Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

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### General Considerations for Choice of Infant Prophylaxis

All HIV-exposed infants should receive postpartum antiretroviral (ARV) drugs to reduce perinatal transmission of HIV. The most important contributors to the risk of HIV transmission to an HIV-exposed infant are whether the mother has received antepartum/intrapartum antiretroviral therapy (ART) and her viral load; the risk of transmission is increased if maternal antepartum/intrapartum treatment was incomplete or not received and if maternal viral load is detectable, particularly if it is very high. There is a spectrum of transmission risk that depends on these and other maternal and infant factors, including mode of delivery, gestational age at delivery and maternal health status.

In all situations, infant prophylaxis should be initiated as soon as possible after delivery.

The interval during which infant prophylaxis can be initiated and still be of benefit is undefined; however, most studies support providing prophylaxis as early as possible after delivery.\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)

In the following sections, we present available data and recommendations for management of infants born to mothers who:

- Received antepartum/intrapartum ARV drugs with effective viral suppression
- Are at higher risk of transmitting HIV infection to their infant including those who
  - Received neither antepartum nor intrapartum ARV drugs
  - Received only intrapartum ARV drugs
  - Received antepartum and intrapartum ARV drugs but who have detectable viral load at delivery, particularly if delivery was vaginal

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**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion
• Have unknown HIV status
• Have known ARV drug-resistant virus.

**Infant Zidovudine Prophylaxis**

Zidovudine was shown in the PACTG 076 study to effectively reduce perinatal HIV transmission and is recommended for all neonates born to mothers with HIV infection. The optimal minimum duration of neonatal zidovudine prophylaxis has not been established in clinical trials. A 6-week infant zidovudine regimen was studied in PACTG studies 076 and 316 (both performed during an era when a greater proportion of women did not receive antenatal ART). However, in the United Kingdom and many other European countries, a 4-week neonatal zidovudine prophylaxis regimen is now recommended for infants born to mothers who have received ART regimens during pregnancy and have viral suppression, with no apparent increase in the overall HIV perinatal transmission rate. In addition, a 4-week zidovudine regimen has been reported to allow earlier recovery from anemia in otherwise healthy infants compared with the 6-week zidovudine regimen.

Therefore, Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission (the Panel) recommends a 4-week neonatal zidovudine prophylaxis regimen for full-term infants if the mother has received standard ART during pregnancy with sustained viral suppression (usually defined as confirmed HIV RNA level below the lower limits of detection of an ultrasensitive assay) and there are no concerns related to maternal adherence. In all other cases, the infant should receive a 6-week course of zidovudine as part of a combination infant prophylaxis regimen. Dosing recommendations for zidovudine are available for premature infants and an intravenous preparation is available. Table 7 shows recommended zidovudine dosing based on gestational age, birthweight, and the status of maternal antepartum ARV regimens.

**Infant Combination Antiretroviral Prophylaxis**

A combination infant prophylaxis regimen is recommended for infants at higher risk of HIV acquisition including those born to HIV-infected women who have not received antepartum or intrapartum ARV drugs or have received only intrapartum ARV drugs or have received antepartum ARV drugs but do not have viral suppression near delivery.

There is a paucity of data from randomized clinical trials to guide the optimal selection of an infant combination prophylaxis regimen. To date, the NICHD-HPTN 040/PACTG 1043 study is the only randomized clinical trial of combination prophylaxis in infants at high risk of HIV acquisition. In this study, 1,746 formula-fed infants born to HIV-infected women who did not receive any ARV drugs during pregnancy were randomized to 1 of 3 infant prophylaxis regimens: the standard 6-week zidovudine regimen; 6 weeks of zidovudine plus three doses of nevirapine given during the first week of life (first dose at birth–48 hours, second dose 48 hours after first dose, and third dose 96 hours after second dose); and 6 weeks of zidovudine plus 2 weeks of lamivudine/nelfinavir. Forty-one percent of mothers received zidovudine during labor. The risk of intrapartum transmission was significantly lower in the 2- and 3-drug arms (2.2% and 2.5%, respectively, vs. 4.9% for 6 weeks of zidovudine alone; \( P = .046 \) for each experimental arm vs. zidovudine alone). Although transmission rates with the 2 combination regimens were similar, neutropenia was significantly more common with the 3-drug regimen than with the 2-drug or zidovudine-alone regimen (27.5% vs. 15%, \( P < .0001 \)). Based on this study, the 2-drug regimen of 6 weeks of zidovudine plus 3 doses of nevirapine has previously been recommended by the Panel for infants at higher risk of HIV acquisition.

Data from Europe and the United States indicate increasing use of combination infant prophylaxis in HIV-exposed infants. In the United Kingdom and Ireland, use increased from 9% of HIV-exposed infants in 2001 to 2004 to 13% between 2005 to 2008 and in a poll of 134 U.S.-based providers, 62% reported using combination prophylaxis in high-risk infants. However, interpretation of these observational studies are complicated by the definition of combination prophylaxis, dosages of drugs in the regimen, and combining heterogeneous combination prophylaxis regimens to compare safety and efficacy with zidovudine monotherapy. Many include single-dose nevirapine in combination with another ARV, usually zidovudine, as

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combination therapy. Most do not report whether nevirapine was administered at the prophylaxis dose or at a higher dose needed for treatment of HIV infection.

More recently, many experts are recommending a three-drug infant prophylaxis regimen using treatment doses of ARV drugs in infants at high risk of HIV acquisition. Enthusiasm for this approach followed a case of a “functional cure” of HIV in an infant reported in 2013. The infant was born by vaginal delivery at 35 weeks’ gestation to a woman who received no prenatal care and was diagnosed as HIV-infected by expedited testing during labor; delivery occurred before maternal intrapartum ARV drugs could be given. At age 30 hours, the infant initiated a regimen of zidovudine, lamivudine, and nevirapine (the latter drug administered at a higher therapeutic dose rather than standard prophylactic dosing). The infant was found to have a positive HIV DNA polymerase chain reaction (PCR) in a sample obtained at age 30 hours and an HIV RNA level of 19,812 copies/mL on an HIV RNA PCR assay performed at age 31 hours. Based on these tests, the infant was continued on treatment for HIV infection, thought to be acquired in utero. At age 18 months, the mother discontinued combination therapy; levels of plasma RNA, proviral DNA, and HIV antibodies remained undetectable in the child for over 2 years on no therapy. Unfortunately, virologic rebound was identified shortly before the child turned 4 years of age. Of interest, another case of virologic rebound following 4 years of suppression in an infant treated since birth has subsequently been reported.

Further support of a 3-drug infant prophylaxis regimen comes from Canadian investigators who have reported outcomes in 136 infants considered at high risk of HIV acquisition (born to HIV-infected women who had detectable viral load and/or poor adherence to therapy prior to delivery) who received treatment doses of triple ARV prophylaxis within 72 hours of birth. Of the infants born into scenarios associated with higher risk of HIV transmission, 12 were found to be HIV-infected and no major toxicities were identified. There was no control group to permit comparison of safety or efficacy of this approach relative to single-drug or two-drug prophylaxis regimens. Another Canadian study compared the safety of combination prophylaxis using treatment doses of ARV drugs in 148 infants with high-risk exposure (incomplete maternal virologic suppression at delivery or, in the absence of maternal viral load results, a maternal history of incomplete adherence or non-adherence to ART, or late pregnancy initiation of ART) and 145 control low-risk infants who received only zidovudine. Thirty-three infants in the combination ARV group were HIV-infected, 5 with a positive HIV NAT within the first 48 hours of life, suggesting in utero infection. No infant in the low-risk zidovudine-only group was HIV-infected. The infants receiving a combination ARV regimen demonstrated more non-specific signs and symptoms (e.g., vomiting, diarrhea, rash, jitteriness, irritability) potentially attributable to medication-related adverse effects compared to none of the infants receiving zidovudine only (10.2% vs. 0%, P < .001). ARV drug treatment was also more likely to be discontinued prematurely in the infants receiving combination ARV drugs (9.5% vs. 2.1%, P = .01).

Use of ARV regimens of three drugs at treatment doses in infants is consistent with Center for Disease Control and Prevention recommendations for occupational and non-occupational post-exposure prophylaxis in adults, where risk of infection is often lower than in infants at high risk of HIV acquisition. However, there are two key safety issues related to the choice and dose of ARV drugs in these infants. First, although the use of nevirapine to prevent perinatal transmission has been found to be safe in neonates and low-birthweight infants (see Antiretroviral Drug Dosing for Premature Infants), these prophylaxis-dose regimens target trough drug levels of 100 ng/mL, with peak levels averaging 1,000 to 1,500 ng/mL. There are very limited data in infants under age 2 weeks to determine the appropriate dosing or safety of nevirapine administered at therapeutic doses designed to maintain trough drug concentrations above 3,000 ng/mL and peak levels below 10,000 ng/mL for treatment of HIV-infected individuals. Recent data from a nevirapine pharmacokinetic (PK) model and 2 observational studies suggest that nevirapine, 6 mg/kg twice daily, meets these target treatment parameters. Second, lopinavir/ritonavir is not recommended for neonates younger than age 14 days because of the potential for significant toxicity (see Short-Term Antiretroviral Drug Safety and Choice for Neonatal Prophylaxis). Therefore, the risks of this approach in terms of infant toxicity (particularly in preterm infants) and efficacy require further study before a general recommendation can be made.
There are three ongoing clinical trials investigating a three-drug infant ARV prophylaxis regimen containing zidovudine, lamivudine, and nevirapine at treatment doses shortly after birth in infants at high-risk of HIV infection (international multisite IMPAACT P1115, ClinicalTrials.gov identifier NCT02140255), or those known to be infected (BHP-074 in Botswana, NCT02369406, and the Leopard Study in South Africa, NCT02431975). Additional safety and PK data from these studies will guide future recommendations.

At this time, the Panel recommends a combination ARV prophylaxis regimen in infants at high risk of HIV acquisition. However, the Panel was unable to reach clear consensus on the specific ARV prophylaxis regimen in these infants. The NICHD-HPTN 040/PACTG 1043 study supports the recommendation of 6 weeks of zidovudine plus three doses of nevirapine at prophylactic doses given during the first week of life (first dose at birth–48 hours, second dose 48 hours after first dose, and third dose 96 hours after second dose). Many Panel members recommend a three-drug infant ARV prophylaxis regimen using treatment doses of zidovudine, lamivudine, and nevirapine, administering nevirapine at 6 mg/kg twice daily under investigation in IMPAACT P1115 as the initial regimen. This nevirapine dosage is currently under investigation in IMPAACT P1115. All infants should receive 6 weeks of zidovudine. The optimal duration of lamivudine and nevirapine is unknown. Many experts recommend continuation of nevirapine for a 6-week course while others recommend discontinuation after 2 weeks of life if HIV a nucleic acid amplification test (NAAT) is negative at birth. Table 7 provides dosing information based on gestational age, birthweight, and the status of maternal antepartum ARV regimens.

The National Perinatal HIV Hotline

The National Perinatal HIV Hotline (888-448-8765) is a federally funded service providing free clinical consultation for difficult cases to providers caring for HIV-infected pregnant women and their infants, and can provide referral to local or regional pediatric HIV specialists.

Recommendations for Infant Antiretroviral Prophylaxis in Specific Clinical Situations

Infants Born to Mothers Who Received Antepartum/Intrapartum Antiretroviral Drugs with Effective Viral Suppression

The risk of HIV acquisition is small in infants born to women who received standard ARV treatment regimens during pregnancy and labor and had undetectable viral loads at delivery. A 4-week infant zidovudine regimen is recommended in full-term infants when a mother has received standard ART during pregnancy with sustained viral suppression. In infants born to women with effective viral suppression, combining zidovudine with additional ARV drugs to reduce transmission risk is not recommended because the risk of transmission is low and any potential benefit would be very limited.

Infants Born to Mothers Who Have Received No Antepartum or Intrapartum Antiretroviral Drugs, Intrapartum Antiretroviral Drugs Only, or Who Have Received Combination Antiretroviral Drugs and Do Not Have Sustained Viral Suppression

All infants born to mothers with detectable viral load at the time of delivery, who received intrapartum ARVs only or who have received no ARVs during pregnancy or delivery are at higher risk of HIV acquisition and should receive combination ARV prophylaxis (see Infant Combination Antiretroviral Prophylaxis).\textsuperscript{5,22-26} For those women who received ARV drugs during pregnancy but have a detectable viral load at delivery, the level of viremia in the mother that would trigger the use of combination infant prophylaxis is not definitively known. In 2 large observational studies of women on combination antenatal ARV drugs, perinatal transmission rates were 0.05% and 0.3% when the mother had viral load measurements <50 copies/mL at delivery. Rates of transmission increased to 1.1% and 1.5% when viral load measurements were 50–399 copies/mL and 2.8% and 4.1% when viral load measurements were >400 copies/mL.\textsuperscript{27,28} However, there has been no study to demonstrate relative efficacy of combination infant prophylaxis compared to standard infant prophylaxis at these different thresholds of maternal viremia. While some experts would recommend infant combination
prophylaxis with any level of detectable viremia, others reserve infant combination therapy until higher levels of maternal viral load are documented. The decision to administer infant combination prophylaxis should be made following discussion with the parents weighing the risks and benefits of combination therapy.

In addition to a combination infant ARV prophylaxis regimen, scheduled cesarean delivery is recommended for prevention of perinatal transmission in women who have received antepartum ARV drugs but who have detectable viremia (HIV RNA >1000 copies/mL) near the time of delivery (see Intrapartum Care and Transmission and Mode of Delivery). In PACTG 316, transmission occurred in 0% of 17 infants when maternal HIV RNA levels at delivery were >10,000 copies/mL and delivery was by scheduled cesarean. However, not all women with detectable viremia near delivery will undergo cesarean delivery. The risk of acquisition of HIV will be higher in infants born to mothers with higher viral loads near delivery, particularly if delivery is vaginal or unscheduled cesarean.

Infants Born to Mothers with Unknown HIV Infection Status

Expedited HIV testing of mothers is recommended during labor for women with unknown HIV status and for mothers and/or infants as soon as possible after birth if expedited HIV testing was not performed during labor. Expedited test results should be available within 60 minutes. Commercially available antigen/antibody tests are preferred to those that test only for antibody. Oral fluid-based tests are not recommended for infant testing; blood or serum testing has notably better sensitivity in infants than does oral fluid testing. If expedited testing is positive, infant combination ARV prophylaxis should be initiated immediately, without waiting for the results of supplemental tests as described above. Expedited HIV testing should be available on a 24-hour basis at all facilities with a maternity service and/or neonatal intensive care, special care or newborn nursery.

A positive initial test result in mothers or infants should be presumed to indicate maternal HIV infection until standard supplemental testing clarifies maternal status. A positive HIV antibody test in an infant indicates maternal but not necessarily infant HIV infection; diagnosis of HIV infection in infants younger than age 18 months requires virologic testing using a viral NAT (includes DNA and RNA PCR and related assays). Initial positive HIV antibody tests in the mother can be confirmed using a recommended HIV-1/2 diagnostic testing algorithm. Supplemental tests should be performed on mothers (or their infants) as soon as possible after the initial positive test. If the test results on a mother (or infant) are negative, ARV prophylaxis can be discontinued. If the supplemental test results in the mother are positive or if the mother is unavailable or declines testing, an HIV NAT should be obtained urgently from the newborn to determine the infant’s HIV infection status. If the HIV NAT is positive, ARV prophylaxis should be promptly discontinued and the infant should receive treatment for HIV infection with standard ART according to the Pediatric Antiretroviral Guidelines. Clinicians should be aware of their state laws, as there is variability in the testing allowed without parental consent.

Breastfeeding should be stopped until HIV infection is confirmed or ruled out in a woman who is suspected of being HIV-infected based on an initial positive antibody or antibody/antigen test result. Pumping and temporarily discarding or freezing breast milk can be recommended. If HIV infection is ruled out, breastfeeding can resume. If HIV infection is confirmed, breastfeeding should be discontinued permanently.

Infants Born to Mothers with Antiretroviral Drug-Resistant Virus

The optimal prophylactic regimen for newborns delivered by women with ARV drug-resistant virus is unknown. ARV prophylaxis for infants born to mothers with known or suspected drug resistance should be determined in consultation with a pediatric HIV specialist before delivery or through consultation with the National Perinatal HIV Hotline (888-448-8765).

Data from the WITS study suggest that in women who have mixed zidovudine-resistant and zidovudine-sensitive viral populations, the zidovudine-sensitive virus may be preferentially transmitted. Thus, the 6-week infant zidovudine prophylaxis (along with maternal IV intrapartum zidovudine) continues to be recommended, even when maternal zidovudine-resistant virus with thymidine-associated mutations is identified.
Some studies have suggested that ARV drug-resistant virus may have decreased replicative capacity (reduced viral fitness) and transmissibility. However, perinatal transmission of multidrug-resistant virus has been reported both in the United States and in international settings. The optimal prophylactic regimen for newborns of women with ARV resistance is unknown. Therefore, ARV prophylaxis for an infant born to a woman with known or suspected drug resistance should be determined in consultation with a pediatric HIV specialist, preferably before delivery. However, there is no evidence that neonatal prophylaxis regimens customized based on presence of maternal drug resistance are more effective than standard neonatal prophylaxis regimens.

**Short-Term Antiretroviral Drug Safety and Choice for Neonatal Prophylaxis**

Infant prophylaxis with zidovudine has been associated with only minimal toxicity, consisting primarily of transient hematologic toxicity (mainly anemia), which generally resolves by age 12 weeks (see Initial Postnatal Management). Data are limited on the toxicity to infants of exposure to multiple ARV drugs.

Other than zidovudine, lamivudine is the nucleoside reverse transcriptase inhibitor (NRTI) with the most experience in use for neonatal prophylaxis. In early studies, neonatal exposure to combination zidovudine/lamivudine was generally limited to 1–2 weeks. Six weeks of infant zidovudine/lamivudine exposure also has been reported; these studies suggest that hematologic toxicity may be increased over that seen with zidovudine alone, although the infants also had in utero exposure to maternal combination therapy.

In a French study, more severe anemia and neutropenia were observed in infants exposed to 6 weeks of zidovudine/lamivudine for prophylaxis plus maternal antepartum zidovudine/lamivudine than in a historical cohort exposed only to maternal and infant zidovudine. Anemia was reported in 15% and neutropenia in 18% of infants exposed to zidovudine/lamivudine, with 2% of infants requiring blood transfusion and 4% requiring treatment discontinuation for toxicity. Similarly, in a Brazilian study of maternal antepartum and 6-week infant zidovudine/lamivudine prophylaxis, neonatal hematologic toxicity was common, with anemia seen in 69% and neutropenia in 13% of infants.

Tenofovir disoproxil fumarate (TDF) with and without emtricitabine has been investigated in several small studies to define the safety and PKs of the agents in newborns. However, at this time, TDF and emtricitabine are not generally recommended for use in infant prophylaxis by the Panel because data on appropriate dosing are limited and the safety of these agents in the neonate is not well defined.

Experience with other NRTI drugs for neonatal prophylaxis is more limited. Hematologic and mitochondrial toxicity may be more common with exposure to multiple versus single NRTI drugs.

Nevirapine is the only non-nucleoside reverse transcriptase inhibitor drug with a pediatric drug formulation and neonatal prophylactic (but only preliminary evidence of therapeutic) dosing information (see the Adult and Adolescent Antiretroviral Guidelines). In rare cases, chronic multiple-dose nevirapine prophylaxis has been associated with severe and potentially life-threatening rash and hepatic toxicity. These toxicities have not been observed in infants receiving prophylactic dosing with single-dose nevirapine, the two-drug zidovudine regimen plus three doses of nevirapine in the first week of life in NICHD-HPTN 040/PACTG 1043), or in breastfeeding infants receiving nevirapine prophylaxis daily for 6 weeks to 6 months to prevent transmission of HIV via breast milk. Resistance to nevirapine can occur, however, with exposure to nevirapine in infants who become infected despite prophylaxis.

Of the protease inhibitors, pediatric drug formulations are available for lopinavir/ritonavir, ritonavir, darunavir, tipranavir, and fosamprenavir, but their use in neonates in the first weeks of life is not recommended due to lack of dosing and safety information. In addition, lopinavir/ritonavir oral solution contains 42.4% alcohol and 15.3% propylene glycol, and enzymes that metabolize these compounds are immature in neonates, particularly preterm infants. No PK data are available for any PIs in the first 2 weeks of life. PK data are available for treatment of HIV-infected infants aged 2 to 6 weeks with lopinavir/ritonavir. Although the lopinavir area under the curve (AUC) was significantly lower with dosing 300 mg
lopinavir/75 mg ritonavir/m² body surface area twice daily than observed for infants >6 weeks of age, treatment was well tolerated and 80% of 10 infants had viral control at 6 months. Studies are ongoing but data are not yet available for infants aged <2 weeks. However, in four premature infants (2 sets of twins) started on lopinavir/ritonavir from birth, heart block developed that resolved after drug discontinuation. In studies of adults, both ritonavir and lopinavir/ritonavir cause dose-dependent prolongation of the PR interval, and cases of significant heart block, including complete heart block, have been reported. Elevation of 17-hydroxyprogesterone and dehydroepiandrosterone-sulfate has also been associated with administration of lopinavir/ritonavir compared with zidovudine in the neonatal period. Levels of 17-hydroxyprogesterone were greater in infants who were also exposed to lopinavir/ritonavir in utero compared with those exposed only in the neonatal period. Term infants were asymptomatic but three premature newborns experienced life-threatening symptoms compatible with adrenal insufficiency, including hyponatremia and hyperkalemia with, in one case, cardiogenic shock. Based on these and other post-marketing reports of cardiac toxicity (including complete atroventricular block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, adrenal dysfunction, central nervous system depression, respiratory complications leading to death, and metabolic toxicity, predominantly in preterm neonates, the US Food and Drug Administration (FDA) now recommends that lopinavir/ritonavir oral solution not be administered to neonates before a postmenstrual age (first day of the mother’s last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days. However, a recent study (ANRS 12174) randomized 1,273 infants, 615 assigned to lopinavir/ritonavir and 621 assigned to lamivudine, as prophylaxis during breastfeeding in women with CD4 T lymphocyte (CD4) cell counts above the local threshold for treatment at the time. Infant study prophylaxis was initiated at 7 days of life and only infants greater than 2 kg were randomized. Clinical and biological severe adverse events did not differ between groups suggesting that lopinavir/ritonavir is safe in term infants, 7 days of age and older. At this time, the Panel does not recommend the early use of lopinavir/ritonavir.

Raltegravir is the only integrase inhibitor with an available pediatric drug formulation. However, it is not FDA-approved for use in infants aged <4 weeks or weight <3 kg. Raltegravir readily crosses the placenta; its elimination was highly variable and extremely prolonged in some infants following maternal dosing. Raltegravir competes with bilirubin for albumin binding sites, which could increase unbound (free) unconjugated bilirubin levels in the neonate. An in vitro study has demonstrated that the effect of raltegravir on neonatal bilirubin binding is unlikely to be clinically significant unless raltegravir concentrations 50- to 100-fold higher than typical peak concentrations with usual dosing are reached. Raltegravir is currently being studied in IMPAACT P1110, a phase I multicenter trial enrolling full-term HIV-1-exposed neonates at high risk of acquiring HIV-1-infection, with or without in utero raltegravir exposure. Study design includes 2 Cohorts: Cohort 1 infants receive 2 single raltegravir doses 1 week apart; Cohort 2 infants receive daily raltegravir dosing for first 6 weeks of life. PK results from Cohort 1 were combined with that from older infants and children receiving daily dosing in a population PK model and simulations performed to develop a daily raltegravir dosing regimen under evaluation in Cohort 2. The raltegravir dosing regimen chosen and currently under investigation in Cohort 2 for infants unexposed to raltegravir in utero is: 1.5 mg/kg daily starting within 48 hours of life through day 7; 3 mg/kg twice daily aged 8 days through 28 days; 6 mg/kg twice daily after 4 weeks of age. Preliminary findings have been reported on the first 12 infants enrolled and the PK targets and safety guidelines have been met for those patients. Use of raltegravir in neonates is not recommended until adequate PK and safety data are available.
Neonatal Antiretroviral Drug Dosing

Table 7. Neonatal Dosing for Prevention of Perinatal Transmission of HIV

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dosing</th>
<th>Duration</th>
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<tbody>
<tr>
<td>ZDV</td>
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<tr>
<td>Note: Twice-daily dosing prophylaxis should be started as soon after birth as possible, preferably within 6–12 hours of delivery.</td>
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<td>For infants unable to tolerate oral agents, the IV dose is 75% of the oral dose while maintaining the same dosing interval.</td>
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<tr>
<td>≥35 Weeks’ Gestation at Birth:</td>
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<td>Birth through 4–6 weeks&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Birth to Age 6 Weeks:</td>
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<tr>
<td>• 4 mg/kg orally twice daily</td>
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<tr>
<td>Simplified Weight-Band Dosing for Infants ≥35 Weeks:</td>
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</tr>
<tr>
<td>Weight Band (kg)</td>
<td>ZDV 10 mg/mL Oral Syrup Twice Daily</td>
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<tr>
<td>2 to &lt;3 kg</td>
<td>1 mL</td>
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<td>3 to &lt;4 kg</td>
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<td>4 to &lt;5 kg</td>
<td>2 mL</td>
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<tr>
<td>≥30 to &lt;35 Weeks’ Gestation at Birth:</td>
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<td>Birth through 6 weeks</td>
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<td>Birth to Age 2 Weeks:</td>
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<tr>
<td>• 2 mg/kg orally twice daily</td>
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<td>Age 2 Weeks to 4–6 Weeks:</td>
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<tr>
<td>• 3 mg/kg orally twice daily</td>
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<tr>
<td>&lt;30 weeks’ Gestation at Birth:</td>
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<td>Birth through 6 weeks</td>
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<tr>
<td>Birth to Age 4 Weeks:</td>
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<tr>
<td>• 2 mg/kg orally twice daily</td>
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<tr>
<td>Age 4 Weeks to 6 Weeks:</td>
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<tr>
<td>• 3 mg/kg orally twice daily</td>
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Additional Antiretroviral Prophylaxis Agents for HIV-Exposed Infants Who are at High Risk of HIV Acquisition

Initiated as soon after delivery as possible

NICHD-HPTN 040/PACTG 1043 Study Regimen

NVP
In addition to ZDV as shown above

Birth Weight 1.5–2 kg:
- 8 mg dose PO (Note: No calculation is required for this dose; this is the actual dose, not a mg/kg dose.)

Birth Weight >2 kg:
- 12 mg dose PO (Note: No calculation is required for this dose; this is the actual dose, not a mg/kg dose.)

Three Doses in the First Week of Life:
1. Within 48 hours of birth
2. 48 hours after first dose
3. 96 hours after second dose

Three-Drug Infant Combination Antiretroviral Prophylaxis Regimen
This regimen is under investigation, but is already used in clinical practice by some experts

3TC
In addition to ZDV as shown above

≥32 Weeks’ Gestation at Birth:
Birth to Age 4 Weeks:
- 2 mg/kg PO twice daily
Aged 4 Weeks to 6 Weeks:
- 4 mg/kg PO twice daily

Birth through 2–6 weeks

NVP
In addition to ZDV as shown above

≥37 Weeks’ Gestation at Birth:
Birth to Age 6 Weeks:
- 6 mg/kg PO twice daily
34 to <37 Weeks’ Gestation at Birth:
Birth to Age 1 Week:
- 4 mg/kg PO twice daily
Age 1 Week to Age 6 Weeks:
- 6 mg/kg PO twice daily

Birth through 2–6 weeks<sup>b</sup>

<sup>a</sup>A 4-week neonatal ZDV prophylaxis regimen may be used when the mother has received standard ART during pregnancy with sustained viral suppression and there are no concerns related to maternal adherence. All other infants should receive a 6-week course of ZDV.

<sup>b</sup>The optimal duration of NVP is unknown. Some experts recommend continuation of NVP for a 6-week course while others recommend discontinuation after 2 weeks of life if HIV nucleic acid amplification test is negative.

Key to Abbreviations: 3TC = lamivudine; IV = intravenously; NVP = nevirapine; PO = orally; ZDV = zidovudine

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The recommended dose of zidovudine for post-exposure prophylaxis in full-term neonates is 4 mg/kg body weight orally (PO) twice daily, beginning as soon after birth as possible and preferably within 6 to 12 hours of delivery (see Table 7). \(^{25,54,70-77}\) Some PK studies suggest that the standard neonatal zidovudine dosing regimen might be excessive and associated with bone marrow and metabolic toxicity, but no alternative dosing regimens have been studied. \(^{78,79}\) If an infant is unable to tolerate oral medications, the zidovudine prophylaxis regimen can be administered IV. The zidovudine dosing requirements differ for premature infants and term infants (see Table 7 and Antiretroviral Drug Dosing for Premature Infants).

PKs and safety of the single-dose nevirapine regimen to mother and infant\(^{80}\) and chronic prophylactic nevirapine administration to infants to prevent HIV transmission during breastfeeding have been studied. \(^{81}\) The three-dose extended nevirapine regimen that was used in NICHD-HPTN 040/PACTG1043 and is recommended for HIV-exposed infants whose mothers did not receive ARV drugs during the antepartum period has also been studied. \(^{53}\) Nevirapine concentrations were measured in 14 newborns participating in a PK sub-study during the second week of life and in single samples from 30 more newborns on Days 10 to 14. The median nevirapine elimination half-life was 30.2 hours (range: 17.8–50.3 hours) and the concentration remained greater than the target of 100 ng/mL in all infants through Day 10 of life.

**Antiretroviral Drug Dosing for Premature Infants**

Dosing recommendations for premature infants are available for only zidovudine (prophylaxis and treatment) and nevirapine (prophylaxis only) (see Table 7). Zidovudine is primarily cleared through hepatic glucuronidation to an inactive metabolite; this metabolic pathway is immature in neonates, leading to prolonged zidovudine half-life and decreased clearance compared with older infants. Clearance is further decreased in premature infants because their hepatic metabolic function is less mature than in term infants. \(^{82,83}\) The recommended zidovudine dosage for preterm infants is shown in Table 7.

Nevirapine PK has been described in low-birthweight neonates receiving a single postnatal prophylactic dose of the drug. In a study of 81 infants <37 weeks’ gestation, of whom 29.6% were small for gestational age, half-lives were very long—median 59 hours in infants whose mothers received single-dose nevirapine and 69 hours in infants whose mothers did not receive single-dose nevirapine. AUC of nevirapine was higher and clearance lower (\(P < .0001\)) in small-for-gestational-age infants. \(^{84}\)

Use of ARV drugs other than zidovudine, lamivudine and nevirapine cannot be recommended at this time in premature infants because data on dosing and safety are lacking. Immature renal and hepatic metabolism can increase the risk of overdosing and toxicity. However, in situations where there is a high risk of infant HIV infection, consultation with a pediatric HIV specialist is recommended to determine if the benefits of combination ARV prophylaxis with drugs in addition to or other than zidovudine and nevirapine outweigh the potential risks.

**Breastfeeding Infants of Mothers Diagnosed with HIV Infection Postpartum**

Women with suspected HIV infection (e.g., a positive initial screening test) should stop breastfeeding until HIV infection is ruled out. Pumping and temporarily discarding or freezing breast milk can be recommended to mothers who are suspected of being HIV infected but whose infection is not yet confirmed and who want to continue to breastfeed. If HIV infection is ruled out, breastfeeding can resume. Breastfeeding is not recommended for women with documented HIV infection in the United States, including those receiving ART (see Infant Feeding Practices and Risk of HIV Transmission). \(^{85}\)

The risk of acquisition of HIV associated with breastfeeding depends on multiple infant and maternal factors, including maternal viral load and CD4 cell count. \(^{86}\) Infants of women who develop acute HIV infection while breastfeeding are at greater risk of becoming infected than are those whose mothers have chronic HIV infection\(^{87}\) because acute HIV infection is accompanied by a rapid increase in viral load and a corresponding decrease in CD4 cell count. \(^{88}\)

Other than discontinuing breastfeeding, optimal strategies for managing infants born to HIV-infected mothers...
who breastfed their infants prior to HIV diagnosis have yet to be defined. Some experts would consider the use of post-exposure prophylaxis in infants for 4 to 6 weeks after cessation of breastfeeding. Post-exposure prophylaxis, however, is less likely to be effective in this circumstance compared with other non-occupational exposures because the exposure to breast milk is likely to have occurred over a prolonged period rather than in a single exposure.\(^8\)

Several studies of infants breastfed by women with chronic HIV infection have shown that daily infant nevirapine, lamivudine, or nevirapine plus zidovudine can reduce the risk of postnatal infection during breastfeeding.\(^54-56,90\) The NICHD-HPTN 040/PACTG 1043 study demonstrated that combination ARV prophylaxis was more effective than zidovudine prophylaxis alone for preventing intrapartum transmission in mothers who have not received antepartum ARV drugs.\(^5\) However, whether the combination regimens in this trial are effective for preventing transmission after cessation of breastfeeding in mothers with acute HIV infection is unknown.

Because of the high risk of postnatal transmission from a breastfeeding woman with acute HIV infection, an alternative approach favored by some experts would be to offer an ART regimen that would be effective for treatment of HIV, should an infant become infected. If this route is chosen, current recommendations for treatment should guide selection of an appropriate ART regimen (see the Pediatric Antiretroviral Guidelines). Regardless of whether post-exposure prophylaxis or “pre-emptive therapy” is chosen, the optimal duration of the intervention is unknown. A 28-day course may be reasonable based on current recommendations for non-occupational HIV exposure.\(^8\) As in other situations, decisions regarding administration of a prophylactic or pre-emptive treatment regimen should be accompanied by consultation with a pediatric HIV specialist and maternal counseling on the potential risks and benefits of this approach.

Infants should be tested for HIV infection at baseline and 4 to 6 weeks, 3 months, and 6 months after recognition of maternal infection to determine HIV status. In infants younger than age 18 months, HIV NAT should be used for diagnosis. HIV DNA PCR testing may be preferable for infants who are receiving combination ARV prophylaxis or preemptive treatment, because HIV RNA assays may be less sensitive in the presence of combination ARV drugs, which might lower infant plasma viral RNA to undetectable levels. However, HIV DNA PCR assays available in the United States may not detect non-subtype B or group O HIV as well as do many HIV RNA assays. Therefore, if non-subtype B or group O HIV infection is considered possible in an infant, both HIV DNA and RNA assays should be obtained from the infant. HIV antibody assays can be used in infants older than age 18 months.

If an infant is already receiving post-exposure ARV prophylaxis and is found to be HIV-infected, prophylaxis should be discontinued and treatment for HIV infection initiated with standard ART according to the Pediatric Antiretroviral Guidelines. Resistance testing should be performed and the ART regimen modified if needed (see the Pediatric Antiretroviral Guidelines).

References


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