Objectives

1. Describe the scope of mother-to-child transmission of HIV within the context of the human immunodeficiency virus (HIV) pandemic.
2. Review current concepts on the timing of HIV transmission from mother to child.
3. Review the risk factors associated with transmission of HIV from mother to child.
4. Discuss the four components of the World Health Organization (WHO) framework for approaching the prevention of mother-to-child transmission (PMTCT).
5. Identify and discuss interventions applicable for each component of PMTCT.
6. Discuss WHO recommendations for infant feeding, including an explanation of the risk of transmitting HIV by breastfeeding and how this risk may be lowered.
7. Address efforts under way to scale up access to PMTCT services globally.

Key Points

1. A growing proportion of HIV-infected individuals worldwide, particularly in southern Africa, are young women of reproductive age.
2. Infants are infected with HIV through the perinatal route: in utero, during labor and delivery, or postpartum through breast milk.
3. Risk factors for mother-to-child transmission of HIV include maternal, obstetric, and postnatal factors, including choice of infant feeding strategy.
4. In a breastfeeding population, as much as 40% of total mother-to-child transmission of HIV may take place during breastfeeding.
5. Mixed feeding carries a higher risk of mother-to-child transmission than does either exclusive breastfeeding or exclusive formula feeding. With proper assessment, counseling, and support, mothers can successfully avoid mixed feeding.
6. Antiretroviral medications reduce mother-to-child transmission of HIV.
7. Mothers who qualify for highly active antiretroviral therapy on the basis of their own health should have access to such treatment.
8. PMTCT consists of more than simply giving antiretrovirals to an HIV-positive mother. The WHO offers a comprehensive strategic approach to the prevention of HIV infection in infants and young children that includes the following four components:
   - Primary prevention of HIV infection among women of childbearing age
   - Preventing unintended pregnancies among women living with HIV
   - Preventing HIV transmission from a woman living with HIV to her infant
   - Providing appropriate treatment, care, support to mothers living with HIV and their children and families
9. Globally, access to PMTCT is low, but specific advice on how to achieve improved access exists.
10. Application of a package of PMTCT interventions that have proven efficacy can reduce rates of mother-to-child transmission to less than 2%.
11. Effective PMTCT can be delivered in resource-limited settings.
12. Timely identification of HIV-positive status and enrollment in PMTCT services is crucial to the overall success of a PMTCT program.

Introduction

At the end of November 2009, UNAIDS released the latest data on the number and distribution of persons living with human immunodeficiency virus (HIV)/AIDS worldwide. Estimates are that of the more than 33 million persons living worldwide with HIV/AIDS, a growing proportion are young women of reproductive age. And as the World Health Organization (WHO) and UNICEF detail in the Guidance to Global Scale-up of the Prevention of
Prevention of Mother-to-Child Transmission of HIV Infection

Mother-to-Child Transmission of HIV, in countries with a high burden of HIV infection, AIDS has become a leading cause of illness and death among this population.

Women living with HIV infection can give birth to infants infected with HIV—a process known as mother-to-child transmission (MTCT), the prevention of which is known as the prevention of MTCT (PMTCT). More than 1,100 children younger than 15 years become infected with HIV every day—approximately 430,000 in 2008—almost all through MTCT. More than 90% of these are in southern Africa, and all told, children represent more than 15% of new HIV infections worldwide.

MTCT may take place during pregnancy, labor and delivery, or postpartum via breastfeeding. Risk factors for MTCT are well defined and include prenatal maternal factors such as high viral load, low CD4 cell count, and advanced clinical stage; obstetric factors such as prolonged rupture of membranes and invasive obstetrical procedures; and postnatal factors such as breastfeeding itself and breast conditions such as mastitis.

The overall population risk of MTCT varies with whether the population is breastfeeding or nonbreastfeeding and whether the population’s setting is in a developed country or is resource limited, owing to the relative ability to access a full range of MTCT interventions. In a nonbreastfeeding population, and with no intervention designed to decrease MTCT, the risk of MTCT is 15%-30%. Approximately 70% of transmission in a nonbreastfeeding population is believed to occur before delivery, with roughly 30% of transmission occurring during delivery and the passage of the infant through the birth canal.

In a breastfeeding population, the added risk of postnatal transmission from breastfeeding adds 5%-20% to the baseline risk, such that the total risk increases to as much as 50% (average range, 20%-50%). These percentages are averages of transmission rates; an individual patient could have much higher or lower risk depending on the particular clinical scenario.

Although historically most breastfeeding-associated MTCT has been believed to take place early in the postnatal period (first 6-8 weeks), it is now well appreciated that the risk of transmission from breastfeeding extends into the late postnatal period. In a study from Malawi of a population of HIV-positive mothers that breastfed up to age 24 months, the cumulative risk of transmission between the ages of 6-8 weeks and 24 months was 9.68%; of this figure, more than 85% of transmission was believed to have taken place after age 6 months.

The maximum effect demonstrated from strategies to reduce MTCT has differed by setting. In a nonbreastfeeding population in a developed country, the risk of MTCT can be reduced to less than 2% by a package of interventions that includes antiretroviral (ARV) drugs (highly active antiretroviral therapy [HAART]) given to women during pregnancy and labor, obstetrical interventions including cesarean delivery (prior to rupture of membranes), the complete avoidance of breastfeeding, and ARVs administered to the infant for the first several weeks of life.

In a resource-limited setting, several of these interventions may prove difficult to implement. Cesarean delivery is often not safely available. Patients often do not meet AFASS criteria (acceptable, feasible, affordable, sustainable, and safe), defined by WHO and UNICEF as necessarily present prior to replacement feeding being recommended. As a result, in resource-limited settings most of the PMTCT focus has traditionally been on strategies targeting transmission around the time of labor and delivery. A landmark study (HIVNET 012) from Uganda showed that even a regimen as simple as one dose of nevirapine (a nonnucleoside reverse transcriptase inhibitor [NNRTI]) given to mother at the onset of labor and to the baby within the first 72 h of life (but as close to birth as possible) was associated with a 41% relative reduction in the risk of transmission through to 18 months. Many PMTCT programs in resource-limited settings with high HIV burdens have begun moving toward more effective prenatal ARV regimens, including initiating prophylaxis at or before 28 weeks of pregnancy.

Such expanded ARV prophylaxis strategies are effective, even in resource-limited settings, with reductions in MTCT rates as low as 2%-4%. But in breastfeeding populations, there is still sizable risk of postnatal transmission via breastfeeding, such that overall transmission rates remain considerable. There is significant interest in approaches that can reduce the risk of transmission during breastfeeding.

In developed-country settings, MTCT of HIV is a rare event, given the wide availability of a comprehensive package of MTCT prevention interventions. In contrast, in many resource-limited settings many pregnant,
HIV-infected women cannot access even basic PMTCT interventions, such as counseling and testing and ARV prophylaxis. As of the beginning of 2007, that only 20% of HIV-positive, pregnant women in low- and middle-income countries could access ARVs to reduce the risk of MTCT of HIV.

The global health community has paid considerable attention to this reality over the past several years, and, indeed, today’s figures, while still low, represent an improvement. In 2001, the United Nations General Assembly Special Session (UNGASS) on HIV/AIDS set specific targets for countries to aspire to in the provision on PMTCT services. In 2005, UNGASS raised the PMTCT ARV prophylaxis uptake target (on a country basis) to 40% and called for eventual universal PMTCT coverage (∼80% coverage within each country), with an eye toward an HIV/AIDS-free generation by 2015. By 2007, at least eight resource-constrained countries had achieved that mark (80% coverage), including one in sub-Saharan Africa, Botswana.

To approach PMTCT, the WHO in 2003 adopted a comprehensive strategic approach to the prevention of HIV infection in infants and young children that includes the following four components:

- Primary prevention of HIV infection among women of childbearing age
- Preventing unintended pregnancies among women living with HIV
- Preventing HIV transmission from a woman living with HIV to her infant, and
- Providing appropriate treatment, care, and support to mothers living with HIV and their children and families.

The rest of this chapter will examine each component.

**WHO PMTCT Component 1: Primary Prevention of HIV Infection Among Women of Childbearing Age**

**WHO PMTCT Component 2: Preventing Unintended Pregnancies Among Women Living with HIV**

As the building blocks of PMTCT, these first two strategies mesh. Women who do not get infected with HIV cannot, of course, transmit HIV perinatally to a child. Similarly, enabling women living with HIV to avoid unintended pregnancies reduces the demand on a given health system’s PMTCT program, allowing scarce resources to potentially flow into much needed scaleup of PMTCT services. As well, the interventions effective in enhancing these two strategies often synergize, so considering them in tandem is helpful.

Perhaps most important, interventions targeting these first two components of the WHO’s PMTCT strategy may be among the most effective interventions available. In the Guidance to Global Scale-up, authors comment on the fact that minimally reducing the prevalence of HIV infection among women of childbearing age and moderately reducing the number of unintended pregnancies among HIV-positive women of childbearing age can reduce infant HIV infection similarly to single-dose nevirapine (Sd-NVP)-based PMTCT interventions. Moving beyond “minimally” and “moderately,” the potential effects of these strategies are significant.

The primary route of infection with HIV among women of childbearing age is sexual transmission. Although this topic is well covered elsewhere in this text, the WHO recommends strategies to enhance efforts in this regard.
- Expanding entry points to service delivery, including
  - Antenatal, maternity, and postpartum care
  - Family planning
  - HIV/AIDS care and treatment (for adults and children)
  - Sexually transmitted infection (STI) diagnosis and treatment
  - Voluntary counseling and testing
- In high-burden countries, other entry points that could be expanded include
  - Child immunization and Under-5 clinics
  - Workplace clinics

Historically, in many resource-limited settings, PMTCT programs have not given significant attention to services for women who test HIV negative. Because a woman’s risk of acquiring HIV may be higher during pregnancy and lactation, women accessing antenatal care (ANC) services require increased access to primary HIV prevention services.

Institutionalization of provider-initiated testing and counseling (PITC) into standard maternal-child health packages (including ANC) is appreciated as a critical feature of programs in both developed-country and resource-limited settings that have high coverage of PMTCT and pediatric HIV services. Improving access to family planning improves the efficacy of PMTCT
programs and is cost-effective in decreasing HIV infection in infants. In many high-prevalence settings, particularly in sub-Saharan Africa, where the burden of HIV and pressure on PMTCT programs is the greatest, up-to-date contraceptive prevalence rates are very low (<25%) and unmet need for family planning is high (13%-35%). A substantial opportunity exists for addressing these unmet needs and decreasing the number of infants exposed to HIV.

Specific services enhance primary prevention strategies and unintended pregnancies and can be provided in the preceding settings. Providing information and counseling on ways of reducing the risk of sexual transmission of HIV can extend its influence by involving male partners as well as increasing overall awareness of the issue of perinatal transmission of HIV infection. Also, such counseling can increase awareness that pregnant and postpartum women are at increased risk of HIV infection and help male partners appreciate their responsibility for practicing less risky sex.

By nature, HIV testing and counseling underpins prevention efforts. Specific items recommended to be promoted include augmenting PITC, including PMTCT and family planning counseling into general HIV counseling, and supporting couple counseling, partner testing, and safe and voluntary disclosure.

Promotion of male and female condom availability and use are a key part of prevention interventions. Of particular importance are the promotion of condom use during pregnancy and breastfeeding because of the significant risk of MTCT when HIV is contracted during these periods, as well as offering guidance on how to negotiate condom use with partners. In general, efforts should be made to increase the availability of a full range of contraception options within family planning services, including condoms. The issue of whether to promote using diaphragms in addition to condoms has been raised. A recent study showed no added protective benefit against HIV infection when diaphragm and lubricant gel were provided in addition to condoms and a comprehensive HIV prevention package.

With further respect to family planning services, recent emphasis has been given to the importance of promoting PITC and linking PITC to counseling on reproductive choices and awareness of PMTCT. A global approach that promotes family planning counseling and contraceptives through HIV care and treatment and voluntary counseling and testing, ANC, and postpartum services has been suggested.

Additional preventive benefit can be seen through improved management of STIs, including intensifying antenatal screening and treatment of STIs and targeting high-risk groups with prevention and treatment services for STIs.

Gender-based violence is appreciated as a contributing factor to increased risk of HIV transmission, particularly in high-prevalence settings such as southern Africa. Providing comprehensive management and support for victims of gender-based violence and involving men in reducing gender-based violence have been suggested as important priorities in addressing this concern.

Social and economic determinants play an important role in the risk of HIV acquisition. In Botswana and Swaziland, food insufficiency has been shown to be an important risk factor for sexual risk-taking among women. It has been suggested that targeting food assistance and income generation programs in conjunction with efforts to enhance women’s legal and social rights be incorporated into a comprehensive approach to PMTCT.

Over the past several years there has emerged a growing interest in the role of preexposure prophylaxis in the prevention of HIV acquisition, and by extension, in a comprehensive approach to PMTCT. There is strong evidence that male circumcision markedly reduces a man’s likelihood of acquiring HIV infection, and it has been suggested that this measure also benefits women indirectly; on a population basis, fewer HIV-positive men should translate into fewer male-to-female HIV transmissions. The use of topical microbicides has been disappointing as a means of reducing HIV transmission. Doing so is either ineffective (C-31G) or actually increases the risk of transmission (cellulose sulfate), and no benefit has been shown from this approach. Also, ongoing research on a vaccine against HIV has thus far been disappointing.

Postexposure prophylaxis using a variety of ARVs has significant efficacy in many settings and is widely used, particularly in occupational or sexual assault exposure (see corresponding chapter in this text for details). Accordingly,
there is interest in the use of ARVs by high-risk populations before exposure (preexposure prophylaxis) as a means of reducing HIV transmission. Currently, tenofovir (TFV) and Truvada (a fixed-dose combination of tenofovir and emtricitabine) are being looked at for preexposure prophylaxis in a phase II study in the United States. In developing-country settings, TFV is being investigated in IVDU in Thailand, whereas Truvada is being studied in heterosexual men and women in Botswana and men who have sex with men in Peru and Ecuador.

**WHO PMTCT Component 3: Prevention of HIV Transmission from Mothers Living with HIV to Their Infants**

With no intervention, between 20% and 50% of infants born to HIV-infected mothers will themselves become infected with HIV. With an estimated risk of 5%-10% during pregnancy, 10%-20% during labor and delivery, and 5%-20% during breastfeeding, these risks can be reduced to less than 2% by applying a package of interventions.

**Risk Factors for MTCT of HIV**

Risk factors for MTCT of HIV are well defined. Maternal immunologic and virologic factors predictably influence the risk of HIV transmission. Lower CD4+ counts are associated with a higher risk of MTCT, and higher CD4+ counts are associated with a lower risk of MTCT. This association fits with the fact that low CD4 counts are associated with more advanced disease, and sicker mothers are more likely to transmit the virus than HIV-infected mothers who are still clinically healthy.

There is a direct relationship between maternal viral load and perinatal transmission risk—the higher the viral load, the higher the transmission risk. Like low CD4 counts, high viral loads tend to be associated with more advanced disease. In a study of 552 HIV-infected women, MTCT did not occur among 57 women with RNA levels of less than 1,000 copies/mL. However, there are other reports of MTCT among women whose viral loads were too low to be counted. Therefore, it cannot be concluded that there is a viral load threshold below which there is no risk of perinatal transmission.

Any type of placental inflammation can increase the risk of MTCT. A study from Mombasa, Kenya, showed that chorioamnionitis (inflammation of the lining of the amniotic sac and the womb) slightly increased the risk of MTCT of HIV. Ordinarily, the placenta forms a barrier between maternal and fetal circulation. Although nutrients and waste products are exchanged between the mother and fetus, their circulatory systems are separate. HIV transmission is increased when there is placental inflammation or chorioamnionitis because the barrier that separates the mother’s and baby’s blood and other secretions is compromised. This breach could provide a portal for HIV to enter the baby’s circulation.

Delivery is a time of increased risk of HIV transmission, and a long duration of ruptured membranes increases this risk. During delivery, the baby of an HIV-infected woman is exposed to secretions in the maternal genital tract, which contain HIV. An analysis of 15 studies involving 4,721 deliveries to HIV-infected women illustrates this point. The risk of MTCT of HIV increased by about 2% for every additional hour of duration of ruptured membranes. For women diagnosed with AIDS (not simply HIV infection), the probability of transmission increased by 8% with duration of ruptured membranes of 2 h and by 31% with duration of 24 h. This association remained even after controlling for other risk factors, such as mode of delivery, receipt of ARV therapy, and maternal CD4+ count.

Also important during delivery are limitations on cervical examinations and avoiding unnecessary procedures and instrumentation, such as episiotomies and vacuum and forceps delivery. Whether birth canal exposure itself is a significant risk is controversial, with recent data from trials of birth canal cleansing with virucides showing no reduction in MTCT of HIV. Until recently it was thought that the first born of twins was more likely to contract HIV, but new data suggest this may not be the case.

The well-appreciated risk of transmitting HIV infection during breastfeeding appears to vary with several maternal and infant factors. Advanced clinical stage, lower CD4 counts, higher viral loads, and breast conditions such as mastitis are maternal factors increasing MTCT risk during breastfeeding. The underlying factor favoring transmission in the presence of these factors has been suggested to be that all are associated with increased levels of HIV in breast milk. Infant factors favoring breastfeeding-based MTCT include most importantly the failure to receive post-natal antiretrovirals (discussed below), mixed feeding (the mixing of breastfeeding with other non-breast milk liquids or solids) and the presence of infections such as oral or esophageal candidiasis which break down the infant’s protective gastrointestinal mucosal barrier. The concept
of a breakdown in mucosal barrier augmenting an infant’s propensity to be infected by HIV-infected breast milk underlies the recommendation that infants not mixed feed. The introduction of non-breast milk foods to the immature infantile gastrointestinal tract is believed to cause inflammation in the tract similar to that caused by infections, as mentioned above.

**Timing of MTCT of HIV**

Recently published work has tried to specify the timing of HIV transmission in both breastfeeding and nonbreastfeeding populations. Kourtis et al. analyzed 18 major clinical trials of ARV regimens used to reduce MTCT and concluded that for nonbreastfeeding populations, half of MTCT takes place at the end of pregnancy, near the time of labor, whereas for breastfeeding populations the largest fraction of transmissions take place in the postnatal period (Table 1).

For breastfeeding populations, this model suggests that if the period of breastfeeding is shortened from the 18-24 months (as is common in resource-limited settings) to the 6-12 months recommended by WHO, breastfeeding-associated HIV transmission falls markedly, as does the total rate of MTCT. This assertion has significant implications for infant feeding policies.

**Testing and Counseling**

The ability to offer a PMTCT intervention begins with the identification of HIV-positive expectant mothers—if a woman's HIV status is unknown during pregnancy and the postnatal period, the opportunity for offering a PMTCT intervention is lost. In resource-rich settings, including the United States, opt-out testing—in which an HIV test is performed as part of standard prenatal laboratory testing unless the pregnant mother expressly refuses testing—is the norm, and similar provider-initiated testing is recommended by WHO for resource-limited settings.

The latest WHO guidance on testing and counseling refers to testing and counseling as a pivotal component of PMTCT programs. It is essential for identifying women who can benefit at the time of diagnosis either from HAART and other HIV/AIDS-related care and treatment services or from ARV prophylaxis and other interventions shown to prevent MTCT. WHO recommends that the offer to test and counsel all pregnant women, as early in pregnancy as possible, should be considered a routine part of ANC. If women miss the opportunity to be tested during pregnancy, they should have testing made available in labor or shortly after childbirth; indeed, WHO recommends that HIV testing and counseling be made a part of routine labor and delivery service for all women who present in labor without a known HIV test result. Even if not carried out until the postpartum period, and even if too late for antepartum and intrapartum PMTCT interventions, identification of HIV-positive status at any point allows a woman to access HIV prevention, care, and treatment services, as well as to receive counseling on infant feeding, all with the goal of reducing MTCT.

Opt-out testing increases the proportion of identified HIV-infected pregnant mothers compared with traditional patient-directed voluntary counseling and testing. This concomitantly increases the proportion of HIV-infected women obtaining a PMTCT intervention in a given locale.

Knowledge of and attitudes toward PMTCT of personnel involved in prenatal and maternity care are important factors in determining the degree to which PMTCT services, including testing and counseling, are offered in a given locale. Work from several resource-limited settings has shown less than universal appreciation of the importance and efficacy of PMTCT. Educational programs targeted at such personnel increase knowledge of and promote more favorable attitudes toward PMTCT. Such programs may increase the uptake of HIV testing and PMTCT interventions in resource-poor settings. Avoiding delays in HIV diagnosis and

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</tr>
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BF, breastfeeding; N/A, not applicable.
enrollment in PMTCT services is crucial in achieving good PMTCT outcomes (see PMTCT Timeline at end of this chapter).

**HAART versus Prophylaxis**

**Use of ARVs in Pregnant Women**

In both developed-country and resource-limited settings, ARV medications, either alone or in combinations of two or three medications, lower the risk of MTCT. Through time, multiple trials and studies have monitored one another and evaluated many different ARV regimens. By decreasing viral replication in the mother and protecting the HIV-exposed fetus, these regimens are effective in reducing the risk of MTCT. Most regimens evaluated have also included a phase of administration of ARVs to the newborn infant, thereby protecting the infant after exposure as well.

Data from developed-country settings suggest that the effectiveness of PMTCT regimens that use three ARVs are superior to regimens that use only one or two. Results from the Women and Infants Transmission Study (WITS) conducted in the United States showed that HIV transmission was directly related to the complexity of ARV treatment. Transmission occurred with 20% of HIV-infected mothers who received no ARV therapy, 10.4% of those receiving zidovudine (known as ZDV or AZT) monotherapy, and 1.2% of those receiving three-drug ARV therapy, also known as HAART. Indeed, in developed-country settings the use of HAART has become the standard ARV regimen for the prevention of MTCT. Results similar to those observed in WITS have subsequently been shown in Brazil and other developing countries in Latin America, and in this region, too, HAART for the sole purpose of PMTCT has become the norm.

In discussing the use of ARVs in pregnant women, we must distinguish the use of ARVs for the *treatment* of HIV infection (with triple-drug HAART) in eligible women (as determined by clinical stage and, where available, by CD4 count) from *prophylaxis* against HIV transmission.

**Treatment of HIV Infection**

**HAART to Protect a Mother’s Health**

The chief priority in making decisions about whether to offer prophylaxis versus HAART to a pregnant woman is the protection of the pregnant woman’s health. Not only is HAART in such a case the most effective means of preventing MTCT, but for a woman with such an indication, HAART also reduces maternal mortality and morbidity. Particularly in resource-limited settings, a mother’s healthy survival is essential for ensuring her child’s survival. In Haiti and in several sub-Saharan African settings, healthy survival of mothers has been directly associated with the odds of their children surviving, regardless of the child’s HIV status. There is concern that progression of HIV disease or death in mothers may erode the likelihood of infant survival after effective PMTCT interventions.

WHO has published recommendations for initiating HAART in pregnancy that, like those described in the Antiretroviral Treatment chapter of this book, guide the decision whether to use HAART by assessing both the woman’s clinical stage (I-IV) and CD4 count. WHO emphasizes that CD4 testing is not universally available in many resource-limited settings; indeed, recent data from low- and middle-income countries demonstrate that less than 50% of HIV-positive pregnant women receiving ARVs for PMTCT were assessed for treatment eligibility. When CD4 counts are not available, WHO recommends initiating HAART in all women who meet clinical stage III or IV, but not clinical stage I or II. However, when CD4 counts are available, WHO recommends a CD4-guided approach that would initiate ART for all HIV-infected pregnant women with CD4 cell counts <350 cells/mm³, and for all HIV-infected pregnant women in WHO clinical stage III or IV.

Clearly, where CD4 counts are not available, some women who are clinical stage I or II will also have CD4 less than 350; these women will miss the opportunity to be initiated on HAART in the absence of CD4 availability. To this end, WHO emphasizes the need for broader CD4 availability in resource-limited settings where it currently is not available.

In developed-country settings, a decision-making process similar to that for the initiation of HAART in pregnancy is used. United States Public Health Service Task Force (USPHSTF) guidelines recommend that the same parameters (clinical stage and CD4 count) be used in making HAART-initiation decisions in pregnant women as are used in nonpregnant women, and that pregnant women be eligible for the same recommended HAART regimens as nonpregnant women.
Safety of ARVs in Pregnancy
When the decision has been made to initiate HAART, careful thought must be given to the choice of ARV agents to avoid adverse events in the developing fetus. Many studies have assessed the safety of using ARV agents during pregnancy.

Nucleoside reverse transcriptase inhibitors (NRTIs). Zidovudine (ZDV, AZT) and lamivudine (3TC) are the preferred NRTIs for use during pregnancy. Extensive experience in clinical trials indicates that they are both safe and efficacious; indeed, WHO recommends first-line ART regimens in pregnancy contain a ZDV + 3TC backbone. When ZDV or 3TC is unavailable, alternative agents include abacavir (ABC) and emtricitabine (FTC). The combination of stavudine (d4T) and didanosine (ddI) should be avoided during pregnancy because of a potential increased risk of lactic acidosis attributed to this combination of agents. Also, the combination of ZDV and d4T should always be avoided because of the potential for drug antagonism. Zalcitabine (ddC) is not recommended for use in pregnancy because of its potential for teratogenicity.

NNRTIs. Among NNRTIs, nevirapine (NVP) is the preferred agent. Extensive studies show that it is relatively safe for use in pregnancy. However, caution should be exercised in initiating this agent in women with CD4+ counts greater than 250 cells/µL because of an apparent increased risk of cutaneous and hepatic adverse events. Efavirenz (EFV), another NNRTI, should be avoided in the treatment of pregnant women in the first trimester of pregnancy and women of childbearing age who are not using a reliable method of family planning. This agent has been linked with the development of neural tube defects when the fetus is exposed to EFV during the first trimester. It is considered a safe alternative to NVP during the second and third trimesters. It is often used as part of HAART regimens when patients are receiving concomitant therapy for tuberculosis.

Protease inhibitors (PIs). Long-term use of PIs has been associated with certain metabolic derangements, including dyslipidemia, lipodystrophy, and hyperglycemia. Pregnancy itself is a risk factor for hyperglycemia, and pregnant patients who take PIs should be monitored for the development of hyperglycemia and gestational diabetes.

Given the increasing numbers of women worldwide who can access HAART when their own health requires, special attention should be directed at women who become pregnant while already on HAART. Although the chief consideration for a woman receiving HAART who becomes pregnant is always her health and the optimization of her treatment, consideration also needs to be given to the potential risks to the fetus of in utero exposure to ARV drugs. In general, with the exception of efavirenz, the ARVs recommended as adult first- and second-line therapies, in both resource-rich and resource-limited settings (see ART chapter), are considered to have benefits substantially greater than risks when used in pregnancy. The Antiretroviral Pregnancy Registry longitudinally assesses the risk of birth defects associated with ARVs. The prevalence of birth defects in infants exposed in utero to ARVs does not differ significantly from birth defect rates in the general population.

The case for efavirenz is somewhat different. Teratogenic effects observed in monkeys, and case reports of neural tube and other birth defects in human newborns exposed in utero to efavirenz, have led to recommendations that efavirenz not be used in the first trimester of pregnancy. Accordingly, many clinicians will not allow adolescent and women of childbearing age to use efavirenz as part of their HAART regimen unless a reliable form of birth control is also used.

When it is realized in the first trimester that a woman taking efavirenz has become pregnant, WHO recommends that nevirapine be substituted for efavirenz or that a triple NRTI- or PI-based regimen be given in replacement. When switching from efavirenz, nevirapine should be started at 200 mg twice daily, as opposed to the usual recommendation to start at once daily for the first 2 weeks and then titrate up, as in ARV-naïve patients being initiated on HAART.

Monitoring for hepatotoxicity, including laboratory assessment of liver enzyme levels, should be used in the first 12 weeks of therapy for women who have experienced a robust immune response to EFV-based HAART. NVP-associated hepatotoxicity is more frequent in women with CD4 counts greater than 250 (although chiefly seen in women who are naïve to ARVs at the time nevirapine is initiated), although data from several case series suggest that nevirapine is generally well tolerated in pregnancy and that there may be a significant
contribution to hepatotoxicity associated with nevirapine from underlying chronic viral hepatitis and other hepatobiliary disorders.

Outcome evidence from pregnancies in which infants were exposed to efavirenz in the first trimester is limited, particularly in the developing world. One study from Botswana showed no EFV-associated congenital anomalies among 22 consecutive first-trimester-exposed live born infants. WHO recommends that for women in whom pregnancy is not realized until the second or third trimester, efavirenz may be continued; the high-risk period of pregnancy (first trimester) has already concluded. Current recommendations are that exposure to efavirenz in utero not be considered an indication for abortion and that temporary cessation of HAART is not necessary.

Some concerns have been raised about the potential for tenofovir to be associated with abnormal fetal bone development. However, current recommendations are that women taking tenofovir who become pregnant should continue tenofovir; the benefits of continuing treatment exceed the theoretical orthopedic risk to the infant. Tenofovir + 3TC (or FTC) is a recommended alternative first-line backbone in pregnancy, when ZDV not available.

Effects of HAART on Pregnancy Outcomes

Although ZDV monotherapy prophylaxis appears to be safe to both mother and infant, the question of whether HAART is associated with adverse pregnancy outcomes has been difficult to definitively answer. Study data have been contradictory. Typical side effects of ARV drugs appear to be common, with a Swiss study showing that more than 75% of women experienced one or more of anemia, nausea/vomiting, elevation of liver enzymes, or hyperglycemia. In this study 10 of 30 infants were born prematurely. Further study data supporting an association of HAART with prematurity came from the European Collaborative Study and the Swiss Mother + Child HIV-1 Cohort Study, which detailed the effects of combination ARVs in a population of 3,920 mother-child pairs. After adjusting for CD4 count and intravenous drug use, the study found a 2.6-fold (95% confidence interval, 1.4-4.8) increased odds of preterm delivery for infants exposed to HAART compared with no treatment. A limitation to the study was that only 323 (8%) of the women were exposed to HAART. ZDV monotherapy was not associated with prematurity.

However, in an observational study of pregnant women in the United States with HIV-1 infection (PACTG 367) in which 1,150 (78%) of the women received combination therapy, no association was found between having received combination therapy and preterm birth. Further evidence supporting a lack of association between HAART and significant adverse pregnancy outcome comes from a sizable meta-analysis of seven clinical trials that included 2,123 HIV-1-infected pregnant women who gave birth to infants during 1990-1998 and had received antenatal ARV therapy and 1,143 women who did not receive antenatal ARV therapy. In this meta-analysis, use of combination ARV therapy compared with one drug was not associated with a variety of adverse pregnancy outcomes, including rates of preterm labor, preterm birth, low birth weight, low Apgar scores, or stillbirth. More support for a lack of a specific association between ARV therapy and prematurity comes from a meta-analysis that looked at subjects recruited through 2002 and data published through 2006. This study showed only a small, non-statistically significant risk of prematurity with PI-containing regimens, slightly greater if the PI-containing regimen was started in the first trimester of pregnancy. In this analysis, monotherapy was associated with a small, non-statistically significant decrease in rates of prematurity, and non-PI HAART was associated with no difference.

Use of ARVs for Prophylaxis Against MTCT

ARVs have utility in the prevention of MTCT of HIV-1 infection even when mothers would not otherwise qualify for HAART (per WHO or developed-country criteria) on the basis of their own health. Over more than a decade, various prophylactic ARV regimens have been evaluated for safety and efficacy in the prevention of MTCT in both developed-country and resource-limited settings.

Use of ARV prophylaxis in developed-country settings—ZDV monotherapy.

PACTG 076, the Pediatric AIDS Clinical Trials Group Protocol 076, was the first major study of perinatal transmission prevention. This randomized, double-blind, placebo-controlled study evaluated the use of ARV prophylaxis with ZDV monotherapy. In this study, neither the woman nor her doctor knew whether she was receiving ZDV or a placebo (a sugar pill substitute). Women with CD4+ counts greater than 200 cells/µL who had not received prior HIV treatment were randomized to a three-part regimen of ZDV versus placebo. The sample
size was 409. ZDV was given to the mother beginning at 14-34 weeks of pregnancy, at a dose of 100 mg, by mouth, five times per day. Therapy was avoided during the first trimester to reduce the risk of possible birth defects. During labor, intravenous ZDV was given to the mother as a loading dose of 2 mg/kg of body weight over 1 h followed by a continuous infusion of 1 mg/kg/h until delivery. Finally, oral ZDV was given to the newborn for the first 6 weeks of life, at a dose of 2 mg/kg every 6 h. Women in this study were instructed not to breastfeed their infants.

At 18 months, there was a dramatic relative risk reduction of 67.5% in MTCT in the ZDV treatment group compared with the placebo group. HIV transmission occurred with 25.5% of women receiving the placebo and with 8.3% of women receiving ZDV. Patients receiving ZDV also showed a slight reduction in viral load, but the researchers estimated that reduction in viral load accounted for only 17% of the reduction in HIV transmission. Experts speculate that ZDV may also exert its effect by reducing the concentration of HIV within cervicovaginal secretions. Furthermore, unlike other nucleoside drugs such as d4T and ddI, ZDV becomes fully active within the placenta, which may also explain some of its protective ability.

Infants in the ZDV group experienced temporarily lower hemoglobin concentrations than infants in the placebo group; however, this resolved without treatment. No significant differences were observed between the study groups in growth, neurodevelopment, or other developmental indicators. No unexpected ophthalmologic, cardiac, or other organ system problems were observed, and no malignancies have been observed in follow-up to 10 years of age.

Because PACTG 076 looked at the efficacy of ZDV chemoprophylaxis only in women with CD4 counts greater than 200, the question arose of whether ZDV chemoprophylaxis would be similarly effective in a population with different characteristics—i.e., clinically advanced HIV-1 disease and/or CD4 counts less than 200. Also, the question arose of whether ZDV chemoprophylaxis would be effective in women with prior exposure to ZDV. This question was evaluated by a separate perinatal transmission protocol, PACTG 185, which enrolled pregnant women with advanced HIV-1 disease and low CD4 counts who were receiving ARV therapy (24% had received ZDV before the current pregnancy). All women and infants received the preceding three-part ZDV regimen described as per PACTG 076 as well as either infusions of hyperimmune HIV-1 immunoglobulin (HIVIG) containing high levels of antibodies to HIV-1 or standard intravenous immunoglobulin (IVIG) without HIV-1 antibodies. Because advanced maternal HIV-1 disease is a risk factor for perinatal HIV transmission, the study design predicted the transmission rate in the control group in the 11%-15% range, even though ZDV was being given. PACTG 185 was ultimately stopped early after its first interim analysis showed that there was no significant difference in transmission rates among those who had received HIVIG compared with those who had received IVIG. In the combined group—again, with no significant difference between them—the transmission rate was only 4.8%, confirming the efficacy of ZDV in preventing perinatal HIV transmission and extending it to women with clinically advanced disease, low CD4 count, and a history of prior ZDV use.

**Use of ARV prophylaxis in resource-limited settings.**

Because of its potent preventative benefit, the PACTG 076 ZDV prophylaxis regimen swiftly became part of routine practice in developed-country settings. But its complexity and cost (long prenatal and infant courses of ZDV, intravenous ZDV) have caused PACTG 076 to be difficult to implement in settings where not only are health care resources limited but there is often much higher prevalence of HIV than in North America and Europe. This has particularly been the case in sub-Saharan Africa.

With a need to find less complicated and less costly, but nonetheless effective, regimens for PMTCT, attention in resource-limited settings turned to ARV regimens focused on the periods of pregnancy and childbirth where transmission is believed to be most common: the critical intrapartum period, along with the late antepartum and early postpartum periods.

**Short-course ZDV in resource-limited settings, nonbreastfeeding populations.** The first study to address the needs of resource-poor settings was a trial conducted in Thailand in 1998, the CDC Short-Course ZDV trial, Thailand. In this study, a shorter course of ZDV therapy was provided than was used in the PACTG 076 protocol. This was a randomized, double-blind, placebo-
controlled trial of 397 HIV-infected women from two Bangkok hospitals. Oral ZDV (300 mg twice daily) was given to pregnant women, beginning at 36 weeks of gestation. This was followed by oral ZDV given to the mother during labor, at a dose of 300 mg administered every 3 h until delivery. Unlike PACTG 076, this trial had no newborn-treatment component. The mothers did not breastfeed. Results from this study showed that a shortened course of ZDV therapy can reduce the risk of MTCT by approximately 50%. The rate of HIV transmission was 18.9% in the placebo group and 9.4% in the ZDV group. The study also suggested that, in a nonbreastfeeding population, most cases of vertical transmission occur in the peripartum period.

Another trial carried out in Thailand looked at whether giving ZDV from a later point in pregnancy than did the CDC short-course ZDV trial, Thailand (38 weeks versus 36 weeks) as well as in labor but not to babies made a difference in the efficacy of ZDV. It did. Efficacy was markedly reduced (at 6 months in this nonbreastfeeding population), with only 9% MTCT risk reduction compared with CDC short-course ZDV trial, Thailand’s 50% figure, confirming the need to start ZDV earlier than 38 weeks for significant efficacy to be seen. As a result, starting AZT by 36 weeks has become standard practice in most resource-limited setting guidelines on the use of ZDV monotherapy prophylaxis, and whether a mother has received at least 4 weeks of prelabor ARV is a key point in the decision making recommended by the WHO and other authorities on choice of labor and postpartum prophylaxis regimens.

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**Short-course ZDV in resource-limited settings—breastfeeding populations.** PACTG 076 and the Thai trials showing efficacy for long-course and then short-course AZT prophylaxis were performed in nonbreastfeeding populations. But because most HIV-infected women in low-income settings do not have the resources to provide formula for their children, it has been essential to assess the efficacy of prophylaxis in sites where breastfeeding is unavoidable. The short-course regimen of ZDV used in Thai CDC was replicated in Abidjan, Cote d’Ivoire (CDC short-course ZDV trial, Cote d’Ivoire), in a population of 260 breastfeeding women. The use of ZDV resulted in a 44% reduction at age 4 weeks, a 37% reduction in the transmission of HIV by the time the infants were 3 months old, and 26% efficacy at 24 weeks. The Cote d’Ivoire study showed that the CDC short-course ZDV trial, Thailand, regimen of ZDV was effective in a breastfeeding population, although the reduction in transmission was not as large as that in the Thai CDC study, most likely because of postnatal transmission through breast milk.

The DITRAME trial also evaluated the use of a short course of ZDV prophylaxis in a breastfeeding population in Burkina Faso and Cote d’Ivoire. In this trial, ZDV was given as in the CDC short-course ZDV trial, Thailand, from 36 weeks; also, a postpartum maternal course of ZDV was given for 1 week, with the goal of reducing the transmission of HIV through breast milk. At 6 months, the treated group showed a 38% reduction in HIV transmission compared with the group receiving a placebo. The effect was sustained at 18 months postpartum, where the efficacy versus placebo was 30%. Hence, the added week of ZDV did not contribute to any further reduction in the transmission of HIV. Analysis of data from the Cote d’Ivoire (CDC short-course ZDV trial, Cote d’Ivoire) and DITRAME trials at 24 weeks postpartum revealed a persistent effect of short-course ZDV prophylaxis despite continuation of breastfeeding. At 24 weeks, the relative decrease in HIV transmission was 26% compared with placebo.

**ZDV Plus 3TC in Resource-limited Settings—Breastfeeding Populations.** Once short courses of ZDV were found to be effective, subsequent trials evaluated the efficacy of ARV prophylaxis combining ZDV with 3TC (lamivudine). A randomized, double-blind, placebo-controlled trial known as the PETRA trial, which was conducted in South Africa, Uganda, and Tanzania,
Prevention of Mother-to-Child Transmission of HIV Infection

evaluated the use of ZDV with 3TC in a resource-poor setting where the rate of breastfeeding was 74% and the median duration of breastfeeding was 28 weeks.

Between June 1996 and January 2000, 1,797 HIV-infected pregnant women were randomized to one of four (A, B, C, plus placebo) regimens (Table 2). At 6 weeks postpartum, results showed that regimens A and B were effective (5.7% and 8.9% transmission, respectively, versus 15.3% for placebo—efficacy, 63% and 42% versus placebo, respectively) in reducing HIV transmission, though the benefits had diminished considerably after 18 months. Regimen C (intrapartum ZDV + 3TC only) was not effective (14.2% transmission versus 15.3% for placebo). By 18 months postpartum, efficacy of the A and B regimens had diminished considerably (14.9% and 18.1% transmission versus 22.2% for placebo—efficacy, 34% and 18% versus placebo). As has been shown in other studies in resource-poor settings, this finding reflects continued HIV transmission via breastfeeding.

Nevertheless, short-course ZDV with 3TC remains a valid option for the prevention of MTCT of HIV in resource-poor settings. Indeed, a meta-analysis of individual data records from several African PMTCT trials indicates that the combination of ZDV and 3TC from 36 weeks of pregnancy is more effective in PMTCT than either ZDV from 36 weeks of pregnancy or Sd-NVP, and a recent Cochrane review supports regimens similar to PETRA A as among the most effective ARV prophylaxis regimens available in resource-limited settings.

**Sd-NVP.** Although less expensive and less complicated than the long-course PACTG 076 AZT protocol used in resource-rich settings, short-course AZT and AZT + 3TC protocols still prove too financially and logistically challenging for some resource-limited settings. An even simpler and less expensive regimen uses a single-dose of nevirapine (Sd-NVP), an NNRTI ARV with a potent mechanism of action and a long half-life, given to the mother at the onset of labor and one dose of nevirapine given to the infant within 72 h of birth. This simple and inexpensive regimen is effective for PMTCT.

This regimen was formally evaluated in a landmark trial known as HIVNET 012, conducted among 619 HIV-infected pregnant women and their infants in Kampala, Uganda. In one arm of the study, one 200-mg oral dose of nevirapine was given to mothers at the onset of labor, and one 2 mg/kg oral dose of nevirapine was given to infants within 72 h of birth. The other study arm consisted of an ultrashort course of ZDV, in which oral ZDV was given to mothers beginning at the onset of labor, at an initial dose of 600 mg, followed by 300 mg every 3 h during labor. Oral ZDV was given to infants at a dose of 4 mg/kg twice per day for the first 7 days of life. In both arms of the study, infants were breastfed by their mothers. Infant infection status was analyzed at 6-8 weeks, 14-16 weeks, and 18 months of life.

The two doses of nevirapine reduced transmission by 47% compared with an ultrashort course of ZDV by 14-16 weeks postpartum. No significant adverse effects were noted. HIV transmission rates among the 311 infants receiving nevirapine and the 308 infants receiving ZDV were as follows:

- 8.1% versus 10.3% at birth
- 11.8% versus 20.0% at 6-8 weeks
- 13.6% versus 22.1% at 14-16 weeks
- 15.7% versus 24.1% at 18 months (42% reduction)

Advantages of the Sd-NVP approach include obvious cost and feasibility concerns. Nevirapine is relatively inexpensive. As well, the regimen is suitable for women who first come to medical attention at the onset of labor or who receive their first HIV-positive test result at such time. The medication may be stored at room temperature, is orally administered, and has a pediatric formulation widely available in resource-limited settings.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>HIV Transmission to the Baby at 6 Weeks of Life</th>
<th>HIV Transmission to the Baby at 18 Months of Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. ZDV+3TC starting at 36 weeks of gestation, oral intrapartum dosing, and 7 days postpartum dosing of mothers and infants</td>
<td>5.7%</td>
<td>15%</td>
</tr>
<tr>
<td>B. ZDV+3TC starting with oral intrapartum dosing and 7 days postpartum dosing of mothers and infants</td>
<td>8.9%</td>
<td>18%</td>
</tr>
<tr>
<td>C. ZDV+3TC oral intrapartum doses only</td>
<td>14.2%</td>
<td>20%</td>
</tr>
<tr>
<td>D. No intervention</td>
<td>15.3%</td>
<td>22%</td>
</tr>
</tbody>
</table>

This table shows the results obtained in the PETRA trial, which evaluated the use of different regimens for the prevention of MTCT of HIV.
A traditional concern in resource-limited settings, particularly in sub-Saharan African locales where HIV rates are greatest and health systems among the world’s most poor functioning, is that results seen in a trial such as HIVNET 012 are not reproducible in a real-world operational context. Such concerns are particularly acute in sub-Saharan Africa. Yet, Sd-NVP can be implemented with effectiveness similar to that seen in clinical trials in a variety of sub-Saharan African settings, including rural health facilities and home births. And Sd-NVP is indeed an effective PMTCT regimen, recently validated in several systematic reviews of current ARV prophylaxis regimens. Ideally, however, national PMTCT programs will go beyond sd-NVP, utilizing other, more efficacious PMTCT regimens, as outlined in this chapter and recommended by WHO.

**Resistance to NNRTIs After Sd-NVP.** In addition to efficacy as compared with other PMTCT approaches, sd-NVP has other drawbacks. A chief concern is the development of NNRTI resistance. NNRTIs, such as nevirapine and efavirenz, need only one mutation to take place for the virus to obtain class resistance to other NNRTIs. Given nevirapine’s long half-life, administering one dose of nevirapine affects a relative monotherapy for the half-life of the drug (generally 24-30 h, but in some women it can persist for up to 21 days). With only one mutation required to impart resistance to the NNRTI class, resistance to Sd-NVP is common.

Indeed, such resistance has been seen in the follow-up to Sd-NVP trials in resource-limited settings. Sizable fractions of women (especially those with more advanced disease and higher viral loads) and of infants who become infected despite Sd-NVP develop resistance mutations to NNRTIs as a result of NVP-exposure. Because nevirapine is a first-line component of adult and pediatric HAART regimens in WHO’s current guidelines for ARV use in resource-limited settings, and efavirenz is commonly used as well around the world, the development of resistance to NNRTIs is of significant concern. Sd-NVP-induced resistance seems to wane over time, such that the effectiveness of Sd-NVP when used for PMTCT in subsequent pregnancies does not seem to be impaired. Sd-NVP-induced resistance compromises both subsequent maternal treatment with NVP-based HAART regimens (although the compromise is less if HAART started more than 6 months after exposure to Sd-NVP) and similar treatment in infants who become infected despite Sd-NVP.

Administering other ARVs, particularly a combination of zidovudine and lamivudine, can reduce the frequency with which nevirapine resistance develops after Sd-NVP. In particular, the TOPS study from South Africa showed that addition of intrapartum plus 4-7 days of maternal postpartum zidovudine-lamivudine reduced nevirapine resistance from 57% to 9%-13% in a population of women who received no antenatal ARVs. As a result of this data, WHO recommends that all women who receive Sd-NVP for PMTCT, whether as an isolated intervention or as part of an expanded antepartum-intrapartum regimen, receive a 7-day “tail” of zidovudine-lamivudine to reduce the likelihood of NNRTI resistance. A longer ZDV/3TC tail to cover the potentially persistent drug levels of Sd-NVP.

The WHO offers guidelines to the complex decision of whether to breastfeed.
is not recommended because of the possibility of 3TC resistance.

Recent results from a randomized clinical trial in Zambia suggest that a simpler method than 7 days of zidovudine-lamivudine may be possible for the reduction of NNRTI resistance after Sd-NVP. In this trial, 400 HIV-infected pregnant women who sought prenatal care at two public health facilities in Lusaka were enrolled to receive the local standard of care for PMTCT consisting of short-course antenatal zidovudine plus Sd-NVP at delivery. After one patient was excluded, 200 women were randomized into an arm where they received an additional at-delivery dose of 300 mg of tenofovir with 200 mg of emtricitabine under direct observation, whereas 199 received no study drug. Women who received the intervention were 53% less likely than control subjects to have a mutation that conferred NNRTI resistance at 6 weeks after delivery. Although the results of this study cannot be extended to women who take only Sd-NVP without antenatal zidovudine, current WHO recommendations recommend such short-course zidovudine plus Sd-NVP, as received by the women in this study. The study’s findings suggest that the addition of single-dose tenofovir-emtricitabine to short-course zidovudine and Sd-NVP is an effective approach that may prove more feasible than 7 days of postpartum zidovudine-lamivudine, while still conferring similar protection against the development of NNRTI resistance.

**Addition of Sd-NVP to ZDV-based ARV regimens for PMTCT.** Because a major cohort study conducted in the U.S. in the early 1990s showed that a combination of ARVs is more powerful than one agent, there has been interest in using combinations of ARVs for PMTCT. Indeed, in developed countries maternal HAART solely for PMTCT is the standard of care for women with detectable viral loads, as it is in many resource-limited settings such as Brazil, where data for the power of HAART to reduce transmission rates to less than 2% also exist.

Yet implementing HAART widely for the sole purpose of PMTCT faces sizable cost and operational feasibility issues in many resource-limited settings. As a result, much work has gone into looking closely at simpler combinations of prophylactic regimens that build on work done on ZDV-based short-course regimens and Sd-NVP.

**Combination ZDV-3TC versus Sd-NVP.** After PETRA and HIVNET 012 demonstrated the efficacy of short courses of medication in reducing MTCT, a study called SAINT (South African Intrapartum Nevirapine Trial) compared the two regimens. Women and their newborn infants were randomized to either nevirapine or ZDV-3TC arms. In the nevirapine arm, women received 200 mg orally in labor plus an additional 200 mg if still in labor after 48 h, as well as 200 mg 24-48 h postpartum; including the postpartum dose was a departure from the labor-only maternal dosing studied in HIVNET 012. In the ZDV-3TC arm, mothers received ZDV-3TC during labor (loading dose with subsequent dosing every 12 h until delivery) and twice daily for 7 days after delivery. Infants in the ZDV-3TC arm received ZDV and 3TC twice daily for 7 days (as in PETRA B [Table 3]). Results showed similar efficacy for intrapartum nevirapine and for combination ZDV-3TC at 8 weeks (12.3% and 9.3%, respectively, a non-statistically significant difference) in reducing MTCT of HIV. In this study, as in HIVNET 012, delivery near the time of nevirapine dosing increased the odds of transmission; the odds of intrapartum infection were threefold higher in SAINT when the maternal dose was given less than 2 h before delivery. This finding led the study authors to recommend that women who are tested during the antenatal period be given the Sd-NVP by the antenatal clinic and be advised to take it at the first sign of labor; this recommendation has gained widespread favor throughout sub-Saharan Africa and is now common practice in most PMTCT programs using maternal Sd-NVP.

**Combination nevirapine-ZDV in resource-limited settings.** To evaluate the efficacy of adding Sd-NVP to a short course of ZDV (300 mg by mouth twice a day starting at 28 weeks of gestation, 300 mg by mouth every 3 h intrapartum, and to the newborn 2 mg/kg by mouth every 6 h for 1 week), Perinatal HIV Prevention Trial (PHPT) investigators in Thailand in 2001-2003 randomized 1,844 nonbreastfeeding women to ZDV alone or ZDV combined with nevirapine. Results at 6 months revealed a transmission rate of 6.3% in the ZDV-alone group and 1.1% in the ZDV-nevirapine group. This finding confirmed that adding nevirapine to short-course ZDV further reduces MTCT of HIV in nonbreastfeeding women, and can, when added to short-course ZDV, achieve PMTCT results similar to those seen with full triple therapy (HAART)—less than 2%.
To assess the same regimen in a breastfeeding population, investigators in Cote d’Ivoire and Burkina Faso conducted an open-label study, called DITRAME-Plus, in which Sd-NVP was given along with short-course ZDV (similar to the CDC short-course ZDV study, Thailand). Combination therapy resulted in a transmission rate of 7% at 3 months postpartum, compared with 13% in previously documented cases without nevirapine. Thus, even in a population of breastfeeding women, adding Sd-NVP to short-course ZDV appears efficacious.

Because of the success of the Thai and DITRAME-Plus trials, the WHO recommends short-course ZDV with Sd-NVP as the best option for PMTCT of HIV in resource-limited settings when the mother does not otherwise qualify for HAART, recommending ZDV from as close to 28 weeks gestation as possible.

Investigators in Malawi tried adding a 1-week neonatal course of ZDV to the HIVNET 012 nevirapine protocol in a predominantly breastfeeding population. However, giving the newborn ZDV did not result in a statistically significant difference in the rates of transmission. At 6 weeks, the rate of transmission was 14.1% in infants who received only nevirapine and 16.3% in infants who received both nevirapine and ZDV.

**Combination nevirapine-ZDV in developed-country settings.** The PACTG 316 trial studied the effects of combining intrapartum/newborn nevirapine with standard ZDV-based antenatal prophylaxis in well-resourced settings. Nonbreastfeeding women in the United States, Europe, Brazil, and the Bahamas were randomized to standard ZDV-based ARV therapy (along with other ARVs required for treatment) with or without nevirapine. Results revealed no statistical difference in the rate of transmission: 1.4% with nevirapine and 1.6% without nevirapine. Hence, there appears to be no benefit to adding nevirapine to standard ZDV-based prophylaxis in more developed settings in which breastfeeding does not take place.

**WHO Recommendations on Adding Nevirapine to Short-Course ZDV Regimens in Resource-Limited Settings**

However, WHO recommends that where breastfeeding is common there is particular importance to including Sd-NVP as part of the PMTCT regimen because the long half-life of nevirapine prevents early postnatal transmission via breast milk. This is an effect not noted with zidovudine prophylaxis alone and is a significant contributor to the long-term efficacy of a PMTCT regimen, traditionally lower in breastfeeding populations because of the ongoing risk of acquiring HIV infection during the breastfeeding period. Early breast milk, with a high concentration of colostrum, has more HIV than breast milk that has transitioned.

Generally, it is recommended that in settings where breastfeeding is common both mother and baby receive nevirapine per the HIVNET 012 protocol. But data from a recent clinical trial in Botswana demonstrate that the maternal dose of nevirapine may be omitted if mother receives at least 4 weeks of AZT and the infant receives Sd-NVP as well as 4 weeks of AZT. In this trial, where all mothers received a background of zidovudine from 34 weeks, and all infants received Sd-NVP plus 4 weeks of zidovudine, mothers were randomized to either Sd-NVP or placebo at delivery. Transmission rates were very low in both arms—4.3% in the maternal nevirapine arm versus 3.7% in the placebo arm—a nonsignificant difference.

That mothers may forgo the Sd-NVP dose if they receive at least 4 weeks of AZT is an important finding: not receiving Sd-NVP obviates a mother from having to receive intrapartum lamivudine or the 7-day zidovudine-lamivudine “tail” described in the previous section to reduce the risk of subsequent nevirapine resistance.

**HAART for PMTCT Regardless of CD4 Count**

In general, combinations of ARVs are more efficacious in preventing MTCT than one ARV. The Women and Infants Transmission Study (WITS) showed that transmission was directly related to the duration and complexity of ARV treatment. This and other studies confirm that the rate of MTCT of HIV correlates with the maternal serum HIV viral load at delivery: the higher the mother’s viral load, the greater the chance of HIV transmission. HAART provides the means to more effectively lower patients’ viral load and thus further reduce MTCT of HIV.

Accordingly, the use of HAART solely for PMTCT (i.e., otherwise not required for the mother’s health) has become standard practice in most of the developed world and in Latin America and other developing regions, where data show MTCT rates comparable to those in North America, Europe, and other wealthy settings. Current U.S. guidelines
advise that standard combination ARV regimens (typically two NRTIs and either a NNRTI, or more commonly in the U.S., a PI) for the treatment of HIV infection should be discussed and offered to all pregnant women with HIV infection regardless of viral load. For women with HIV RNA levels greater than 1,000 copies/mL they are recommended (when HAART is not used, ZDV monotherapy is used instead).

Until recently, little information was available on the efficacy and safety of HAART used exclusively for PMTCT in resource-limited settings with high HIV seroprevalence populations. But with much ongoing study in this area, this has changed. The Drug Resource Enhancement against AIDS and Malnutrition (DREAM) program is a large ARV treatment program financed by the Treatment Acceleration Program (TAP) of the World Bank. In addition to ARV treatment, the DREAM program also focuses on nutritional supplementation and a comprehensive approach to PMTCT. In the DREAM program, HIV-infected pregnant women are offered HAART, from as early as 25 weeks’ gestation, irrespective of their clinical, immunologic, or virologic status. All infants receive postexposure prophylaxis. From 2004 to 2006, in Mozambique, Malawi, and Tanzania, of 1,150 infants born to mothers who had received HAART, only 11 were HIV infected, a 0.95% rate of transmission, comparable to data from resource-rich settings. In this cohort, HAART when used for PMTCT was safe for both mothers and infants, as has been shown when HAART is used for treatment of mothers who qualify on clinical, immunologic, or virologic grounds.

In November 2009, WHO for the first time recommended as an option for all HIV-infected pregnant women not eligible for ART, prophylaxis with HAART starting from as early as 14 weeks of gestation until one week after all infant exposure to breast milk has ended; further discussion of antiretrovirals in the context of infant feeding will be discussed below.

ARVs to the Infant after Birth

As first shown in PACTG 076 and discussed earlier in the context of several trial results-based PMTCT regimens, provision of ARVs to the infant after birth is a key component of effective PMTCT. Postexposure prophylaxis is highly effective in noninfant populations exposed to HIV (see the HIV postexposure prophylaxis section of this text), and the same is true for the newborn, even when an HIV-infected mother has received no antepartum or intrapartum ARV-based PMTCT intervention. Although early data called into question the benefit of neonatal-only prophylaxis, later work has repeatedly shown a benefit, particularly when started within 12–24 h of birth, although benefit has still been shown with longer windows. Epidemiologic studies from New York State support the use of a 6-week course of neonatal-only ZDV to prevent the vertical transmission of HIV. In a nonbreastfeeding population, the risk of transmission dropped from 27% to 9% when neonatal-only prophylaxis was started within 48 h of delivery.

Investigators in South Africa compared the efficacy of single-dose, neonatal-only nevirapine against 6 weeks of neonatal-only ZDV for the prevention of vertical transmission of HIV in predominantly nonbreastfeeding women. Respective transmission rates were 11.9% and 13.5% at 6 weeks and 14.3% and 18.1% at 12 weeks. Hence, as an infant-only prophylaxis strategy, Sd-NVP may be at least as effective as neonatal-only ZDV for the prevention of MTCT of HIV.

Finally, the NVAZ Randomized Clinical Trial studied the effect of single-dose neonatal-only nevirapine compared to single-dose neonatal-only nevirapine combined with 1 week of neonatal-only ZDV in a predominantly breastfeeding population in Malawi. Results showed that postexposure prophylaxis with nevirapine and 1 week of ZDV was superior to nevirapine alone. Newborns receiving nevirapine alone had an infection rate of 12.1%, whereas newborns receiving the combination of nevirapine and ZDV had an infection rate of 7.7%, for a relative reduction of 36%.

Indeed, it is now believed that most of the benefit of regimens that cover only the peripartum and postnatal periods, such as Sd-NVP (HIVNET 012) or peripartum zidovudine-lamivudine is due to the newborn postnatal component, because the transmission rates reported in those studies differ little from those reporting data from studies involving infant postnatal prophylaxis only. This supposition is further supported by the findings from the PHPT trial in Thailand that added Sd-NVP to ZDV from 28 weeks and showed an 80% reduction in transmission risk, as well as the conclusion from the Mashi trial in Botswana that infant-only Sd-NVP gives similar benefit as Sd-NVP to both mother and infant.
The Mashi data indicate that infant-only Sd-NVP has comparable efficacy to mother-and-infant Sd-NVP only when mother has received at least 4 weeks of antepartum ARVs and the infant receives 4 weeks rather than 1 of postnatal zidovudine. Indeed, the PHPT investigators report that modeling based on their trials supports the key role of prolonged neonatal prophylaxis in averting late intrauterine transmissions to the infant, especially when the mother initiated ARV prophylaxis toward the end of pregnancy.

Longer courses of antiretrovirals for breastfeeding infants of HIV-infected mothers are now recommended by WHO, and will be discussed below.

**How ARVs Might Work to Prevent MTCT of HIV**

The question of how ARVs work to reduce transmission risk in an infant is not entirely clear. But it was recently shown that approximately 18% of uninfected (as shown by DNA PCR) infants born to HIV-1-infected mothers have evidence of only partially reverse-transcribed, and thus nonintegrated, HIV in their peripheral blood mononuclear cells. This finding gives rise to the hypothesis that until the “infected” cell receives the proper activation cues, which may take time after birth to occur, the HIV remains nonintegrated, and the mononuclear cell thus remains without an infection established. This “window” between the entry of HIV into the mononuclear cell and the activation of the mononuclear cell may provide the opportunity necessary for a critical intervention such as ARV therapy to avert establishing HIV infection in the newborn.

### Recommendations for the Using ARV Agents for PMTCT of HIV in Developed-Country Settings


### Recommendations for PMTCT of HIV in Resource-Limited Settings

The following are the ARV Prophylaxis options recommended by WHO for HIV-infected pregnant women who do not need treatment for their own health (maternal and infant options)(Table 3).

### Obstetrical PMTCT Measures

Several obstetrical PMTCT principles should be implemented when possible. These standard procedures typically do not require significant resources, increased financial demand, or special training. Thus, implementation in resource-limited settings through proper training can be expected.

All intrapartum obstetrical recommendations are based on the core concepts of HIV transmission risks. Anything that increases maternal-to-fetal vaginal secretion exposure and maternal-to-fetal blood exposure, including inflammation, will increase the risk of HIV transmission to the newborn. Thus, it would follow that shortening the time of rupture of membranes to delivery whenever safely possible is recommended. HIV-positive pregnant women in labor should be monitored to ensure that they are progressing toward labor at an acceptable pace.

<table>
<thead>
<tr>
<th>Option A - Maternal ZDV</th>
<th>Option B - Maternal triple ARV (HAART) prophylaxis</th>
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</thead>
<tbody>
<tr>
<td><strong>Mother</strong></td>
<td><strong>Mother</strong></td>
</tr>
<tr>
<td>♦ Antepartum ZDV (from as early as 14 weeks gestation)*</td>
<td>Triple ARV from 14 weeks until one week after all exposure to breast milk has ended:</td>
</tr>
<tr>
<td>♦ sd-NVP at onset of labor*</td>
<td>♦ ZDV+3TC+LPV/r</td>
</tr>
<tr>
<td>♦ ZDV+3TC during labor and delivery*</td>
<td>♦ ZDV+3TC+ABC</td>
</tr>
<tr>
<td>♦ ZDV+3TC for 7 days postpartum*</td>
<td>♦ ZDV+3TC+EFV</td>
</tr>
<tr>
<td>*sd-NVP and ZDV+3TC may be omitted if mother receives &gt;4 weeks of ZDV antepartum</td>
<td>♦ ZDV+3TC (or FTC) + EFV</td>
</tr>
<tr>
<td><strong>Infant</strong></td>
<td><strong>Infant</strong></td>
</tr>
<tr>
<td>Breastfeeding infant</td>
<td>Breastfeeding infant</td>
</tr>
<tr>
<td>♦ Daily NVP from birth until one week after all exposure to breast milk has ended</td>
<td>♦ Daily NVP from birth to 6 weeks</td>
</tr>
<tr>
<td>Non-breastfeeding infant</td>
<td>Non-breastfeeding infant</td>
</tr>
<tr>
<td>♦ ZDV or NVP daily for 6 weeks</td>
<td>♦ ZDV or NVP daily for 6 weeks</td>
</tr>
</tbody>
</table>
rate. Pharmaceutical augmentation of labor should be used when acceptable according to standard obstetrical protocols to avoid prolonged labor. Cesarean delivery, when safely available, may be an acceptable alternative to prolonged labor but not used as a prevention measure after rupture of membranes. Cervical exams should be performed only when necessary, thus reducing the risk of chorioamnionitis and MTCT of HIV.

During vaginal delivery of the newborn, standard operating procedures should be followed for PMTCT. These include avoiding unnecessary instrumentation such as vacuum deliveries, forceps deliveries, and episiotomies. Most up-to-date obstetrical practitioners feel that episiotomies are rarely indicated and generally do not lead to improved newborn outcomes.

Health care providers should appropriately protect themselves from exposure as well through the use of gloves and protective eyewear, and they should use extreme caution with suturing and other sharp instrumentation.

In developed-country settings, cesarean delivery reduces MTCT. A meta-analysis of the mode of delivery was conducted using 15 prospective cohort studies representing 8,533 mother-infant pairs. The results of this analysis suggest that elective cesarean delivery reduces the risk of transmission of HIV from mother to infant independently of the effects of treatment with ZDV. Among women who had a cesarean delivery and no ZDV, the risk of transmission was 10.4%. Among women who received ZDV but had a vaginal delivery, the risk of transmission was 7.3%. Among women who had an elective cesarean delivery and received ZDV, the risk of transmission was 2%. For cesarean delivery to be most effective, it must be performed electively, prior to rupture of membranes.

Several studies have looked at whether HIV-infected women have an increased risk of postoperative complications after cesarean deliveries. In one early study, HIV-infected women appeared to be at increased risk. In a later study involving a much larger sample, complication rates for HIV-infected women overall were within the range of complication rates reported for HIV-negative women. However, women with CD4+ lymphocyte counts of fewer than 200 cells/µL did have an increased rate of complications. In summary, for most HIV-infected women, cesarean delivery is probably about as safe as it is for HIV-negative women, but for women with advanced disease or AIDS, cesarean delivery may carry a higher risk.

The U.S. Public Health Service Task Force (USPHSTF) recommends that scheduled cesarean delivery at 38 weeks be performed for women with HIV RNA levels of more than 1,000 copies/mL near delivery (whether receiving or not receiving antepartum ARV drugs) and for women with unknown HIV RNA levels near delivery. For women taking ARVs who have HIV RNA levels of fewer than 1,000 copies/mL, the USPHSTF advises that data are insufficient to evaluate the potential benefit of cesarean delivery to prevent MTCT. WHO recommendations for PMTCT in resource-limited settings do not include cesarean delivery as a part of standard PMTCT, largely because of cost and availability barriers and the limited benefit expected over properly applied ARV-based PMTCT regimens in such settings.

Finally, newborn care of HIV-exposed infants should ensure proper handling of the infant. The infant should be washed with clean water immediately after delivery so that the baby is free of maternal blood and secretions. It is especially important to clean the areas of the baby where newborn vitamin K and vaccines are given, so as not to introduce HIV to the newborn iatrogenically. If the newborn is to receive ARV prophylaxis, it should be started as soon as possible after delivery.

**Infant Feeding**

Implementing a package of PMTCT measures can generate HIV transmission rates at birth of 1%-2% in both high-income and resource-limited settings. And yet these impressive rates of PMTCT are not sustained in a breastfeeding population, where breastfeeding is the cause of up to 40% of overall transmission, and absolute risk approaches 15% if women carry out prolonged breastfeeding to 2 years.

Several factors increase the risk of breastfeeding transmission, including advanced maternal clinical stage, low maternal CD4 count, high maternal viral load, mastitis, and mixed feeding. The highest risk of HIV-1 transmission during breastfeeding is believed to be during early lactation; colostrum contains higher viral loads than milk produced later in lactation.

Yet transmission risk from breastfeeding is not restricted to the early lactation period. The Breastfeeding and HIV International Transmission Study (BHITS) meta-analysis has shown the risk to continue throughout the breastfeeding period. In BHITS, the risk of postnatal HIV
transmission after 4 weeks of age was 8.9 transmissions per 100 child-years of breastfeeding, and the rate was generally constant from 1 to 18 months of age. In follow-up of the NVAZ studies in Malawi, the risk of late postnatal transmission (after age 6 weeks) from breastfeeding was 9.68%; 85% of this occurred after 6 months. Data from NVAZ also suggest that in mothers who received 5d-NVP for PMTCT but whose infants still contracted HIV the risk of breastfeeding-associated MTCT may actually be higher after 6 months postpartum than before, owing to the propensity for 5d-NVP to induce resistant virus in the mother—virus that may have less fitness to be transferred to the infant but which regains its infectivity as resistance fades after 6 months.

Issues Associated with Formula Feeding in Resource-Limited Settings

Complete and exclusive formula feeding by nature obviates the risk of transmission through breastfeeding. Indeed, in high-income settings such an approach to infant feeding is the standard of care in the presence of maternal HIV infection. Yet in resource-limited settings, exclusive formula feeding is associated with several issues. Even when postnatal vertical HIV infection is dramatically reduced or eliminated by exclusive formula feeding, study data are mixed as to the overall infant survival benefits compared with breastfeeding. A randomized controlled trial conducted in a well-resourced PMTCT setting in urban Kenya where mothers had access to clean water, free and ready supplies of formula, and strong support by health workers showed a 40% lower risk of HIV transmission in the formula-fed versus the breastfed group, but findings showed similar 24-month mortalities. The DITRAME PLUS study carried out in Cote d’Ivoire showed a similar outcome. Also looking at an urban setting with strong support, DITRAME PLUS allowed women a choice of formula feeding or exclusively breastfeeding their infants with early weaning. Those who chose to formula feed were given free replacement feeds and supplies for 9 months. There were no significant differences in rates of infant illness and death at 24 months between formula-fed and breastfed infants, lending further support to the notion that where women have access to clean water, free transport to health care facilities and free health care, free formula and feeding supplies, and bountiful support, safe formula feeding can be accomplished in an overall resource-limited setting. However, other studies in resource-limited settings have shown serious morbidity and mortality risks to be associated with formula feeding. In Botswana’s Mashi trial, cumulative all-cause mortality at 7 months was significantly higher (9.3% versus 4.9%, p=0.003) in infants randomly assigned to formula feeding versus those assigned to breastfeeding plus zidovudine, and HIV-free survival at 18 months was equivalent between the two groups, showing that the early mortality increase seen with formula feeding negates the benefits of reduced HIV transmission. Data from a Kenyan study showed higher early mortality (11% versus 9%) in formula-fed infants, and that from a South African study showed cumulative 3-month mortality in infants given replacement feeds of 15.1%, whereas the corresponding rate in exclusively breastfed infants was only 6.1%. And in the first quarter of 2006 more than 22,000 Botswanan infants experienced diarrhea (compared with 9,166 in the same period in 2005) and the number of deaths in children younger than 5 years increased by 20-fold. Almost all the deaths were in nonbreastfed infants, suggesting a lack of protective immunity in formula versus breastfed infants, a finding consistent with the long-appreciated benefit ascribed to breastfeeding of transfer of maternal mucosal protective immunity.

Importance of and Barriers to Avoiding Mixed Feeding

The risk of breastfeeding transmission varies by whether breastfeeding is exclusive (taking breast milk only, plus oral medicines, if required) or mixed (supplementing with non-breast milk liquids or solids). Several studies have associated mixed breastfeeding with increased risks of transmission compared with exclusive breastfeeding. Data extracted from two randomized controlled trials of the effects of vitamin A supplementation on MTCT (no effect seen) indicate approximately a threefold risk of mixed feeding compared with exclusive breastfeeding. A recently published large intervention cohort study from KwaZulu Natal, South Africa, found a twofold increased risk of transmission by age 6 months in infants who had been uninfected at age 6 weeks but were subject to mixed feeding with milk formula in addition to breast milk and found an 11-fold increase in risk if the mixed feeding included solids (generally home-prepared cereal or commercial infant porridges). Reasons hypothesized to increase risk of transmission among infants who mix feed include increased risk of maternal mastitis, which causes an increase in breast milk viral load, as well as the
introduction of proteins to the infant’s intestinal tract, which may provoke inflammation reducing the intestinal tract’s intrinsic integrity.

Complicating matters is the fact that mixed feeding is the most common form of breastfeeding worldwide and that even mothers who express a desire to breastfeed exclusively generally find it difficult to consistently do so. Data from two studies in South Africa and Zimbabwe that examined infant feeding and MTCT of HIV showed only 26% and 8% of infants, respectively, still being breastfed exclusively at 3 months. In the NVAZ studies, exclusive breastfeeding was common early (99% at week 1, 90% at week 6) but dropped to only 56% by age 3 months and further to 3% by age 6 months.

Several factors probably influence the difficulty women generally have in maintaining either exclusive breastfeeding or exclusive formula feeding. Studies in several different types of communities in South Africa suggest that neither exclusive breastfeeding nor exclusive nonbreastfeeding are the cultural norms in most African settings; indeed, this is probably also the case in a wide range of resource-limited settings outside Africa.

In one study set in the context of South Africa’s PMTCT program (where women are counseled to choose either exclusive breastfeeding with early weaning at 4-6 months or exclusive formula feeding with free infant formula provided until 6 months), 80% of women who had chosen exclusive breastfeeding had introduced other liquids in the first month because of pressures placed on them by the family. In the same study, nearly all the mothers reported periods when no formula was available from clinics, as well as high rates of confusion regarding their choice of infant feeding, a finding that suggests a lack of adequacy in initial counseling and community health worker follow-up. Also, mothers reported a lack of comfort with disclosing their HIV-positive status, even within the family—a finding shown consistently to be associated with low rates of adherence to multiple PMTCT interventions, including adherence to ARVs, and here to adherence to exclusive formula feeding.

And yet, quality data from the intervention cohort study in KwaZulu Natal showed that, with good support, HIV-infected women in a resource-limited setting can develop both appropriate and ideal feeding practices and sustain either exclusive breastfeeding for 6 months, as well as carry out a rapid wean, or exclusive formula feeding (and thus not the deleterious mixed feeding described earlier). In this study, mothers and infants were visited three or four times in the first 2 weeks of life and every 2 weeks thereafter until the infant was aged 6 months. Counselors and clinic nurses were tasked specifically with supporting mothers in one form of exclusive feeding or the other. Median duration of exclusive breastfeeding was 159 days, and 67% of mothers were still exclusively breastfeeding at 3 months, supporting the notion that with adequate support, exclusive breastfeeding can be achieved. The rate of transmission at 26 weeks in infants who were negative at 6 weeks was 4.04% and this in the setting of predominantly clade C virus, more likely to be transmitted perinatally than the A and D clades commonly encountered in other parts of Africa.

**WHO Infant Feeding Recommendations**

The WHO recommends that mothers known to be HIV-infected (and whose infants are HIV-uninfected or of unknown HIV status) should exclusively breastfeed their infants for the first 6 months of life, introducing appropriate complimentary foods thereafter, and ceasing breastfeeding only once a nutritionally adequate and safe diet without breast milk can be provided. Mothers known to be HIV-infected should only give commercial infant formula as a replacement feed to their HIV-uninfected infants or infants who are of unknown HIV status, when specific conditions are met: that replacement feeding is acceptable, feasible, affordable, sustainable, and safe (AFASS criteria).

WHO recommends that in all cases in which mothers choose not to breastfeed from birth or for any reason discontinue breastfeeding later, they should be provided with specific guidance and support for at least the first 2 years of the child’s life to ensure adequate replacement feeding. Because the cessation of breastfeeding is a time of increased risk to the infant in the form of increased transmission risk from mixed feeding and negative nutritional consequences from the withdrawal of this primary food source, WHO recommends that specific guidance and support be made available to mothers at the time of weaning, including specific assistance with avoiding malnutrition and poor breast health.
Quality Infant-Feeding Counseling and Support Is Critical

The quality of infant-feeding counseling given to mothers for whom replacement feeding is technically an option (such as in programs as Botswana’s and South Africa’s where free formula milk is available) must be improved. Deciding what the AFASS criteria mean in field operation is challenging, and some evidence suggests that more specific criteria should be applied when advising an HIV-infected woman on which choice of feeding strategy is best for her and her infant. Researchers in South Africa recently looked at factors that were associated with improved infant HIV-free survival among women choosing to formula feed in three sites across South Africa and found three such factors: piped water in the home; electricity, gas, or paraffin for fuel; and disclosure of HIV status. Of 311 women who met these criteria for formula feeding, 95 (30.5%) chose to breastfeed. Of 289 women who did not meet these criteria, 195 (67.4%) chose to formula feed. Infants of women who could have formula fed under these criteria were needlessly exposed to the risk of HIV infection. Even worse, infants of women who chose to formula feed without fulfilling the criteria had the highest risk of HIV transmission and/or death, with a hazard ratio of 3.63. Including an assessment of individual and environmental criteria in support of appropriate infant feeding choices when counseling mothers may improve the operational effectiveness of the WHO’s infant feeding guidelines.

What AFASS Criteria Should Mean in the Field

Recently, in Rapid Advice on HIV and Infant Feeding: Revised Principles and Recommendations, November 2009, WHO clarified in “everyday language” what AFASS criteria should mean in the field. This is summarized in Table 4.

Other Options for Infant Feeding

WHO lists other infant feeding options, including home-modified animal milk and heat-treated breast milk, as interim feeding methods appropriate for some instances. In many developing countries, HIV-positive mothers are often aware that exclusive breastfeeding has been recommended until the child is 6 months of age, and thus they wean when the child reaches that age. Many of these mothers still have not met AFASS criteria but find themselves in a position where they cannot afford replacement feeds but have already weaned. Modified (boiled) animal milk is sometimes the only economically viable milk-based nutritional option for these mothers (although it is not recommended for infants less than 6 months of age). Many mothers have access to animal milk at a fraction of the price of formula or can access it for free because of animal ownership. In such situations, boiled animal milk may be utilized as part of a diet providing adequate micronutrient intake.

For heat-treated breast milk, WHO lists two heating methods: direct boiling and pasteurization. Both options, however, are problematic. Direct boiling causes significant degradation of breast milk’s nutritional properties, whereas the pasteurization method commonly used in breast milk bank centers requires temperature gauges and timing devices not typically available in many resource-limited communities. Flash-heating, a simpler pasteurization method that is technically more feasible for resource-limited communities than traditional pasteurization, was recently studied in a cohort of HIV-positive mothers in a periurban settlement in South Africa. In this study, detectable HIV was found the breast milk samples of 26 (31%) of 84 mothers. After flash-heat treatment all samples showed undetectable levels of cell-free HIV. With the simplicity of flash-heat treatment of breast milk, it has been suggested as an option for use during times of increased transmission risk, as during episodes of mastitis or during the transition from exclusive breastfeeding to replacement feeds or the addition of complementary foods. Flash-heat-treated breast milk retains breast milk’s nutritional and immunologic properties, critical elements lost by

<table>
<thead>
<tr>
<th>Table 4. Conditions needed to safely formula feed</th>
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<tbody>
<tr>
<td>1. Safe water and sanitation are assured at the household level and in the community, and,</td>
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<tr>
<td>2. The mother or other caregiver can reliably provide sufficient infant formula milk to support normal growth and development of the infant, and,</td>
</tr>
<tr>
<td>3. The mother or caregiver can prepare it cleanly and frequently enough so that it is safe and carries a low risk of diarrhea and malnutrition, and,</td>
</tr>
<tr>
<td>4. The mother or caregiver can, in the first six months, exclusively give infant formula milk, and,</td>
</tr>
<tr>
<td>5. The family is supportive of this practice, and,</td>
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<tr>
<td>6. The mother or caregiver can access health care that offers comprehensive child health services</td>
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</table>
infants during weaning and necessary until the infant has established adequate replacement feeding.

**ARV Drugs for Preventing HIV Transmission During Breastfeeding**

Much recent attention has been given to other means of reducing the risk of mother-to-infant HIV transmission during lactation. Results from studies carried out in breastfeeding populations (HIVNET 012, PETRA, SAINT) have demonstrated efficacy in reducing MTCT without a reduction in maternal viral load (i.e., a prepartum course of ARVs of sufficient length). However, the regimens used in these studies did not address prevention of late breastfeeding transmission after the first few weeks of life—transmission described earlier to be a significant contributor to overall MTCT in breastfeeding populations.

Other interventions that do potentially address late breastfeeding-associated transmission of HIV, including prophylactic ARV administration to the uninfected infant during breastfeeding and the administration of HAART to mothers while breastfeeding, have been well-studied. Animal data from newborn macaques demonstrate the efficacy of tenofovir in preventing experimentally-induced simian immunodeficiency virus (SIV) infection, including when very high SIV doses and doses of partially tenofovir-resistant SIV were given.

Additional information on the efficacy of ARVs administered during breastfeeding in preventing breastfeeding-associated MTCT of HIV comes from several sources, including the Mashi trial and several extended NVP studies in breastfeeding infants.

**Mashi Trial**

Conducted in Botswana, the Mashi trial was a randomized 2 × 2 factorial clinical trial for HIV-infected pregnant women and their infants. It was designed to compare interventions for both preventing perinatal HIV transmission and reducing postnatal HIV infection and mortality. The postnatal portion of Mashi compared the efficacy and safety of breastfeeding plus infant ZDV prophylaxis for 6 months to formula feeding from birth plus 1 month of infant ZDV. A total of 1179 infants were studied, and points evaluated were HIV infection by age 7 months and HIV-free survival by 18 months. The study also evaluated safety in the form of occurrence of infant adverse events by 7 months of age. The 7-month

HIV infection rates were 5.6% in the formula-fed group and 9.0% in the breastfed-plus-ZDV group (p = 0.04). Cumulative mortality or HIV infection rates at 18 months were 13.9% formula fed and 15.1% breastfed plus ZDV (p = 0.60). Infant mortality at 7 months was significantly higher for the formula-fed group (9.3%) versus the breastfed-plus-ZDV group (4.9%; p = 0.003), but this difference faded after 7 months to where time-to-mortality distributions through age 18 months were not significantly different. Conclusions of the Mashi trial were that breastfeeding with ZDV prophylaxis for 6 months was not as effective as formula feeding in PMTCT but was safer in the short term (to 7 months). Both strategies had comparable HIV-free survival at 18 months. Given the significant number of infant HIV infections that occurred after 1 month of age in the breastfed-plus-ZDV group compared with the formula-fed group, the study authors concluded they could not recommend extended infant ZDV prophylaxis for prevention of breastfeeding-related MTCT, despite the intervention being shown to be feasible.

**Extended Nevirapine Regimens for Breastfeeding Infants**

Recent work from sub-Saharan Africa and India has demonstrated that an extended course of NVP given to breastfeeding infants reduces both breastfeeding-associated HIV transmission and infant mortality when compared with Sd-NVP regimens, while demonstrating comparable safety.

Between 2001 and 2007, the SWEN studies enrolled nearly 2,000 mother-infant pairs in three coordinated studies in Ethiopia, India, and Uganda. When compared with infants receiving the local standard of care (Sd-NVP to mother during labor and to infant shortly after birth in all three settings), infants receiving the study regimen of Sd-NVP (2mg/kg) shortly after birth plus a daily dose of NVP (5mg) from days 8 to 42 (previous studies having shown that Sd-NVP shortly after birth protects against breastfeeding-associated HIV transmission for several days) had significantly lower combined rates of HIV infection or death at both 6 weeks (3.7% versus 6.4%) and 6 months of life (8.0% versus 11.0%).

A separate study, performed in Malawi (PEPI-Malawi) and having enrolled 3,276 mother-infant pairs between 2004 and 2007, investigated whether a 14-week course of NVP (2mg/kg/day during second week of life, then
4mg/kg/day during weeks 3-14) alone or in combination with ZDV could reduce HIV transmission and death in breastfeeding infants of HIV-infected mothers more than Malawi's current standard of care for infants of Sd-NVP plus 1 week of ZDV. The combined rate of HIV infection or death for infants receiving the standard of care was 10.6% at 9 months, compared with 5.2% for extended NVP alone and 6.4% for extended NVP plus ZDV.

As a result of the data derived from extended infant NVP studies, WHO recently endorsed extended courses of NVP for breastfeeding infants, as detailed in Table 3.

**HAART to Mothers During Breastfeeding**

Another approach to reducing breastfeeding-associated MTCT of HIV involves administering ARVs to HIV-infected mothers during breastfeeding. It is logical that for an infant to become infected via breast milk there must be HIV present in the breast milk the infant consumes. Mothers with advanced clinical stage, lower CD4 counts, and higher serum viral loads have higher breast milk viral loads, and there is a well-demonstrated propensity for MTCT to be related to these factors. Data from the DREAM project in Mozambique discussed earlier show that in women receiving HAART (zidovudine, lamivudine, and nevirapine) from as early as 28 weeks gestation to 1 month postpartum, breast milk viral loads were significantly lower than in a comparison group of untreated women (2.3 log versus 3.4 log at delivery and 1.9 log versus 3.6 log at day 7). In this study, breast milk levels of ARVs were the same or higher than serum levels. Whether this or the reductions seen in breast milk HIV RNA would be similar with other ARV regimens is not known.

The DREAM project looked further at whether providing HAART during breastfeeding (in mothers who otherwise would not have qualified for HAART on the basis of clinical stage or CD4 count) was associated with a reduction in MTCT. In a Mozambican cohort studied between 2005 and 2006, women (otherwise nonqualifiers for HAART) receiving HAART from as early as the 25th week of pregnancy through up to 6 months of breastfeeding were compared with a cohort of women with similar characteristics who also received HAART similarly but chose to formula feed. Endpoints evaluated were HIV MTCT rates, infant morbidity, and mortality. At age 1 month 4 (1.2%) of 341 breast fed infants had contracted HIV, whereas 7 (0.8%) of 809 formula-fed infants had contracted HIV. At age 6 months, HIV transmission rates were 2 (0.8%) of 251 among breastfed infants and 15 (1.8%) of 809 among formula-fed infants, a difference that was non-statistically significant (p = 0.38). Nutritionally, both cohorts did better than the general infant population, as reflected by greater observed Z scores (a measure of nutritional status) in the study populations versus the general infant population. Rates of anemia were also lower than in the general infant population. Mortality rates, too, were lower than the general Mozambican infant population (101 per 1000 person-years): at age 6 months were 27/1000 person-years among formula-fed infants and 28.5 per 1,000 person-years among breastfed infants. Key conclusions of this study were that providing HAART to mothers in the third trimester and during breastfeeding was both safe and efficacious, with MTCT rates comparable to those seen in high-income countries and no additional risk of late postnatal HIV transmission to the infant by age 6 months.

WHO has recently endorsed the use of maternal triple ARV prophylaxis during breastfeeding, as outlined in Table 3. Indeed, where such strategies are available to breastfeeding mothers, WHO recommends continuing breastfeeding for up to 12 months, including after introduction of complementary foods when infants turn 6 months.

**Ineffective PMTCT Approaches**

**Vaginal Cleansing**

In resource-limited settings, where cost, personnel, and other logistic factors inhibit the scaleup of effective testing/ARV-based interventions, there has been much interest in low-cost, safe, and simple interventions that may be either used alone or in concert with ARV-based approaches to PMTCT. One such method that has been studied is the use of vaginal disinfection. Early studies confirmed the safety of disinfection of the vagina with aqueous chlorhexidine during labor, and the procedure was subsequently shown to reduce neonatal morbidity and mortality caused by Group B streptococci. In vitro, chlorhexidine at a concentration of 0.2% inactivates HIV-1.

A study in Malawi looked at whether vaginal cleansing with 0.25% chlorhexidine solution every 4 h during labor and washing the baby with chlorhexidine at birth was associated with a reduction in MTCT. Whereas global
MTCT was not affected by the procedure, in a subset of women with time since rupture of membranes greater than 4 hours, MTCT was significantly lower.

Whereas the Malawi study was performed using cotton wool soaked with chlorhexidine, a study in Kenya repeated the Malawi protocol with slight modifications. Disinfection was carried out every 3 h and via lavage rather than cotton wool sponging. This approach yielded no difference in either rates of global MTCT or intrapartum MTCT. A similar approach using benzalkonium chloride also failed to show a reduction in MTCT.

**Vitamin Supplementation**

Maternal nutritional factors may play a role in MTCT. Several studies have evaluated the contribution of maternal micronutrient levels, particularly vitamin A, to transmission risk. Vitamin A plays a key role in maintaining the surface integrity of the mucosa, and vitamin A deficiency is associated with immunologic alterations, including diminished CD4+ cell number and function. A study in Durban, South Africa, examined whether vitamin A supplementation was associated with reduced MTCT. Women were randomized to receive either vitamin A supplements or a placebo. The two groups showed no difference in the risk of HIV infection by 3 months of age. There was also no difference in overall fetal mortality. However, there were significantly fewer preterm births in the vitamin A group than in the group that received the placebo. Also, among the women who had preterm deliveries, those assigned to the vitamin A group were less likely to transmit HIV than those assigned to the placebo group.

Two other studies from Africa, looking at either vitamin A or multivitamin supplementation, have confirmed these findings. None of the three studies showed that vitamin supplementation was effective in reducing overall MTCT. However, all three showed that vitamin supplementation reduced adverse pregnancy outcomes. Multivitamin supplements are inexpensive and easy to administer and are recommended for HIV-infected pregnant women.

In one study carried out in a periurban South African setting, maternal multivitamin use was significantly correlated with increased levels of HIV RNA in the mothers’ breast milk. The clinical significance of this finding is not clear, but to date there have not been reports of maternal multivitamin use being linked to increased rates of breastfeeding-associated MTCT. Most clinicians recommend continuing to supplement lactating mothers with multivitamins, particularly given the well-appreciated nutritional stress that breastfeeding puts on mothers.

**HIV-2**

Throughout this chapter, when we have used the term “HIV,” we have generally referred to HIV-1. HIV-1 is far more common and geographically distributed than HIV-2, and most study data cited here refer to HIV-1. Yet HIV-2 infection also has consequences, and PMTCT of HIV-2 deserves special commentary.

Although transmitted in the same manner as HIV-1, data indicate HIV-2 to be much less transmissible from mother to child. Among breastfed infants and without any interventions, HIV-2 has rates of MTCT in the 0%-4% range. HIV-2 is endemic in West Africa, where testing for both HIV-1 and HIV-2 is recommended for PMTCT programs. A key feature of HIV-2 as relates specifically to PMTCT regimens recommended by the WHO for HIV-1 in resource-limited settings is that NNRTI drugs, including nevirapine, are not effective against HIV-2. HIV-2 may progress to AIDS in a similar fashion to HIV-1, although typically progression is much slower. When a woman living with HIV-2 infection requires HAART for her own health, a regimen of triple NRTIs is recommended rather than an NNRTI-based regimen (using nevirapine or efavirenz), because HIV-2 is inherently resistant to NNRTIs. Similarly, when a pregnant woman does not meet HAART treatment criteria for her own health she should be provided with ARV prophylaxis against MTCT.

The recommended regimen for ARV prophylaxis against MTCT in HIV-2-infected women is ZDV starting at 28 weeks’ gestation or as soon as is feasible thereafter and ZDV during labor. Because no nevirapine is given during labor (because of NNRTIs’ inherent inactivity versus HIV-2), the mother does not need ZDV and 3TC during labor, nor does she need the postpartum course of ZDV plus 3TC given to HIV-1-infected mothers who receive SD-NVP to prevent NNRTI resistance. Infants born to HIV-2-infected mothers should receive ZDV for 7 days after birth. WHO recommendations for infant feeding in the presence of maternal HIV-1 infection also apply in the presence of HIV-2 infection. In women coinfected with both HIV-1 and HIV-2, the recommendations detailed...
for PMTCT in the presence of HIV-1 infection should be followed; HIV-1 is much more likely to be transmitted from mother to child than HIV-2 (Table 5).

**WHO PMTCT Component 4: Care, Treatment, and Support for Mothers Living With HIV, Their Children, and Families**

Traditionally, PMTCT has been focused on component 3 of the WHO four-component strategy—the prevention of transmission from mothers living with HIV to their children. As well, until recently PMTCT programs did not offer mothers much beyond these interventions. Yet it is well appreciated that the longitudinal health of a mother directly affects the health and survival of her child—HIV infected or not. Providing care, treatment, and support for mothers and their families after component 3 interventions, therefore, is critical to the ultimate goal of PMTCT: an HIV-free generation with a significant reduction in the number of children orphaned as a result of HIV/AIDS.

The concept of a continuum of care for maternal, newborn, and child health has been discussed in many forums and settings over the past recent years. Studies have suggested that high utilization and quality of essential packages of integrated, continuum-focused services could avert up to two-thirds of child and neonatal deaths in 60 priority countries worldwide, as well as assist major reductions in maternal mortality. Included in these proposed packages of services is a comprehensive approach to PMTCT, including linkages from prevention of HIV infection through diagnosis, PMTCT, to infant diagnosis and family-based HIV/AIDS care and treatment.

Indeed, for HIV-infected women, PMTCT programs offer an ideal opportunity to link diagnosis and PMTCT services with ongoing, longitudinal care. Although health systems are weak in many of the locales that have the highest prevalence of HIV, up to 70% of women in these locales attend at least one ANC visit. Using this encounter—possibly the only one a woman may ever make with the health system—as an opportunity to establish a longitudinal, family-based relationship with the mother is critical.

Opportunity exists for making PMTCT services a gateway for HIV-infected women and their families to longitudinal, comprehensive HIV care and treatment. Where this has been accomplished, even in part, evidence suggests a tangible benefit to global PMTCT success. In South Africa’s Western Cape, all HIV-infected women identified via the province’s PMTCT program are stratified into “treatment” or “prophylaxis” groups by clinical stage and CD4 count, as described earlier. Treatment groups are fast-tracked to HAART initiation via a linkage to ART services provided by the PMTCT program. This linkage, and the more effective care provided through it, with less loss to follow-up than when the referral to ART is non-linked, adds approximately 6%-8% to overall PMTCT efforts in the province and facilitates the entry of women into long-term HIV treatment. This approach can be key in obtaining good outcomes: for both adults and children, late entry into care is associated with poorer outcomes in response to HAART.

**Family-Based Care**

However, even in this improved system there is significant loss to follow-up because mothers still must move from one site (PMTCT clinic) to another (ART clinic). To combat this, cutting-edge models such as those created in Africa by MSF, ICAP, and BIPAI, among others, have begun to show the feasibility of offering longitudinal family-based care with mothers identified as HIV-positive during ANC screening as their index cases. Especially when such care can be delivered in one setting, even more so all family members together during one visit, rates of uptake of HIV/AIDS diagnosis, prevention, and care and treatment services can be maximally affected on a family- and community-wide basis. Particularly for HIV-infected children, a family-based approach may realize improved access to care-and-treatment services and reduce the risk of defaulting from care than if parents’ and children’s services are delivered separately. Indeed, there is growing

**Table 5. PMTCT considerations in the presence of HIV-2 Infection**

<table>
<thead>
<tr>
<th></th>
<th>Maternal ART indicated</th>
<th>Maternal ART not indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mother</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antepartum</td>
<td>AZT+3TC+ABC</td>
<td>AZT starting at 28 weeks gestation or as soon as feasible thereafter</td>
</tr>
<tr>
<td>Intrapartum</td>
<td>AZT+3TC+ABC</td>
<td>AZT</td>
</tr>
<tr>
<td>Postpartum</td>
<td>AZT+3TC+ABC</td>
<td></td>
</tr>
<tr>
<td><strong>Infant</strong></td>
<td>AZT x 7 days</td>
<td>AZT x 7 days</td>
</tr>
</tbody>
</table>
sentiment that, on the whole, PMTCT programs in resource-limited settings will ultimately not be able to duplicate the success seen in better-resourced settings without a successful merging of specific mother-child strategies with longitudinal care and treatment services.

**Scaling Up**

The recently released *Guidance to Global PMTCT Scale-up* promotes a country-targeted approach to reaching universal access to services. Key in the *Guidance* is the above-mentioned integration of all four components of the WHO PMTCT strategy into a comprehensive, longitudinal model of care.

The *Guidance* urges international coordinating bodies, such as WHO, UNAIDS, and UNICEF; national governments; and integral international nongovernmental organization partners (of which BIPAI is one) to work together in a common strategy to realize soon universal access to PMTCT services worldwide, on the way to an AIDS-free generation by 2015.

The *Guidance* offers 10 guiding principles in this regard:

1. Urgent scaleup to achieve national coverage and universal access
2. Country ownership and accountability
3. Emphasizing the participation of people living with HIV and communities
4. Strong, coordinated, and sustained partnerships
5. Aiming for both effectiveness and quality
6. Delivering a comprehensive package of services based on the United Nations four-element strategy, including links between services and integration with maternal, newborn, and child health services
7. Giving priority to providing ARV therapy for treating eligible pregnant women
8. Family-centered longitudinal care
9. The importance of male involvement
10. Improving maternal and child survival

**Conclusion**

The benefits of PMTCT are both obvious and substantial. Well supported with evidence and experience, PMTCT interventions offer an opportunity to significantly reduce the scope of the pediatric HIV pandemic. Extending the success seen in resource-rich settings to resource-limited locales is both a necessary and urgent ethically sound goal. PMTCT interventions do not exist in isolation from one another. Scaleup of the integration of all four components of the WHO approach into a family-based longitudinal care model offers the best opportunity for realizing the promise that PMTCT offers to individuals, families, and communities around the globe.

**References**

health and interventions to reduce perinatal HIV transmission in the United States. 2 November 2007.


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**PMTCT timeline**

<table>
<thead>
<tr>
<th>20 weeks</th>
<th>22 weeks</th>
<th>24 weeks</th>
<th>28 weeks</th>
<th>40 weeks</th>
<th>Birth to 4 week postpartum</th>
<th>Birth to 12 months postpartum</th>
<th>Ongoing longitudinal HIV/AIDS care and treatment for mother and affected family members</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient presents to ANC for voluntary care and testing and then draw CD4</td>
<td>Encourage disclosure, readiness for ART, start cotrimoxazole and multi-vitamins</td>
<td>Review CD4 results with patient—decide on HAART versus ARV prophylaxis</td>
<td>Start either HAART or ART prophylaxis</td>
<td>At onset of labor—HAART continues versus ART prophylaxis regimen; Delivery of newborn with safe delivery practices</td>
<td>Postpartum ART for mother and baby</td>
<td>Postpartum infant feeding counseling</td>
<td>Lifetime</td>
</tr>
<tr>
<td><strong>Until 4 weeks prior to delivery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This timeline presents the ideal for PMTCT: Early recognition of HIV-positive status, early evaluation of CD4 and decision as to HAART versus ARV prophylaxis as well as intrapartum, postpartum, and longitudinal care for mother, infant, and family. A key message is the realization that a delay in initiating the timeline (diagnosis of HIV positive, entry of mother into PMTCT services) delays all subsequent events. As the text of the chapter notes, ideally mothers receive at least 4 weeks of ART prior to delivery. This goal becomes difficult to achieve—and PMTCT efficacy suffers—when the initiation of the timeline is delayed.


72. HIV Prevention Trials Network. HPTN 046: Phase III Trial to Determine the Efficacy and Safety of an Extended Regimen of Nevirapine in Infants Born to HIV Infected Women to Prevent Vertical HIV Transmission During Breastfeeding.


