Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection

(Last updated December 29, 2020; last reviewed December 29, 2020)

Panel's Recommendations

• All newborns who were exposed perinatally to HIV should receive postpartum antiretroviral (ARV) drugs to reduce the risk of perinatal transmission of HIV **(AI)**.
• Newborn ARV regimens administered at doses that are appropriate for the infant's gestational age should be initiated as close to the time of birth as possible, preferably within 6 hours of delivery **(AII)**.
• A newborn's ARV regimen should be determined based on maternal and infant factors that influence the risk of perinatal transmission of HIV **(AII)**. The uses of ARV regimens in newborns include:
  • **ARV Prophylaxis:** The administration of one or more ARV drugs to a newborn without documented HIV infection to reduce the risk of perinatal acquisition of HIV.
  • **Presumptive HIV Therapy:** The administration of a three-drug ARV regimen to newborns who are at highest risk of perinatal acquisition of HIV. Presumptive HIV therapy is intended to be preliminary treatment for a newborn who is later documented to have HIV, but it also serves as prophylaxis against HIV acquisition for those newborns who are exposed to HIV *in utero*, during the birthing process, or during breastfeeding and who do not acquire HIV.
  • **HIV Therapy:** The administration of a three-drug ARV regimen at treatment doses (called antiretroviral therapy [ART]) to newborns with documented HIV infection (see Diagnosis of HIV Infection in Infants and Children).
• A 4-week zidovudine (ZDV) ARV prophylaxis regimen can be used in newborns whose mothers received ART during pregnancy and had viral suppression near delivery (defined as a confirmed HIV RNA level <50 copies/mL) and for whom maternal adherence is not of concern **(BII)**.
• Newborns at high risk of perinatal acquisition of HIV should begin presumptive HIV therapy (see Table 9 for recommended regimens). Newborns at high risk of HIV acquisition include those born to women with HIV who—
  • Have not received antepartum or intrapartum ARV drugs **(AI)**, *or*
  • Have received only intrapartum ARV drugs (AI), *or*
  • Have received antepartum ARV drugs but who did not achieve viral suppression (defined as a confirmed HIV RNA level <50 copies/mL) near delivery **(AII)**, *or*
  • Have primary or acute HIV infection during pregnancy **(AII)**, *or*
  • Have primary or acute HIV infection while breastfeeding **(AII)**.
• If a woman presents with unknown HIV status and has a positive expedited HIV test during labor or shortly after delivery, the infant should begin presumptive HIV therapy **(AII)**. If supplemental maternal testing is negative, the infant's ARV regimen should be discontinued **(AII)**.
• For newborns with HIV infection, ART should be initiated **(AI)**.
• The use of ARV drugs other than ZDV, lamivudine, and nevirapine cannot be recommended for any indication in premature newborns (<37 weeks gestational age) because of the lack of dosing and safety data **(BII)**.
• Providers with questions about ARV management of perinatal HIV exposure should consult the National Perinatal HIV Hotline (1-888-448-8765), which provides free clinical consultation on all aspects of perinatal HIV, including newborn care **(AIII)**.

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

General Considerations for Antiretroviral Management of Newborns Exposed to HIV or Born with HIV

All newborns with perinatal exposure to HIV should receive antiretroviral (ARV) drugs during the neonatal period to reduce the risk of perinatal HIV transmission, with selection of the appropriate ARV regimen guided by the level of transmission risk. HIV transmission can occur *in utero*, intrapartum, or during breastfeeding.

Maternal viral load is the most important risk factor for HIV transmission to a newborn. Newborns are at an increased risk for transmission when their mothers do not receive antiretroviral therapy (ART) during pregnancy, when mothers start antepartum treatment late in pregnancy, or when antepartum treatment does not

result in virologic suppression (defined as a confirmed HIV RNA level <50 copies/mL). Higher maternal viral load, especially in late pregnancy, correlates with higher risk of transmission. A spectrum of transmission risk depends on these and other maternal and infant factors, including mode of delivery, gestational age at delivery, and maternal health status.

Historically, the use of ARV drugs in the newborn period was referred to as ARV prophylaxis because it primarily focused on protection against newborn perinatal acquisition of HIV. More recently, clinicians have begun to identify newborns at highest risk for HIV acquisition and initiate three-drug ARV regimens as presumptive treatment of HIV. In this section, the following terms will be used:

- **ARV Prophylaxis:** The administration of ARV drugs to a newborn without documented HIV infection to reduce the risk of HIV acquisition. ARV prophylaxis includes administration of a single agent—usually zidovudine (ZDV)—as well as combinations of two or three ARV drugs.
- **Presumptive HIV Therapy:** The administration of a three-drug ARV regimen to newborns at highest risk of HIV acquisition. Presumptive HIV therapy is intended to be early treatment for a newborn who is later documented to have acquired HIV, but it also serves as ARV prophylaxis against HIV acquisition for those newborns who are exposed to HIV *in utero*, during the birthing process, or during breastfeeding and who do not acquire HIV.
- **HIV Therapy:** The administration of a three-drug ARV regimen to newborns with documented HIV infection (see Diagnosis of HIV Infection in Infants and Children).

The terms ARV prophylaxis and presumptive HIV therapy describe the clinician's intent when prescribing ARV drugs, which may lead to an overlap between these two terms. For example, a presumptive HIV therapy regimen also provides ARV prophylaxis for a newborn. However, two-drug (or sometimes three-drug) ARV prophylaxis regimens, notably those that use prophylactic doses rather than therapeutic doses of nevirapine (NVP), are not considered presumptive HIV therapy.

The interval during which newborn ARV prophylaxis or presumptive HIV therapy can be initiated and still be beneficial is undefined; however, most studies support providing ARV drugs as early as possible after delivery.[1–6]

Table 8 provides an overview of neonatal ARV management recommendations according to the risk of perinatal HIV transmission to the newborn, and Table 9 summarizes the recommendations for ARV drug dosing in newborns. Additional information about dose selection for newborns, including premature infants (<37 weeks' gestational age), can be found in the Pediatric Antiretroviral Guidelines. Information about infants born to women with HIV-2 infection is available in HIV-2 Infection and Pregnancy and Table 8. In addition, the National Perinatal HIV Hotline (1-888-448-8765) is a federally funded service that provides free clinical consultation on difficult cases to providers who are caring for pregnant women with HIV and their newborns, and consultants can provide referrals to local or regional pediatric HIV specialists.

Table 8. Neonatal Antiretroviral Management According to Risk of HIV Infection in the Newborn

Drug selection and dosing considerations are related to the age and gestational age of the newborn. Consultation is available through the National Perinatal HIV Hotline (1-888-448-8765).

Level of Perinatal HIV Transmission Risk	Description	Neonatal ARV Management
Low Risk of Perinatal HIV Transmission	Mothers who received ART during pregnancy with viral suppression (defined as a confirmed HIV RNA level <50 copies/mL) near delivery and no concerns related to adherence	ZDV for 4 weeks[a]
High Risk of Perinatal HIV Transmission[a,b]	Mothers who did not receive antepartum or intrapartum ARV drugs Mothers who received only intrapartum ARV drugs Mothers who received antepartum and intrapartum ARV drugs but did not have viral suppression (defined as a confirmed HIV RNA level <50 copies/mL) near delivery Mothers with acute or primary HIV infection during pregnancy or breastfeeding (in which case, the mother **should immediately discontinue breastfeeding**)[c]	Presumptive HIV therapy using either ZDV, 3TC, and NVP (treatment dose) *or* ZDV, 3TC, and RAL administered from birth up to 6 weeks.[d]
Presumed Newborn HIV Exposure	Mothers with unconfirmed HIV status who have at least one positive HIV test at delivery or postpartum *or* Mothers whose newborns have a positive HIV antibody test	ARV management as described above for newborns with a high risk of perinatal HIV transmission Infant ARV drugs should be discontinued immediately if supplemental testing confirms that the mother does not have HIV
Newborn with HIV[e]	Positive newborn HIV virologic test/ NAT	Three-drug ARV regimen using treatment doses

[a] A 4-week ZDV prophylaxis regimen is recommended for infants born to mothers with HIV-2 mono-infection, see HIV-2 Infection and Pregnancy. If the mother has HIV-1 and HIV-2 infection, the infant ARV regimen should be based on the determination of low or high risk of HIV-1 transmission as described in the above table. Because HIV-2 is not susceptible to NVP, RAL should be considered.

See text for evidence that supports the use of presumptive HIV therapy and a two-drug ARV prophylaxis regimen.

[b] See Intrapartum Care for guidance on indications for scheduled cesarean delivery and intrapartum IV ZDV to reduce the risk of perinatal HIV transmission for mothers with an elevated viral load at delivery.

[c] Most Panel members would opt to administer presumptive HIV therapy to infants whose mothers had acute HIV during pregnancy because of the higher risk for *in utero* transmission. If acute HIV is diagnosed during breastfeeding, the mother should immediately discontinue nursing.

[d] The optimal duration of presumptive HIV therapy in newborns who are at a high risk for perinatal HIV transmission is unknown. If possible, newborns who are at a high risk for HIV acquisition should receive ZDV for 6 weeks. Additional medications, such as 3TC, RAL, or NVP, may need to administered for 2 to 6 weeks; the recommended duration for these drugs varies depending on HIV NAT results, maternal viral load at the time of delivery, and additional risk factors for HIV transmission. Consultation with an expert in pediatric HIV is recommended when selecting a therapy duration because this decision should be based on case-specific risk factors and interim HIV NAT results. The two-drug regimen used in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)-HIV Prevention Trials Network (HPTN) 040/ Pediatric AIDS Clinical Trials Group (PACTG) 1043 for infants who were at a high risk for HIV acquisition is described in the text (see the Two-Drug Antiretroviral Prophylaxis section).

[e] Most Panel members strongly recommend initiating ART without waiting for the results of confirmatory HIV NAT testing, given the low likelihood of a false-positive HIV NAT.

Note: ARV drugs should be initiated as close to the time of birth as possible, preferably within 6 hours of delivery. See Table 9 for dosing specifics.

Key: 3TC = lamivudine; ART = antiretroviral therapy; ARV =antiretroviral; IV = intravenous; NAT = nucleic acid test; NVP = nevirapine; Panel = Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission; RAL = raltegravir; ZDV = zidovudine

Table 9. Antiretroviral Drug Dosing Recommendations for Newborns

Newborns at Low Risk of Perinatal HIV Transmission	
Recommended Regimen	**Recommended Duration**
ZDV	ZDV administered for 4 weeks at the doses listed below
Newborns at High Risk of Perinatal HIV Transmission	
Recommended Regimen	**Recommended Duration**
Three-drug HIV therapy: ZDV plus 3TC plus (NVP *or* RAL)	ZDV administered for 6 weeks, with no increase to the 12 mg/kg dose unless the infant has confirmed HIV infection. Dosing for 3TC, NVP, and RAL is described below. Duration for these three drugs may vary; see the guidance in footnote.[a]
Newborns with HIV Infection	
Recommended Regimen	**Lifelong Duration Recommended**[b]
Three-drug HIV therapy: ZDV plus 3TC plus (NVP *or* RAL)	Lifelong therapy in accordance with current treatment guidelines. The ARV regimen should be individualized based on the infant's age and clinical determinants. RAL can be used in infants who were born at a postmenstrual age of ≥37 weeks (defined as the time from the first day of the mother's last menstrual period to birth plus the time elapsed after birth) and who weigh ≥2 kg. LPV/r can be used when the infant reaches a postmenstrual age of ≥42 weeks and a postnatal age ≥14 days. DTG tablets for oral suspension (dispersible tablets) can replace LPV/r, NVP, or RAL in infants at least 4 weeks of age and weighing at least 3 kg.

<table>
<tr><th>Drug</th><th>Drug Doses by Gestational Age at Birth</th></tr>
<tr><td>ZDV

Note: For newborns who are unable to tolerate oral agents, the IV dose is 75% of the oral dose while maintaining the same dosing interval.</td><td>≥35 Weeks' Gestation at Birth
Birth to Age 4 Weeks:
• ZDV 4 mg/kg per dose orally twice daily

Age >4 Weeks:
• ZDV 12 mg/kg per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection.

Simplified Weight-Band Dosing for Newborns Aged ≥35 Weeks' Gestation from Birth to 4 Weeks
<table>
<tr><th>Weight Band</th><th>Volume of ZDV 10 mg/mL Oral Syrup Twice Daily</th></tr>
<tr><td>2 to <3 kg</td><td>1 mL</td></tr>
<tr><td>3 to <4 kg</td><td>1.5 mL</td></tr>
<tr><td>4 to <5 kg</td><td>2 mL</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td>≥30 to <35 Weeks' Gestation at Birth
Birth to Age 2 Weeks:
• ZDV 2 mg/kg per dose orally twice daily

Age 2 Weeks to 6 to 8 Weeks:
• ZDV 3 mg/kg per dose orally twice daily

Age >6 to 8 Weeks:
• ZDV 12 mg/kg per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection.</td></tr>
<tr><td></td><td><30 Weeks' Gestation at Birth
Birth to Age 4 Weeks:
• ZDV 2 mg/kg per dose orally twice daily
Age 4 to 8–10 Weeks:
• ZDV 3 mg/kg per dose orally twice daily
Age >8 to 10 Weeks:
• ZDV 12 mg/kg per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection</td></tr>
<tr><td>3TC</td><td>≥32 Weeks' Gestation at Birth
Birth to Age 4 Weeks:
• 3TC 2 mg/kg per dose orally twice daily

Age >4 Weeks:
• 3TC 4 mg/kg per dose orally twice daily</td></tr>
<tr><td>NVP</td><td>≥37 Weeks' Gestation at Birth
Birth to Age 4 Weeks:
• NVP 6 mg/kg per dose orally twice dailyc

Age >4 Weeks:
• NVP 200 mg/m^2 BSA per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection.</td></tr>
<tr><td></td><td>≥34 to <37 Weeks' Gestation at Birth
Birth to Age 1 Week:
• NVP 4 mg/kg per dose orally twice daily
Age 1 to 4 Weeks:
• NVP 6 mg/kg per dose orally twice daily
Age >4 Weeks:
• NVP 200 mg/m^2 BSA per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection.</td></tr>
<tr><td>RAL

Note: If the mother has taken RAL 2–24 hours prior to delivery, the neonate's first dose of RAL should be delayed until 24–48 hours after</td><td>≥37 Weeks' Gestation at Birth and Weighing ≥2 kg[d]
Birth to Age 6 Weeks:
<table><tr><th>Body Weight</th><th>Volume (Dose) of RAL 10 mg/mL Suspension</th></tr><tr><td>Birth to 1 Week: Once-Daily Dosing</td><td>Approximately 1.5 mg/kg per dose</td></tr><tr><td>2 to <3 kg</td><td>0.4 mL (4 mg) once daily</td></tr></table></td></tr>
</table>

<table>
<tr><td>birth; additional ARV drugs should be started as soon as possible.[7]</td><td>
<table>
<tr><td>3 to <4 kg</td><td>0.5 mL (5 mg) once daily</td></tr>
<tr><td>4 to <5 kg</td><td>0.7 mL (7 mg) once daily</td></tr>
<tr><td>1 to 4 Weeks: Twice-Daily Dosing</td><td>Approximately 3 mg/kg per dose</td></tr>
<tr><td>2 to <3 kg</td><td>0.8 mL (8 mg) twice daily</td></tr>
<tr><td>3 to <4 kg</td><td>1 mL (10 mg) twice daily</td></tr>
<tr><td>4 to <5 kg</td><td>1.5 mL (15 mg) twice daily</td></tr>
<tr><td>4 to 6 Weeks: Twice-Daily Dosing</td><td>Approximately 6 mg/kg per dose</td></tr>
<tr><td>3 to <4 kg</td><td>2.5 mL (25 mg) twice daily</td></tr>
<tr><td>4 to <6 kg</td><td>3 mL (30 mg) twice daily</td></tr>
<tr><td>6 to <8 kg</td><td>4 mL (40 mg) twice daily</td></tr>
</table>
</td></tr>
<tr><td>DTG

Note: Only tablets for oral suspension (dispersible tablets) are approved for use in infants > 4 weeks of age and > 3 kg</td><td>
Age > 4 weeks of age AND > 3 kg:
<table>
<tr><th>Pediatric

Body Weight</th><th>Recommended Dose[e]

Dolutegravir Dispersible Tablets</th><th>Number of tablets</th></tr>
<tr><td>3 to <6 kg</td><td>5 mg once daily</td><td>1</td></tr>
<tr><td>6 to <10 kg</td><td>15 mg once daily</td><td>3</td></tr>
<tr><td>10 to <14 kg</td><td>20 mg once daily</td><td>4</td></tr>
<tr><td>14 to <20 kg</td><td>25 mg once daily</td><td>5</td></tr>
<tr><td>≥20 kg</td><td>30 mg once daily</td><td>6</td></tr>
</table>
</td></tr>
</table>

[a] The optimal duration of presumptive HIV therapy in newborns who are at a high risk for perinatal HIV transmission is unknown. If possible, newborns who are at a high risk for HIV acquisition should receive ZDV for 6 weeks. Additional medications, such as 3TC, RAL, or NVP, may need to administered for 2 to 6 weeks; the recommended duration for these drugs varies based on HIV NAT results, maternal viral load at the time of delivery, and additional risk factors for HIV transmission. Consultation with an expert in pediatric HIV is recommended when selecting a therapy duration because this decision should be based on case-specific risk factors and interim HIV NAT results. The two-drug regimen used in NICHD-HPTN 040/PACTG 1043 for infants who were at a high risk for HIV acquisition is described in the text (see the Two-Drug Antiretroviral Prophylaxis section).
[b] For ARV management after the newborn period, see the Pediatric Antiretroviral Guidelines.
[c] This dose is an investigational NVP treatment dose recommended by the Panel; the FDA has not approved a dose of NVP for infants aged <1 month. See the Two-Drug Antiretroviral Prophylaxis section in the text for prophylactic NVP dosing if using the NICHD-HPTN 040/PACTG 1043 prophylaxis regimen.
[d] RAL dosing is increased at 1 and 4 weeks of age because metabolism by UGT1A1 is low at birth and increases rapidly during the next 4–6 weeks of life. No dosing information is available for preterm infants or infants weighing <2 kg at birth.
[e] If certain UGT1A or CYP3A inducers are coadministered, then administer twice daily.

Key: 3TC = lamivudine; ARV =antiretroviral; BSA = body surface area; DTG = dolutegravir; FDA = Food and Drug Administration; IV = intravenous; LPV/r = lopinavir/ritonavir; NAT = nucleic acid test; NVP = nevirapine; the Panel = the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission; RAL = raltegravir; UGT = uridine diphosphate glucotransferase; ZDV = zidovudine

Recommendations for Antiretroviral Drugs in Specific Clinical Situations

In this section and Table 8, the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) presents available data and recommendations for management of newborns with documented HIV and newborns born to mothers who—

- Received antepartum/intrapartum ARV drugs and achieved effective viral suppression (defined as a confirmed HIV RNA level <50 copies/mL)
- Are at high risk for transmitting HIV to their newborns, including mothers who—
  - Received neither antepartum nor intrapartum ARV drugs, *or*
  - Received only intrapartum ARV drugs, *or*
  - Received antepartum and intrapartum ARV drugs but who do not have effective viral suppression (defined as a confirmed HIV RNA level <50 copies/mL) near delivery
- Had acute or primary HIV infection during pregnancy or breastfeeding
- Have unknown HIV status
- Have known ARV drug-resistant virus

Newborns Born to Mothers Who Achieved Viral Suppression on Antepartum/Intrapartum Antiretroviral Drugs

The risk of HIV acquisition in newborns born to women who received ART during pregnancy and labor and who had undetectable viral load near or at the time of delivery is <1 percent. In the PACTG 076 study, ZDV alone reduced the incidence of perinatal HIV transmission by 66 percent, and ZDV is recommended as prophylaxis for neonates whose mothers received ART that resulted in consistent virologic suppression during pregnancy.[8] The optimal minimum duration of neonatal ZDV prophylaxis has not been established in clinical trials. A 6-week ZDV regimen was studied in newborns in PACTG 076. However, the evidence that supports a reduced duration of ZDV prophylaxis in infants born to women who were suppressed virologically during pregnancy and at time of delivery is mounting.[9–11] In the United Kingdom and many other European countries, a 2-week neonatal ZDV prophylaxis regimen is recommended for infants born to women who have been on ART for longer than 10 weeks **and** have had at least two documented maternal HIV viral loads <50 copies/mL at least 4 weeks apart **and** have viral loads <50 copies/mL at or after 36 weeks' gestation. A 4-week course of ZDV is recommended[12] if any of these criteria are not fulfilled but the maternal viral load is <50 copies/mL at or after 36 weeks' gestation. Compared with the 6-week ZDV regimen, 2 to 4 weeks on this regimen has been reported to allow earlier recovery from anemia in otherwise healthy newborns.[13,14]

Currently, the Panel recommends a 4-week neonatal ZDV prophylaxis regimen for newborns if the mother achieved viral suppression on ART during pregnancy (defined as a confirmed HIV RNA level <50 copies/mL) at or after 36 weeks' gestation and maternal adherence is not of concern. Dosing recommendations for ZDV are available for premature newborns, and an intravenous preparation of ZDV is available. Table 9 shows recommended neonatal ZDV dosing based on gestational age and birth weight.

Newborns Born to Mothers Who Received No Antepartum or Intrapartum Antiretroviral Drugs, Who Received Intrapartum Antiretroviral Drugs Only, Who Received Antiretroviral Drugs and Were Not Virally Suppressed Near Delivery, or Who Acquired HIV During Pregnancy or Breastfeeding

The Panel recommends that all newborns born to mothers who do not have viral suppression (defined as a confirmed HIV RNA level <50 copies/mL) near delivery, who received only intrapartum ARV drugs, or who received no ARV drugs during pregnancy or delivery are at high risk for HIV acquisition and **should receive**

presumptive HIV therapy.[5,15–19] Primary or acute HIV infection during pregnancy also is associated with an increased risk of perinatal transmission of HIV. Infants born to women who acquired HIV during pregnancy **should receive presumptive HIV therapy** (see Acute HIV Infection). The experience with these two strategies is described below.

Presumptive HIV Therapy

Early effective treatment of HIV infection in infants restricts the viral reservoir size, reduces HIV genetic variability, and modifies the immune response.[20–28] Because of these potential benefits of early ART, the Panel recommends a three-drug ARV presumptive HIV therapy regimen consisting of ZDV, lamivudine (3TC), and either NVP (at treatment dose) or raltegravir (RAL) for newborns at high risk of perinatal acquisition of HIV.

Although no clinical trials have compared the safety and efficacy of presumptive ART with single-drug or two-drug regimens, emerging data suggest that early presumptive HIV therapy has not been associated with serious adverse events. Many infants develop anemia or neutropenia that may be drug-related regardless of whether the ARV drugs are administered as prophylaxis or treatment.[29–33] In a prospective cohort in Thailand, infants who received a presumptive HIV therapy regimen that contained ZDV, 3TC, and NVP were more likely to have Grade 2 or higher anemia at 1 and 2 months of life compared with infants who received ZDV alone (48.5% vs. 32.3%; $P = 0.02$). However, no difference was found in the incidence of severe anemia (Grade 3) between the two groups.[34] Additionally, in a Canadian study, nonspecific signs and symptoms (e.g., vomiting, diarrhea, rash, jitteriness, irritability) that were potentially attributable to medication-related adverse effects were reported among the newborns who received presumptive HIV therapy but not among those who received ZDV only (10.2% vs. 0%; $P < 0.001$). Infants were more likely to discontinue presumptive HIV therapy prematurely than a regimen of ZDV alone (9.5% vs. 2.1%; $P = 0.01$).[30]

The Centers for Disease Control and Prevention recommend a three-drug ARV regimen for HIV-postexposure prophylaxis following occupational and nonoccupational HIV exposure. HIV acquisition risk in these circumstances is often lower than for newborns who are at high risk for HIV acquisition.[35,36] The pharmacokinetic (PK) and safety data of presumptive HIV therapy have provided reassuring evidence for its use in the neonatal period. Although the use of NVP to prevent perinatal HIV transmission has been found to be safe in neonates and newborns of low birthweight, these prophylaxis-dose regimens target trough drug levels that are ≥10-fold lower than targeted therapeutic levels. However, recent studies of therapeutic doses of NVP and RAL have established safe doses that achieve targeted PK parameters.[37–42]

At this time, if a presumptive HIV therapy regimen is required, the Panel recommends using a combination of ZDV, 3TC, and NVP (treatment dose) or ZDV, 3TC, and RAL (see Tables 6 and 7). The optimal duration of presumptive HIV therapy in newborns at high risk of perinatal HIV transmission is unknown. Some Panel members opt to discontinue additional medications if birth nucleic acid test (NAT) results are negative, whereas others would continue presumptive HIV therapy for 2 to 6 weeks depending on the risk of HIV transmission. In all cases, ZDV should be continued for 6 weeks. If HIV infection is confirmed and the infant is receiving NVP, a switch from NVP to lopinavir/ritonavir (LPV/r) is recommended when the infant reaches a postmenstrual age (defined as the time from the 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 ≥14 days; when a switch to dolutegravir (DTG) can be made at 4 weeks of age; and when a switch to RAL can be made at any age (see What to Start in the Pediatric Antiretroviral Guidelines). Consulting an expert in pediatric HIV is recommended when selecting a therapy duration based on case-specific risk factors and interim HIV NAT results.

Two-Drug Antiretroviral Prophylaxis

To date, the NICHD-HPTN 040/PACTG 1043 trial is the only randomized clinical trial of multi-ARV prophylaxis in newborns at high risk of HIV acquisition.[5] In this study, 1,746 formula-fed infants born to

women with HIV who did not receive any ARV drugs during pregnancy were randomized to receive one of three newborn prophylaxis regimens: the standard 6-week ZDV regimen; 6 weeks of ZDV plus three doses of NVP given during the first week of life (first dose given at birth or within 48 hours of birth, second dose 48 hours after the first dose, and third dose 96 hours after the second dose); and 6 weeks of ZDV plus 2 weeks of 3TC plus nelfinavir (NFV).

Forty-one percent of the mothers received ZDV during labor. The risk of intrapartum transmission was significantly lower in the two-drug and three-drug arms (2.2% and 2.5%, respectively, vs. 4.9% for 6 weeks of ZDV alone; $P = 0.046$ for each experimental arm vs. ZDV alone).[5] The NICHD-HPTN 040/PACTG 1043 regimen was associated with nucleoside reverse transcriptase inhibitor (NRTI) resistance in three of 53 participants (5.7%) with *in utero* infection who were treated with ZDV alone and in six of 33 participants (18.2%) who were treated with ZDV plus NVP ($P > 0.05$). In addition, the third drug in the three-arm regimen was NFV, which has highly variable PKs in this age group and did not reach the NFV target plasma concentration in 46 percent of study participants.[43]

Although transmission rates with the two regimens were similar, neutropenia was significantly more common with the three-drug regimen than with the two-drug or ZDV-alone regimens (27.5% vs. 14.9% vs. 16.4%; $P < 0.001$ for both comparisons). For newborns who are at a high risk for HIV acquisition, the two-drug regimen used in NICHD-HPTN 040/PACTG 1043 is an option for preventing HIV transmission in infants aged ≥32 weeks' gestation with a birthweight of ≥1.5 kg. This two-drug regimen consists of 6 weeks of ZDV plus three doses of the prophylactic dose of NVP, with the NVP doses given within 48 hours of birth, 48 hours after the first dose, and 96 hours after the second dose. The prophylactic doses are NVP 12 mg per dose orally for infants weighing >2 kg and NVP 8 mg per dose orally for infants weighing 1.5 kg to 2 kg. **These are the actual doses, not the milligram per kilogram doses**. ZDV dosing is shown in Table 9.

Choosing between Presumptive HIV Therapy and Two-Drug Antiretroviral Prophylaxis

Because a spectrum of transmission risk depends on maternal viral load **and** other maternal and infant factors **and** no randomized trials have compared the safety and efficacy of presumptive HIV therapy and two-drug ARV prophylaxis, experts have differing opinions about when to initiate presumptive HIV therapy and when to initiate two-drug prophylaxis. For instance, among women who received ARV drugs during pregnancy but who have a detectable viral load near delivery (on or after 36 weeks' gestation), the level of maternal viremia that would prompt the use of a two-drug ARV prophylaxis regimen or presumptive HIV therapy is not definitively known.

In two large observational studies of women on combination antenatal ARV drugs, perinatal transmission rates were 0.05 percent and 0.3 percent when the mother had a viral load <50 copies/mL at delivery. Rates of transmission in these studies increased to 1.1 percent and 1.5 percent when viral load was 50 to 399 copies/mL and 2.8 percent and 4.1 percent when viral load was >400 copies/mL.[44,45] Although most Panel members would recommend initiating presumptive HIV therapy with any detectable level of viremia near delivery, others may opt for a two-drug prophylaxis regimen if maternal viral load was less than 200 to 400 copies/mL. Emerging data about the lack of serious safety issues associated with presumptive HIV therapy in newborns is reassuring, even though mild-to-moderate adverse events may occur more frequently.

In summary, in scenarios where the infant is at high risk for HIV transmission, most Panel members recommend presumptive HIV therapy. In some situations, a two-drug ARV prophylaxis regimen may be considered (see Two-Drug Antiretroviral Prophylaxis in the text). Choosing between these regimens will depend on the clinician's assessment of the likelihood of HIV transmission, and a decision should be made after weighing the risks and benefits of the proposed regimen and discussing these transmission prevention strategies with the parents.

Consulting an expert in pediatric HIV or the National Perinatal HIV Hotline (1-888-448-8765) is recommended when selecting a regimen based on case-specific risk factors.

Newborns Born to Mothers with Unknown HIV Status Who Present in Labor

Expedited HIV testing is recommended during labor for women with unknown HIV status; if testing is not performed during labor, it should be performed as soon as possible after birth for the mothers and/or their newborns (see Maternal HIV Testing and Identification of Perinatal HIV Exposure). Expedited test results should be available within 60 minutes. If maternal or infant expedited testing is positive, the newborn **should begin presumptive HIV therapy immediately** without waiting for the results of supplemental tests. Expedited HIV testing should be available on a 24-hour basis at all facilities with a maternity service and/or neonatal intensive care unit or special care or newborn nursery.

A positive initial test result in mothers or newborns should be presumed to indicate maternal HIV until supplemental testing clarifies maternal and newborn status. If appropriate test results for a mother (or newborn) are negative, newborn ARV drugs can be discontinued. Clinicians should be aware of their state laws because not all states allow HIV testing in infants without parental consent.

A nursing mother who is suspected of having HIV based on an initial positive antibody or antibody/antigen test result should discontinue breastfeeding immediately until HIV is confirmed or ruled out. Pumping and temporarily discarding or freezing breast milk can be recommended. If HIV is ruled out, breastfeeding can resume. If HIV is confirmed, breastfeeding should be discontinued permanently.[46]

Newborns Born to Mothers with Antiretroviral Drug-Resistant Virus

The optimal ARV regimen for newborns born to women with ARV drug-resistant virus is unknown. Although some studies have suggested that ARV drug-resistant virus may have decreased replicative capacity (reduced viral fitness) and transmissibility,[47] perinatal transmission of multidrug-resistant virus does occur.[48–53] Whether resistant virus in the mother increases the antepartum/intrapartum risk of HIV acquisition by the infant also is unknown. A recently reported secondary analysis of data from the NICHD-HPTN 040/PACTG 1043 study demonstrated that the risk of perinatal transmission was not related to the presence of drug resistance mutations in mothers who had not received ARV drugs before the start of the study (adjusted odds ratio 0.8; 95% confidence interval, 0.4–1.5).[53] Maraviroc (MVC) was approved recently for infants ≥2 kg and may provide an additional treatment option for newborns of women carrying multidrug resistant HIV-1 that remains CCR5-trophic. However, the lack of data about MVC as prophylaxis or treatment in infants weighing <10 kg and the risk of drug interactions will limit its role for routine use in neonates. The ARV regimen for newborns born to mothers with known or suspected drug resistance should be determined in consultation with a pediatric HIV specialist before delivery or through consultation via the National Perinatal HIV Hotline (1-888-448-8765). Additionally, no evidence exists that shows that neonatal prophylaxis regimens customized based on presence of maternal drug resistance are more effective than standard neonatal prophylaxis regimens.

Newborns with HIV Infection

Until recently, neonatal ARV regimens were designed for prophylaxis against perinatal HIV transmission and were intended to be as simple as possible for practical use. There was little reason to develop ARV regimens for the treatment of neonates, because the long turnaround times to receive HIV NAT results meant that neonatal infections, in general, were not diagnosed during the first weeks of life. HIV NAT results are now available within a few days, and HIV in newborns is being diagnosed as early as the first days of life in many centers. A positive HIV NAT must be repeated to confirm HIV. However, most Panel members do not recommend delaying the initiation of ART while waiting for the results of the confirmatory HIV NAT, given the low

likelihood of a false-positive HIV NAT. However, evidence that early treatment (before age 2 weeks) will lead conclusively to prolonged remission or better outcomes in newborns with HIV is lacking.

Information regarding the safety of early treatment of HIV in newborns has been reported from two studies. In the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) P1115 study, 54 infants with HIV began presumptive HIV therapy between 0.4 and 40 hours of life. Grade 3 or 4 related events—most of which were hematologic—occurred in 22 of 54 infants (41%) through 52 weeks of the study.[31] Forty infants with HIV in Botswana began treatment with NVP plus ZDV plus 3TC at a median age of 2 days (range 1–5 days) and transitioned to LPV/r plus ZDV plus 3TC at approximately 2 weeks of age. These infants had minimal toxicity during the first 12 weeks of treatment. Only one instance of Grade 3 neutropenia was reported, and no instances of Grade 3 or 4 anemia were reported.[33]

Earlier diagnosis of HIV in newborns and the increasing use of presumptive HIV therapy in newborns at high risk for HIV acquisition have necessitated the investigation of dosing and the safety of ARV drugs in term and preterm newborns. Although data are still incomplete, especially for preterm newborns, PK and safety profiles of ARV drugs are increasingly available. As already noted, the recommended neonatal ARV doses for prophylaxis and for treatment are the same, with the important exception of NVP (see the Pediatric Antiretroviral Guidelines).

Sufficient data exist to provide dosing recommendations for the treatment of HIV in neonates using the following medications (see the Pediatric Antiretroviral Guidelines):

- From birth in term and preterm newborns: ZDV, 3TC, NVP
- From birth in term newborns: emtricitabine, RAL, MVC
- From age 2 weeks in term newborns: LPV/r
- From age 4 weeks in term newborns: DTG

Dosing recommendations for *premature* newborns are available for ZDV, 3TC, and NVP only. Neonatal dosing advice, including dosing advice for premature newborns, is summarized in Table 9. For more detailed information about neonatal dosing recommendations and considerations when using these drugs, please see the Pediatric Antiretroviral Guidelines.

Newborns of Mothers Who Receive an HIV Diagnosis while Breastfeeding

Women with suspected HIV (e.g., a positive initial screening test) should discontinue breastfeeding immediately until HIV is ruled out. Pumping and temporarily discarding or freezing breast milk can be recommended to mothers who are suspected of having HIV but whose HIV serostatus is not yet confirmed and who want to continue to breastfeed. If HIV is ruled out, breastfeeding can resume. Breastfeeding **is not recommended** for women with confirmed HIV in the United States, including those receiving ART (see Counseling and Managing Women Living with HIV in the United States Who Desire to Breastfeed).[54]

The risk of HIV acquisition associated with breastfeeding depends on multiple newborn and maternal factors, including maternal viral load and CD4 T lymphocyte (CD4) cell count.[55] Newborns of women who develop acute HIV while breastfeeding are at greater risk of acquiring HIV than those whose mothers have chronic HIV infection[56] because acute HIV infection is accompanied by a rapid increase in viral load and a corresponding decrease in CD4 count.[57]

Other than discontinuing breastfeeding, optimal strategies for managing a newborn who was breastfed by a mother with HIV (often because the mother just learned of her own HIV diagnosis) have yet to be defined. Some Panel members would consider the use of postexposure prophylaxis in newborns for 4 to 6 weeks after cessation of breastfeeding. Postexposure prophylaxis, however, is less likely to be effective in this circumstance

than with other nonoccupational exposures because the exposure to breast milk is likely to have occurred over a prolonged period rather than during a single exposure to the virus.[58]

Several studies of newborns who were breastfed by women with chronic HIV infection in low-resource settings have shown that a newborn's daily regimen of NVP, 3TC, LPV/r, or NVP plus ZDV can reduce the risk of postnatal infection during breastfeeding.[59–63] No trials have evaluated the use of multidrug regimens to prevent transmission after cessation of breastfeeding in mothers with acute HIV infection.

Given the higher risk of postnatal transmission from a breastfeeding woman with acute HIV infection, an alternative approach favored by some Panel members is to offer presumptive HIV therapy until the infant's HIV status can be determined. If the infant's initial HIV NAT is negative, the optimal duration of presumptive HIV therapy is unknown. A 28-day course may be reasonable based on current recommendations for nonoccupational HIV exposure.[58] When making decisions about ARV management, clinicians should consult a pediatric HIV specialist and counsel the parents on the potential risks and benefits of a particular treatment strategy. The National Perinatal HIV Hotline (1-888-448-8765) can provide referrals to local or regional pediatric HIV specialists.

Newborns exposed to HIV during breastfeeding should be tested for HIV infection prior to initiating presumptive HIV therapy, as well as 4 to 6 weeks and 4 to 6 months after diagnosis of maternal HIV infection and cessation of breastfeeding. An additional virologic test should be performed 2 to 4 weeks after discontinuing presumptive HIV therapy (see Diagnosis of HIV Infection in Infants and Children). If an HIV-exposed newborn is already receiving an ARV prophylaxis regimen other than presumptive HIV therapy and is found to have HIV, prophylaxis should be discontinued and treatment for HIV should be initiated. Resistance testing should be performed, and the ART should be modified if needed (see the Pediatric Antiretroviral Guidelines).

Short-Term Antiretroviral Drug Safety

Newborn prophylaxis with ZDV has been associated with only minimal toxicity, primarily transient hematologic toxicity (mainly anemia), which generally resolves by age 12 weeks (see Initial Postnatal Management of the Neonate Exposed to HIV). Data on toxicities in newborns who were exposed to multiple ARV drugs are limited.

Other than ZDV, 3TC is the NRTI with the most clinical experience for neonatal prophylaxis. In early studies, neonatal exposure to combination ZDV/3TC therapy was limited, in general, to [118,64,65] or 2 weeks.[5] Six weeks of ZDV/3TC exposure in newborns also has been reported. These studies suggest that hematologic toxicity may be greater with ZDV/3TC than with ZDV alone, although the newborns in these studies also had *in utero* exposure to maternal HIV therapy that may have contributed to the toxicity.

In a French study, more cases of severe anemia and neutropenia were observed in newborns who were exposed to 6 weeks of ZDV/3TC prophylaxis plus maternal antepartum ZDV/3TC than in a historical cohort of newborns who were exposed only to maternal and newborn ZDV. Anemia was reported in 15 percent of newborns, and neutropenia was reported in 18 percent of newborns who were exposed to ZDV/3TC, with 2 percent of newborns requiring blood transfusion and 4 percent requiring treatment discontinuation for toxicity.[66] Similarly, in a Brazilian study of maternal antepartum ZDV/3TC and 6 week newborn ZDV/3TC prophylaxis, neonatal hematologic toxicity was common, with anemia seen in 69 percent and neutropenia seen in 13 percent of newborns.[67]

Experience with other NRTI drugs for neonatal prophylaxis is more limited.[68,69] Hematologic and mitochondrial toxicity may be more common with exposure to multiple NRTI drugs than with exposure to a single NRTI.[66,70–73]

In rare cases, chronic multiple-dose NVP prophylaxis in pregnant women has been associated with severe and potentially life-threatening rash and hepatic toxicity.[74] These toxicities have not been observed in newborns receiving prophylactic dosing with single-dose NVP or the two-drug ZDV regimen plus three doses of NVP in the first week of life used in NICHD-HPTN 040/PACTG 1043 or in breastfeeding newborns receiving NVP prophylaxis daily for 6 weeks to 18 months to prevent transmission of HIV via breast milk.[5,59–61,63,75]

The U.S. Food and Drug Administration (FDA) recently approved infant dosing of RAL for term neonates aged ≥37 weeks' gestation at birth and weighing ≥2 kg. Dosing information for RAL is not available for preterm or low-birthweight infants. Infant RAL dosing needs to be increased at 1 week and 4 weeks of age. RAL is metabolized by uridine diphosphate glucuronosyltransferase (UGT) 1A1, the same enzyme responsible for the elimination of bilirubin. UGT enzyme activity is low at birth, and RAL elimination is prolonged in neonates. In addition, bilirubin and RAL may compete for albumin binding sites, and extremely elevated neonatal plasma RAL concentrations could pose a risk of kernicterus.[40] IMPAACT P1110 is a Phase 1, multicenter trial that enrolled full-term neonates who were exposed to HIV and who were at risk for acquiring perinatal HIV-1 infection, with or without *in utero* RAL exposure. Daily RAL was safe and well tolerated during the first 6 weeks of life. Infants were treated for ≤6 weeks from birth and followed for 24 weeks. No drug-related clinical adverse reactions were observed, and only three laboratory adverse reactions were observed: one case of Grade 4 transient neutropenia in an infant receiving a ZDV-containing regimen; and two cases of bilirubin elevations (one Grade 1 and one Grade 2) that were considered nonserious and did not require specific therapy[76] (see the Raltegravir section of the Pediatric Antiretroviral Guidelines for additional information).

The safety and PK data on daily dosing from P1110 are from RAL-naive infants whose mothers did not receive RAL; data collection from infants born to mothers who were receiving RAL is ongoing. However, the FDA currently recommends delaying the first dose of RAL in infants for 24 to 48 hours after birth if the mother received RAL 2 to 24 hours before delivery, and the Panel believes that this recommendation is reasonable based on current data about clearance of the drug in RAL-exposed infants.

DTG tablets for oral suspension recently have been approved by the FDA for use in term infants at least 4 weeks of age and weighing at least 3 kg. Safety profiles were favorable with no Grade 3 or 4 toxicities reported and no drug-related discontinuations. It is important to note that DTG tablets for oral suspension and DTG tablets are not bioequivalent and are not interchangeable on a milligram-per-milligram basis.

Of the protease inhibitors, pediatric drug formulations are available for LPV/r, ritonavir (RTV), darunavir, tipranavir, and fosamprenavir; however, the use of these drugs in neonates during the first 2 weeks of life **is not recommended**, given the lack of dosing and safety information. In addition, LPV/r oral solution contains 42.4 percent alcohol and 15.3 percent propylene glycol. The enzymes that metabolize these compounds are immature in neonates, particularly preterm newborns. Four premature newborns (two sets of twins) who were given LPV/r at birth developed heart block that resolved after drug discontinuation.[77,78] In studies of adults, both RTV and LPV/r caused 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 also has been associated with administering LPV/r during the neonatal period, an association not found with ZDV. The levels of 17-hydroxyprogesterone were greater in newborns who also were exposed to LPV/r *in utero* than in those exposed only during the neonatal period. Term newborns were asymptomatic, but three premature newborns experienced life-threatening symptoms compatible with adrenal insufficiency, including hyponatremia and hyperkalemia with—in one case—cardiogenic shock.[79] Additional studies by these investigators also have demonstrated that LPV was associated with dose-dependent adrenal dysfunction in infants who received LPV/r as prophylaxis during breastfeeding compared with infants who received 3TC and may require further investigation.[80]

On the basis of these and other postmarketing reports of cardiac toxicity (including complete atrioventricular block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, adrenal dysfunction, central nervous system depression, respiratory complications leading to death, and metabolic toxicity[81] predominantly in preterm neonates, the FDA now recommends that LPV/r oral solution **not be administered** to neonates before the infant reaches a postmenstrual age (defined as time from the 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 ≥14 days.[82] However, the ANRS 12174 study randomized 1,273 newborns to receive either LPV/r (n = 615) or 3TC (n = 621) as prophylaxis during breastfeeding in women with CD4 counts above the local threshold for treatment at the time. Newborn study prophylaxis was initiated at 7 days of life, and only newborns weighing >2 kg were randomized. The frequency of clinical and biological severe adverse events did not differ between the groups, suggesting that LPV/r is safe to use in term newborns aged 7 days and older.[83] At this time, the Panel **does not recommend** the use of LPV/r before a postmenstrual age of 42 weeks and a postnatal age of ≥14 days.

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