg/kg q 12 h for 1 wk</td>
<td></td>
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<tr>
<td>ZDV-3TC/Placebo (PETRA) (21) N=1,797</td>
<td>South Africa/ Uganda/ Tanzania</td>
<td>AP+IP+PP</td>
<td>At 6 weeks:</td>
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<tr>
<td></td>
<td></td>
<td>IP+PP</td>
<td>Arm 1, 5.7%</td>
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<tr>
<td></td>
<td></td>
<td>IP only</td>
<td>Arm 2, 8.9%</td>
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<tr>
<td></td>
<td></td>
<td>ZDV/3TC (Arm 1)</td>
<td>Arm 3, 14.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AP=oral ZDV 300 mg q 12 h plus 3TC 150 mg q 12 h starting at 36 weeks' gestation</td>
<td>Placebo, 15.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IP=oral ZDV 300 mg q 12 h plus 3TC 150 mg q 12 h</td>
<td>At 6 weeks, efficacy:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PP (mother)=oral ZDV 300 mg q 12 h plus 3TC 150 mg q 12 h for 1 wk</td>
<td>Arm 1, 63%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PP (infant)=oral ZDV 4 mg/kg q 12 h for 1 wk</td>
<td>Arm 2, 42%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ZDV/3TC (Arm 2)</td>
<td>Arm 3, not significant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AP=none</td>
<td>At 18 months:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IP=oral ZDV 300 mg q 12 h plus 3TC 150 mg q 12 h</td>
<td>Arm 1, 14.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PP (mother)=oral ZDV 300 mg q 12 h plus 3TC 150 mg q 12 h for 1 wk</td>
<td>Arm 2, 18.1%</td>
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<tr>
<td></td>
<td></td>
<td>PP (infant)=oral ZDV 4 mg/kg q 12 h plus 3TC 2 mg/kg q 12 h for 1 wk</td>
<td>Arm 3, 20.0%</td>
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<tr>
<td></td>
<td></td>
<td>ZDV/3TC (Arm 3)</td>
<td>Placebo, 22.2%</td>
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<td></td>
<td></td>
<td>AP=none</td>
<td>At 18 months, efficacy:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IP=oral ZDV 300 mg q 12 h plus 3TC 150 mg q 12 h</td>
<td>Arm 1, 33%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PP (mother)=none</td>
<td>Arm 2, not significant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PP (infant)=none</td>
<td>Arm 3, not significant</td>
</tr>
<tr>
<td>NVP/ZDV (HIVNET 012) (22)(23) N=626</td>
<td>Uganda</td>
<td>IP+PP</td>
<td>At 14 to 16 weeks:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NVP arm:</td>
<td>13.1% NVP versus 25.1% ZDV</td>
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<tr>
<td></td>
<td></td>
<td>AP=none</td>
<td>47% efficacy at 14 to 16 wk</td>
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<tr>
<td></td>
<td></td>
<td>IP=NVP 200 mg × 1</td>
<td>At 18 months:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PP (mother)=none</td>
<td>15.7% NVP versus 25.8% ZDV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PP (infant)=NVP 2 mg/kg × 1 at birth</td>
<td>41% efficacy at 14 to 16 wk</td>
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<td></td>
<td></td>
<td>ZDV arm:</td>
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<tr>
<td></td>
<td></td>
<td>AP=none</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IP=ZDV 600 mg, then 300 mg q 3 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PP (mother)=none</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>PP (infant)=ZDV 4 mg/kg q 12 h for 1 wk</td>
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</tbody>
</table>

(continued)
Combination of Single-dose NVP Plus Short-course ZDV Prophylaxis

Two recent trials conducted in Thailand and West Africa have shown that the addition of a maternal intrapartum/neonatal NVP dose to short-course maternal ZDV (with oral ZDV during labor and either no infant prophylaxis or 1 week of infant ZDV prophylaxis) may provide increased efficacy for reducing perinatal HIV-1 transmission compared with short-course maternal ZDV prophylaxis alone. (29)(30)

In contrast, an international, blinded, placebo-controlled phase III trial conducted in nonbreastfeeding populations in the United States, Europe, Brazil, and the Bahamas found no additional benefit from a two-dose intrapartum/newborn NVP dose when women received prenatal care and standard antenatal antiretroviral therapy, and elective cesarean section was made available (Table 1). (13) All neonates in this study received the standard 6-week ZDV course, and the overall risk of perinatal HIV transmission was very low (1.5%). In this study, NVP resistance developed in 15% of the women who received single-dose intrapartum NVP. (13)(31)

Therefore, the addition of an intrapartum/newborn NVP dose is not recommended in HIV-infected women who have received highly active antiretroviral therapy (HAART) during pregnancy. (10)

Antiretroviral Prophylaxis During the Neonatal Period

The efficacy of postnatal antiretroviral prophylaxis for neonates in the absence of maternal treatment is being investigated. An observational study from the state of New York suggested that administration of oral ZDV for 6 weeks, when started within 24 hours after birth, was beneficial in infants whose mothers had not received ZDV before or during delivery. (17) A recent trial conducted in breastfeeding infants in Malawi comparing the efficacy of single-dose infant NVP versus single-dose infant NVP plus 1 week infant ZDV showed that the combined regimen had a superior efficacy (14.4% versus 21.9% transmission) at 6 weeks of age. (32) A future clinical trial is planned in nonbreastfed populations in the United States and Brazil to assess the efficacy of the standard 6-week infant ZDV regimen compared with two combination regimens (NVP dose at birth, 3 and 7 d of age, and 2-wk course of 3TC/nelfinavir). (1)

Table 2. Antiretroviral Intervention Trials for Reducing Perinatal HIV-1 Transmission in Breastfeeding Populations (cont)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Country</th>
<th>Timing of Prophylaxis</th>
<th>Transmission Rate/ Relative Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>NVP/ZDV-3TC (24) N=1,331</td>
<td>South Africa</td>
<td>IP+PP NVP arm: AP=none IP=NVP 200 mg × 1 PP (mother)=NVP 200 mg × 1 PP (infant)=NVP 2 mg/kg × 1 at birth ZDV/3TC arm: AP=none IP=ZDV 300 mg q 3 h plus 3TC 150 mg q 12 h PP (mother)=ZDV 300 mg q 12 h plus 3TC 150 mg q 12 h for 1 wk PP (infant)=ZDV 4 mg/kg q 12 h plus 3TC 2 mg/kg q 12 h for 1 wk</td>
<td>At 8 weeks: 12.3% NVP versus 9.3% ZDV/3TC Not statistically significant (P=.11)</td>
</tr>
</tbody>
</table>

ZDV=zidovudine; AP=antepartum, IP=intrapartum, PP=postpartum, 3TC=lamivudine, NVP=nevirapine.
710 receiving zidovudine monotherapy, 3.8% (95% CI, 1.1% to 6.5%) for 186 receiving combination antiretroviral therapy without protease inhibitors, and 1.2% (95% CI, 0 to 2.5%) for 250 receiving combination antiretroviral therapy with protease inhibitors. (10) Transmission also varied by maternal HIV-1 RNA level at delivery: 1.0% for less than 400 copies/mL; 5.3% for 400 to 3,499 copies/mL; 9.3% for 3,500 to 9,999 copies/mL; 14.7% for 10,000 to 29,999 copies/mL; and 23.4% for more than 30,000 copies/mL. The odds of transmission increased 2.4-fold (95% CI, 1.7 to 3.5) for every log10 increase in delivery viral load. In multivariate analyses adjusting for maternal viral load, duration of therapy, and other factors, the OR for transmission for women receiving combination therapy with or without protease inhibitors compared with those receiving ZDV monotherapy was 0.30 (95% CI, 0.09 to 1.02) and 0.27 (95% CI, 0.08 to 0.94), respectively. (10) Thus, levels of HIV-1 RNA at delivery and prenatal antiretroviral therapy were independently associated with transmission. The protective effect of therapy increased with the complexity and duration of the regimen, and maternal HAART was associated with the lowest rates of transmission. (10)

**Role of Elective Cesarean Section Delivery**

Recent data from a large international individual patient data meta-analysis and a randomized controlled trial conducted in Europe have shown that cesarean section performed before labor and rupture of membranes reduces perinatal transmission of HIV-1 by 50% to 87% independent of the use of antiretroviral therapy or ZDV prophylaxis. (35)(34) Both of these studies were performed before the advent of combination antiretroviral therapy during pregnancy, and there was no information on maternal viral load. Because maternal viral load is an important determinant of perinatal HIV-1 transmission, (9) it is not clear if elective cesarean section offers any additional benefit in women who have very low or undetectable viral loads or those who are receiving combination antiretroviral therapy. (1) HIV-1 infected women from resource-rich countries who present late in pregnancy on no antiretroviral therapy or with high viral loads may be potential candidates for elective cesarean section to reduce perinatal HIV-1 transmission. Studies in the United States have shown that HIV-infected women who have advanced disease may have a higher risk of complications, such as postpartum fever associated with cesarean section. (35)(36) The role of elective cesarean section to reduce perinatal transmission of HIV-1 may not be applicable in resource-limited countries because of increased risks of postpartum morbidity and operative mortality. (37)

**Nonantiretroviral Interventions**

Simpler, less expensive, and effective nonantiretroviral interventions to reduce perinatal HIV-1 transmission could be implemented in the absence of prenatal HIV-1 testing programs. Hence, several studies were conducted in recent years, including examination of the role of micobicidal vaginal and infant cleansing, nutritional supplementation, and prophylaxis of subclinical chorioamnionitis to reduce transmission. (38)(39)(40) Unfortunately, results have been discouraging from all these trials.

Several trials conducted in sub-Saharan Africa have shown that intrapartum washing of cervicovaginal mucosa with chlorhexidine and the use of 1% benzalkonium chloride vaginal suppositories does not reduce perinatal HIV-1 transmission. (38)(39)(40) However, in one chlorhexidine trial from Malawi, a protective effect was noted in a subset of women whose membranes ruptured for more than 4 hours. (41) Furthermore, a marked reduction in infant morbidity and mortality was noted.

Severe maternal vitamin A deficiency has been identified as a contributory factor to perinatal transmission in Africa. (6) Three randomized, controlled trials of vitamin A or other multivitamin administration conducted in South Africa, Malawi, and Tanzania have failed to show any benefit in reducing perinatal HIV-1 transmission. (42)(43)(44)

However, a beneficial effect with respect to adverse pregnancy outcomes (eg, prematurity, low birthweight) and improvement in neonatal anemia was noted in the South African and Malawi trials. (42)(43) The Tanzania trial demonstrated an increase in maternal CD4 count and reduced the rate of infant mortality with continued postpartum multivitamin (B, C, and E and not vitamin A) administration. (44)(45)

Chorioamnionitis has been associated with perinatal transmission in the United States and Africa. (6) A controlled clinical trial in Malawi showed that empiric treatment for chorioamnionitis with a short course of antibiotics (ie, metronidazole and erythromycin) at 20 to 24 weeks’ gestation and again during labor did not reduce MTCT of HIV-1. (1)

**United States Public Health Service Task Force Guidelines for Preventing Perinatal Transmission of HIV-1**

Current guidelines for prevention of perinatal HIV-1 transmission are summarized in Table 3. Combination
antiretroviral therapy during pregnancy is recommended if the maternal viral load is 1,000 copies/mL or greater. In addition, elective cesarean delivery is recommended if the maternal viral load is 1,000 copies/mL or greater near delivery. Because of the proven benefit of antiretroviral prophylaxis in preventing perinatal HIV-1 transmission in women, including those who have viral loads of less than 1,000 copies/mL, (8) all HIV-infected women should receive prophylaxis using the PACTG ZDV regimen alone or combination antiretroviral therapy. ZDV alone prophylaxis administered to HIV-infected women who have viral loads of less than 1,000 copies/mL has been shown to reduce perinatal HIV transmission to 1%. (11) In addition, no long-term effects on women’s health have been noted among United States women enrolled in PACTG 076 trial in terms of disease progression, mortality, viral load, or ZDV resistance between randomized treatment and placebo arms. (46)

When the woman has not received any therapy during pregnancy, several efficacious intrapartum/postpartum regimens are available:

- Intravenous ZDV during labor followed by oral ZDV for 6 weeks to the infant
- Oral ZDV/3TC given during labor followed by oral ZDV/3TC for 1 week to the infant
- Single-dose NVP to the mother at onset of labor followed by a single dose of NVP to the baby at 48 hours of age
- Combination of intrapartum/postpartum ZDV plus single-dose maternal/newborn NVP regimen

HIV-infected Women Who Have Had No ART Before Labor

- Oral ZDV should be prescribed to the neonate as soon as possible after delivery (preferably within 6 to 12 hours of birth) and then continued for 6 weeks
- Some experts advocate use of postnatal ZDV regimen in conjunction with other antiretroviral agents.

HIV-infected Women Who Have Had No ART Before or During Labor

- Oral ZDV should be prescribed to the neonate for 6 weeks. In such instances, other antiretroviral agents could be added to the postnatal ZDV regimen. (1)

Table 3. United States Public Health Service Task Force Guidelines for Preventing Perinatal HIV-1 Transmission

<table>
<thead>
<tr>
<th>Maternal Viral Load</th>
<th>Recommended Regimens</th>
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<tr>
<td>&gt;1,000 copies/mL</td>
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<tr>
<td>Combination ART (ideally including ZDV after the first trimester), intravenous ZDV infusion during labor, followed by oral ZDV for 6 weeks to the infant</td>
<td></td>
</tr>
<tr>
<td>Elective cesarean section if maternal viral load &gt;1,000 copies near delivery</td>
<td></td>
</tr>
<tr>
<td>&lt;1,000 copies/mL</td>
<td></td>
</tr>
<tr>
<td>ZDV after the first trimester or combination ART (ideally including ZDV after the first trimester), intravenous ZDV infusion during labor, followed by oral ZDV for 6 weeks to the infant</td>
<td></td>
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</table>

HIV=human immunodeficiency virus, ART=antiretroviral therapy, ZDV=zidovudine, 3TC=lamivudine, NVP=nevirapine.

Future Challenges in the Perinatal HIV-1 Epidemic in the United States

Despite dramatic declines, MTCT of HIV-1 continues to occur in the United States. (47) The Centers for Disease Control and Prevention estimates that 300 to 400 infected babies are born annually. (48) This persistence of perinatal HIV-1 transmission reflects populations in which prevention strategies are impeded by lack of prenatal care or lack of HIV-1 testing during pregnancy. (48) Recently, the Mother-Infant Rapid Intervention At Delivery (MIRIAD) study demonstrated the feasibility of rapidly screening women of unknown HIV status in labor for infection at the point of care. (49) The MIRIAD study results have important implications for populations in the United States, but may have a greater impact in southern Africa, where approximately 29% of women do not receive prenatal care. (49) Knowledge of a women’s HIV status during labor is critical for providing antiretroviral therapy to prevent perinatal HIV-1 transmission. (50)

Another significant challenge is prevention of new HIV infections in women of childbearing age, especially adolescent girls of minority race or ethnicity. (47) Finally, prevention of unplanned pregnancy in adolescent women is a vital component of preventing perinatal HIV-1 transmission. (47)
Safety and Toxicity of Antiretroviral Prophylaxis

With widespread use of antiretroviral prophylaxis to prevent perinatal HIV transmission in resource-limited countries and the availability of combination antiretroviral therapy for HIV-infected mothers during pregnancy, increasing numbers of infants will be exposed to antiretroviral agents in utero and during the postnatal period. (3)(51) Animal data have shown that nucleoside analogs may be carcinogenic and can cause mitochondrial dysfunction. (52) However, an extensive review of short- and medium-term data from several studies indicates that antiretroviral therapy during pregnancy has been well tolerated by mothers and infants. (3)(51) Except for mild, transient anemia, (1) no serious short-term maternal or infant adverse effects have been noted with prophylactic ZDV regimens. (53)(54)

An association of low birthweight or preterm delivery with the use of combination antiretroviral agents during pregnancy has been reported in a European study. (55) However, data from a large meta-analysis of seven studies performed in the United States found no association between increased rates of low birthweight, preterm delivery, low Apgar scores, or stillbirths and the use of combination antiretroviral therapy. (56)

Current data indicate that infants exposed to commonly used antiretroviral agents such as ZDV, 3TC, stavudine, NVP, and nelfinavir during early pregnancy are no more likely to have congenital anomalies than those in the general population. (55)(57) The French perinatal cohort study group reported possible mitochondrial abnormalities resulting in fatal outcomes in a large cohort of uninfected infants exposed to ZDV alone or ZDV-3TC during pregnancy or in the neonatal period. (58) Another study from France suggested a possible association of early febrile seizures with perinatal exposure to nucleoside analogs. (59) In contrast, a retrospective review of 16,000 uninfected United States children born to HIV-infected mothers, with and without antiretroviral exposure, failed to identify any deaths related to mitochondrial dysfunction. (60) Short- to medium-term follow-up data from the European Collaborative Study involving 2,414 uninfected children born to HIV-infected mothers and exposed to antiretroviral agents in utero or early life did not show any serious adverse events, including febrile seizures and clinical manifestations suggestive of mitochondrial abnormalities. (61)

However, the long-term outcomes of infants exposed to combination antiretroviral therapy in utero is unknown. Thus, long-term follow-up of all infants born to mothers exposed to antiretroviral therapy is recommended. (52)

Resistance Due to Antiretroviral Prophylaxis

With widespread use of antiretroviral prophylaxis, especially NVP to prevent perinatal HIV-1 transmission in resource-limited settings, antiretroviral drug resistance is a real concern. (62) The issue of NVP resistance has been a major focus because the World Health Organization recommends nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimens as first-line therapy in resource-limited countries. (63) A single gene mutation can result in viral resistance to commonly used antiretroviral agents such as 3TC and NVP. (62) In an open-label study from France, 39% of women receiving ZDV/3TC for more than 4 weeks had genetic mutations associated with 3TC resistance (M184V mutation) at delivery. (26) In the HIVNET 012 study, NVP-resistant mutations (predominantly the K103N mutation) have been detected in 19% of women receiving the single-dose NVP preventive therapy at onset of labor, but the mutations were undetectable 12 to 24 months after delivery. (64) In the same study, NVP resistance mutations were detected in 46% of NVP-treated infants who subsequently became infected, but the mutations faded by 12 months of age. (64) Furthermore, the maternal and infant mutations were different, and no resistant virus was transmitted from mother to infant. Thus, in the absence of continued drug pressure, mutations fade, and transmission of NVP resistant virus appears less likely. (62) In a more recent study, resistant mutations were detected 10 days after delivery in 32% of women who had received intrapartum NVP; women who received intrapartum NVP were less likely to have virologic suppression after 6 months of postpartum treatment with an NVP-containing regimen. (65)

The long-term clinical significance of such antiretroviral resistance on future maternal and infant treatment options is unknown and warrants future research. (66) HIV-infected women at highest risk for development of NVP resistance after receipt of single-dose NVP prophylaxis include those who have a high viral load, low CD4 count, and subtype D rather than A. (67) This subset of women should be considered for combination antiretroviral therapy to improve their own health and reduce the risk of perinatal and possibly postnatal HIV-1 transmission. (62)(66) In contrast, NVP resistance is less likely to develop in women who are healthy and do not require therapy during pregnancy and could benefit from single-dose NVP prophylaxis to prevent perinatal HIV-1 transmission. (66)
Perinatal HIV-1 Transmission in Resource-poor Countries

Although many effective, simple, and less expensive antiretroviral prophylaxis regimens are available to prevent MTCT of HIV-1, these interventions have not been implemented on a large scale, (1) and the perinatal HIV-1 epidemic continues unabated in resource-limited countries. (4) The pediatric HIV-1 epidemic is driven by maternal HIV-1 infection. The Joint United Nations Programme on HIV/AIDS estimates that more than 60 million people have been infected worldwide. (5) Approximately 1 in 5 pregnant women in southern Africa are HIV-infected. (5) Seroprevalence rates among pregnant women have exceeded 20% in many urban populations in sub-Saharan Africa. (4)(5)

There are many barriers to implementing antiretroviral prophylaxis regimens in resource-limited countries, including a variety of complicated cultural, economic, and societal factors. (1)(68) Major challenges include limited access to prenatal care, lack of HIV-1 counseling and testing services, and HIV-1 transmission via breastfeeding. (1)(7)(68) Breastfeeding is the only source of nutrition for HIV-exposed infants because safe, affordable, and feasible alternatives to breastfeeding are not available to many mothers in resource-limited countries. Economic hardships, social and cultural barriers, and political problems compound the dilemma. (68)

Breastfeeding and HIV-1 Transmission

It is estimated that breastfeeding increases the overall risk of MTCT by 14% for established maternal infection and by 29% for primary maternal infection during lactation. (69) Of the estimated 700,000 children who acquired HIV infection in 2003, about 315,000 were infected through breastfeeding. (5) Transmission can occur at any point during breastfeeding. (7) Although exact estimates are not yet reliable, most human milk transmission occurs during the first few months after birth, with a lower but continued risk thereafter. (70)(71) In a randomized, controlled trial of the effect of breastfeeding versus formula feeding on HIV-1 transmission in Kenya, breastfeeding accounted for 44% of all infant infections at age 2 years; 75% of risk difference in transmission between the breastfed and formula-fed groups had occurred by 6 months of age. (70) In a recent individual patient meta-analysis of more than 4,000 breastfed infants from nine international trials, the overall risk of late postnatal transmission was 8.9 transmissions/100 child-years of breastfeeding. (72) In addition, the risk of postnatal transmission generally remains constant throughout breastfeeding, and late postnatal transmission is associated with a lower CD4 count and male sex. (72)

The exact biologic mechanisms for human milk HIV-1 transmission are not yet fully understood.

Risk factors for human milk transmission include women seroconverting during lactation, bleeding or cracked nipples, subclinical and clinical mastitis, and breast abscesses. (7) A South African study reported that mixed feeding was associated with a higher risk of transmission than was exclusive breastfeeding in the first 3 months after birth, possibly because mixed feedings allow both exposure to HIV and increased risk of gastrointestinal infections and disruption of mucosal integrity. (73) However, this finding warrants confirmation by further studies. Limited data suggest that detectable HIV-1 viral load in human milk may be associated with increased transmission. (7)

Prevention of Human Milk HIV-1 Transmission

Despite the success of antiretroviral prophylaxis in reducing perinatal transmission of HIV-1, postpartum transmission through human milk remains a problem in resource-limited settings. (7) Given the overwhelming benefits of breastfeeding, lack of safe alternatives to human milk in resource-limited countries, and the documented risk of HIV-1 transmission via breastfeeding, (7) there is an urgent need to make breastfeeding by HIV-1-infected women safer to prevent postnatal transmission of the virus. (4) Several strategies have been proposed, including maternal or infant postpartum antiretroviral prophylaxis during breastfeeding, infant vaccines and passive immunization, and exclusive breastfeeding with or without early weaning. (7)

Antiretroviral prophylaxis, especially NVP given to the infant during breastfeeding, could protect against postnatal transmission. NVP is a potent NNRTI that has many unique properties favorable for use in preventing transmission through breastfeeding. NVP is highly lipophilic, rapidly crosses the placenta, readily enters human milk, demonstrates excellent bioavailability and a relatively long half-life, and is generally safe and well tolerated. (28) A phase I/II trial (HIVNET 023) in Zimbabwe and South Africa has shown that an extended regimen of NVP is safe and maintains high plasma concentrations when administered daily or twice-weekly to infants for the first 6 months after birth. (74) A phase III study is planned in sub-Saharan Africa to assess the efficacy of an extended infant NVP regimen administered daily to prevent HIV-1 transmission via breastfeeding. (4)
Future Research Priorities

A few of the more pressing research issues related to prevention of perinatal HIV-1 transmission in resource-limited settings include: 1) How best to deliver a proven intervention such as single-dose NVP to prevent perinatal HIV-1 transmission to reach millions of HIV-infected women and their babies in resource-limited settings; 2) How best to prevent postnatal transmission of HIV through breastfeeding; 3) Determining the effect of antiretroviral prophylaxis on infant and maternal health with respect to drug resistance and future response to combination antiretroviral therapy for infected infants and ill mothers; and 4) Identification of newer effective, simple, and less expensive antiretroviral prophylaxis in view of potential development of resistance to current regimens.

Conclusion

Significant progress has been achieved in resource-rich countries where rates of perinatal HIV-1 transmission have been reduced to less than 2%. Antiretroviral treatment, as long- or short-course prophylaxis, significantly reduces the risk of transmission. In contrast, the perinatal HIV/AIDS epidemic continues unabated in resource-limited countries, where access to prenatal care and voluntary counseling and HIV testing is limited, and there is no access to antiretroviral therapy. In addition, transmission of HIV through breastfeeding is a major challenge in resource-limited settings where human milk remains the only feasible infant feeding option. Future efforts to prevent perinatal HIV-1 transmission globally must focus on rapid scale-up and implementation of the current mother-to-child HIV-1 prevention programs, saving the lives of parents through access to antiretroviral therapy and blunting the orphan epidemic in sub-Saharan Africa.

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mens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (PETRA study): a randomised, double-blind, placebo-controlled trial. Lancet. 2002;359:1178–1186


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NeoReviews Quiz

1. Mother-to-child transmission of human immunodeficiency virus (HIV)-1 can occur during gestation (intrauterine), during labor and delivery (intrapartum), or after birth via breastfeeding (postnatal). Of the following, the most critical determinant of both intrauterine and intrapartum transmission of HIV-1 is:

A. Low birthweight.
B. Maternal serum HIV-1 RNA level.
C. Preterm birth.
D. Prolonged rupture of membranes.
E. Vaginal delivery.

2. In resource-limited countries, it may not be possible to prevent postnatal transmission of HIV-1 by avoiding breastfeeding. Accordingly, there is a need for an antiretroviral drug that is highly lipophilic, has a long half-life, is secreted readily in human milk, is safe, and is efficacious. Of the following, the antiretroviral drug that has properties most favorable for prevention of postnatal transmission of HIV-1 through breastfeeding is:

A. Didanosine.
B. Lamivudine.
C. Nelfinavir.
D. Nevirapine.
E. Zidovudine.
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