Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection

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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 the following:
  - 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.
  - 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).
- For newborns at low-risk of perinatal HIV acquisition, a 2-week zidovudine (ZDV) ARV regimen is recommended for ARV prophylaxis if the newborn is ≥37 weeks gestation and is born to a person with HIV who—
  - Is currently receiving and has received at least 10 consecutive weeks of ART during pregnancy (BII); *and*
  - Has achieved and maintained *or* maintained viral suppression (defined as at least two consecutive tests with HIV RNA <50 copies/mL obtained at least 4 weeks apart) for the remainder of the pregnancy (AII); *and*
  - Has a viral load <50 copies/mL at or after 36 weeks (AII); *and*
  - Did not have acute HIV infection during pregnancy (BII); *and*
  - Has reported good ART adherence, and adherence concerns have not been identified (BII).
- Infants born to individuals who do not meet the criteria above or criteria for high risk below but who have a viral load <50 copies/mL at or after 36 weeks gestation should receive ZDV alone for 4 to 6 weeks (BII).
- Newborns at high risk of perinatal acquisition of HIV should receive presumptive HIV therapy with 3-drug regimens administered from birth for 2 to 6 weeks (see Tables 10 and 11); if the duration of the 3-drug regimen is shorter than 6 weeks, ZDV should be continued alone, to complete total of 6 weeks of prophylaxis. Newborns at high risk of HIV acquisition include those born to people with HIV who—
  - Have not received antepartum 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 at least two consecutive tests with HIV RNA level <50 copies/mL obtained at least 4 weeks apart) within 4 weeks of delivery (AIII), *or*
  - Have primary or acute HIV infection during pregnancy (AI).
- All premature infants <37 weeks gestation who are not at high risk of perinatal acquisition of HIV should receive ZDV for 4 to 6 weeks (BII).

- Infants of people who have primary or acute HIV infection while breastfeeding should be managed like infants at high risk of perinatal transmission with presumptive HIV therapy (see Table 12) (AII).
- 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).
- If an individual 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) (see What to Start in the Pediatric Antiretroviral Guidelines).
- People with HIV should receive patient-centered, evidence-based counseling to support shared decision-making about infant feeding. See Infant Feeding for Individuals With HIV in the United States.
- Providers with questions about ARV management of perinatal HIV exposure should consult an expert in pediatric HIV infection or 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 HIV acquisition 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 viral suppression (defined as at least two consecutive tests with HIV RNA level <50 copies/mL obtained at least 4 weeks apart). 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. Most ARV prophylaxis includes administration of a single agent—usually zidovudine (ZDV). In some situations, combinations of two or three ARV drugs may also be administered as ARV prophylaxis.

- **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.
- **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 12 provides an overview of neonatal ARV management recommendations according to the risk of perinatal HIV transmission to the newborn, and Table 13 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 people with HIV-2 infection is available in HIV-2 Infection and Pregnancy and Table 12. 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 people with HIV and their newborns, and consultants can provide referrals to local or regional pediatric HIV specialists.

Table 12. 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) or from an expert in pediatric HIV infection.

Level of Perinatal HIV Transmission Risk	Description	Neonatal ARV Management
Low Risk of Perinatal HIV Transmission	**Infants ≥37** weeks gestation when the mother— • Is currently receiving and has received at least 10 consecutive weeks of ART during pregnancy, *and* • Has achieved and maintained *or* maintained viral suppression (defined as at least two consecutive tests with HIV RNA levels <50 copies/mL obtained at least 4 weeks apart) for the remainder of the pregnancy, *and*	ZDV for 2 weeks[a]

Table 12. Neonatal Antiretroviral Management According to Risk of HIV Infection in the Newborn

Level of Perinatal HIV Transmission Risk	Description	Neonatal ARV Management
	• Has HIV RNA <50 copies/mL at or after 36 weeks and within 4 weeks of delivery, *and* • Did not have acute HIV infection during pregnancy, *and* • Has reported good ART adherence, and adherence concerns have not been identified.	
	Infants born to mothers who do not meet the criteria above or criteria for high risk below but who have a HIV RNA <50 copies/mL at or after 36 weeks gestation	ZDV for 4 to 6 weeks[a]
	Premature infants (<37 weeks gestation) who are not at high risk of perinatal acquisition of HIV	ZDV for 4 to 6 weeks[a]
High Risk of Perinatal HIV Transmission[a,b]	Mothers who did not receive antepartum ARV drugs, *or* Mothers who received only intrapartum ARV drugs, *or* Mothers who received antepartum ARV drugs but did not have viral suppression (defined as at least two consecutive tests with HIV RNA level <50 copies/mL obtained at least 4 weeks apart) within 4 weeks prior to delivery, *or* Mothers with acute or primary HIV infection during pregnancy or breastfeeding (in which case, breastfeeding should be immediately discontinued)[c]	Presumptive HIV therapy using either ZDV, 3TC, and NVP (treatment dose) *or* ZDV, 3TC, and RAL administered together from birth for 2 to 6 weeks; if the duration of the 3-drug regimen is shorter than 6 weeks, ZDV should be continued alone, to complete a total of 6 weeks of prophylaxis[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 newborn has a positive HIV antibody test	ARV management as described above for newborns with a high risk of perinatal HIV acquisition 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. Refer to the What to Start: Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children in the Pediatric Antiretroviral Guidelines for specific treatment recommendations.

[a] ZDV prophylaxis 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 for

Table 12. Neonatal Antiretroviral Management According to Risk of HIV Infection in the Newborn

infants at high risk of perinatal HIV-2 acquisition. See text for evidence that supports the use of presumptive HIV therapy and a two-drug ARV prophylaxis regimen.

[b] See Intrapartum Care for People With HIV for guidance on indications for scheduled cesarean delivery and intrapartum intravenous 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 born to mothers with acute HIV infection during pregnancy because of the higher risk for *in utero* transmission. If acute HIV is diagnosed during breastfeeding, the mother should immediately discontinue breastfeeding.

[d] The optimal duration of presumptive HIV therapy in newborns who are at a high risk for HIV acquisition is unknown. Newborns who are at a high risk for HIV acquisition should receive the ZDV component of the three-drug presumptive HIV therapy regimen for 6 weeks. The other two ARVs (3TC and NVP *or* 3TC plus RAL) may be administered for 2 to 6 weeks; the recommended duration for treatment with three ARVs varies depends on infant HIV NAT results, maternal viral load at the time of delivery, and additional risk factors for HIV transmission including breastfeeding (see sections below). 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 infant HIV NAT results.

[e] Infant ART should be initiated without waiting for the results of confirmatory HIV NAT testing, given the low likelihood of a false-positive HIV NAT. However, the specimen for confirmatory HIV testing should be obtained prior to ART initiation.

Note: ARV drugs should be initiated as close to the time of birth as possible, preferably within 6 hours of delivery. See Table 13 for dosing specifics.

Key: 3TC = lamivudine; ART = antiretroviral therapy; ARV =antiretroviral; NAT = nucleic acid test; NVP = nevirapine; Panel = Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission and Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV; RAL = raltegravir; ZDV = zidovudine

Table 13. Antiretroviral Drug Dosing Recommendations for Newborns[a]

<table>
<tr><th>Drug</th><th>Drug Doses by Gestational Age at Birth</th></tr>
<tr><td rowspan="3">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 or alternative simplified weight-band dosing (see below)

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>
<tr><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; make this dose increase only for infants with confirmed HIV infection.</td></tr>
<tr><td><30 Weeks' Gestation at Birth

Birth to Age 4 Weeks

• ZDV 2 mg/kg per dose orally twice daily

Age 4 to 8 to 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>ABC[c]

Note: ABC is not approved by the FDA for use in neonates and infants aged <1 month. However, dosing</td><td>≥37 Weeks' Gestation at Birth

Birth to 1 Month

• ABC 2 mg/kg per dose orally twice daily

Age 1 Month to <3 Months</td></tr>
</table>

Table 13. Antiretroviral Drug Dosing Recommendations for Newborns

Drug	Drug Doses by Gestational Age at Birth
recommendations have been modeled using PK simulation. Because of ABC-associated hypersensitivity, negative testing for HLA-B5701 allele should be confirmed prior to administration of ABC.	• ABC 4 mg/kg per dose orally twice daily
3TC	**≥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
NVP[d]	**≥37 Weeks' Gestation at Birth** *Birth to Age 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.
	≥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.
	≥32 to <34 Weeks' Gestation at Birth *Birth to Age 2 Weeks* • NVP 2 mg/kg per dose orally twice daily *Age 2 to 4 Weeks* • NVP 4 mg/kg per dose orally twice daily *Age 4 to 6 Weeks* • NVP 6 mg/kg per dose orally twice daily *Age >6 Weeks* • NVP 200 mg/m^2 BSA per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection.

Table 13. Antiretroviral Drug Dosing Recommendations for Newborns

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

Note: If the mother has taken RAL 2 to 24 hours prior to delivery, the neonate's first dose of RAL should be delayed until 24 to 48 hours after birth; additional ARV drugs should be started as soon as possible.[7]</td><td>≥37 Weeks' Gestation at Birth and Weighing ≥2 kg[e]

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>
<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>
</table>

[a] The optimal duration of presumptive HIV therapy in newborns who are at a high risk for perinatal HIV acquisition is unknown. Newborns who are at a high risk for HIV acquisition should receive the ZDV component of the three-drug presumptive HIV therapy regimen for 6 weeks. The other two ARVs (3TC and NVP *or* 3TC plus RAL) may be administered for 2 to 6 weeks; the recommended duration for these ARVs varies depending on infant 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 infant HIV NAT results.

[b] For ARV management of infants with HIV infection, see the What to Start: Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children section in the Pediatric Antiretroviral Guidelines.

[c] ABC is approved by the FDA for use in children aged ≥3 months when administered as part of an ARV regimen. ABC also has been reported to be safe in infants and children ≥1 month of age. More recently, an ABC dosing recommendation using PK simulation models has been endorsed by the WHO using weight-band dosing for full-term infants from birth to 1 month of age. See Abacavir in Appendix A: Pediatric Antiretroviral Drug Information in the Pediatric Antiretroviral Guidelines for additional information about the use of ABC between birth and 1 month of age. At this time, the Panels do not recommend ABC as part of a presumptive HIV therapy regimen. However, in situations where ZDV is not available or the infant has ZDV-associated toxicity, ABC could be considered an alternative to ZDV. This substitution should be considered in circumstances where increased risk of ZDV toxicity may exist, such as in infants with anemia or neutropenia. Because of ABC-associated hypersensitivity, negative testing for HLA-B5701 allele should be confirmed prior to administration of ABC.

Table 13. Antiretroviral Drug Dosing Recommendations for Newborns

[d] The NVP doses for infants ≥32 to <37 weeks gestation at birth and infants ≥37 weeks gestation at birth are not yet approved by the FDA. The FDA also has not approved a dose of NVP for infants aged <1 month. The doses for infants ≥32 to <34 weeks gestation at birth are based on modeling and might underestimate potential toxicity in infants of 32 to <34 weeks gestational age because the doses used to develop the model were lower than the doses now recommended. See Nevirapine in Appendix A: Pediatric Antiretroviral Drug Information in the Pediatric Antiretroviral Guidelines for additional information about dosing.

[e] RAL dosing is increased at 1 week and 4 weeks of age because metabolism by UGT1A1 is low at birth and increases rapidly during the next 4 to 6 weeks of life. No dosing information is available for preterm infants or infants weighing <2 kg at birth. In infants with HIV infection, twice-daily RAL can be replaced with once-daily DTG at ≥ 4 weeks of age (see Dolutegravir and What to Start: Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children in the Pediatric Antiretroviral Guidelines). The current dosing regimen with two dose changes in the first month of life may be challenging for some families. To minimize dosing changes, some experts increase to the 3 mg/kg twice daily dose upon discharge on day 4 or 5 of life.

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BSA = body surface area; DTG = dolutegravir; FDA = U.S. Food and Drug Administration; IV = intravenous; NVP = nevirapine; the Panels = the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission and the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV; PK = pharmacokinetic; RAL = raltegravir; UGT = uridine diphosphate glucotransferase; WHO = World Health Organization; ZDV = zidovudine

Recommendations for Antiretroviral Drugs in Specific Clinical Situations

In this section and Table 12. Neonatal Antiretroviral Management According to Risk of HIV Infection in the Newborn, the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission and the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panels) presents available data and recommendations for management of newborns with documented HIV and newborns born to mothers who—

- Are at low risk for transmitting HIV to their newborns born at ≥37 weeks gestation, including mothers who –
  - Received at least 10 consecutive weeks of antepartum ARV drugs, *and*
  - Achieved and maintained *or* maintained effective viral suppression (defined as at least two HIV RNA level <50 copies/mL obtained at least 4 weeks apart) for the remainder of the pregnancy, *and*
  - Had a HIV RNA <50 copies/mL at or after 36 weeks, *and*
  - Did not have acute HIV infection during pregnancy, *and*
  - Have reported good ART adherence and adherence concerns have not been identified.
- Are at high risk for transmitting HIV to their newborns, including mothers who—
  - Did not receive antepartum ARV drugs, *or*
  - Received only intrapartum ARV drugs, *or*
  - Received antepartum ARV drugs but do not have effective viral suppression (defined as at least two consecutive tests with HIV RNA level <50 copies/mL obtained at least 4 weeks apart) within 4 weeks prior to 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 and Maintained or *Maintained Viral Suppression on Antepartum Antiretroviral Drugs*

The risk of HIV acquisition in newborns born to people who received ART during pregnancy and labor and who had undetectable viral load near or at the time of delivery is <1%. In the Pediatric AIDS Clinical Trials Group (PACTG) 076 study, ZDV alone reduced the incidence of perinatal HIV transmission by 66%, and ZDV is recommended as prophylaxis for neonates whose mothers received ART that resulted in consistent viral 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, evidence supporting a reduced duration of ZDV prophylaxis in infants born to people who were suppressed virologically during pregnancy and at the 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 people who have a very low risk of HIV transmission. These people have been on ART for longer than 10 weeks **and** have had at least two documented

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 **or** the infant is born prematurely (< 34 weeks gestation) but most recent maternal viral load is <50 copies/mL. 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] The Swiss Federal Office of Public Health does not recommend infant ARV prophylaxis for infants of people with regular follow-up, ART use during pregnancy, and where maternal viral load is <50 copies/mL, ideally sustained throughout pregnancy, but at least at the last two consecutive measurements before delivery where viral load testing is performed at least 4 weeks apart and the last viral load is measured after week 36 of pregnancy.[15] Among 87 infants born to women with HIV RNA levels <50 copies/mL in the last trimester, none acquired HIV infection.[16]

The Panels recommend 2 weeks of ZDV prophylaxis for newborns born at ≥37 weeks gestation if the mother is receiving ART and has received at least 10 consecutive weeks of ART during pregnancy **and** achieved and maintained or maintained viral suppression (defined as at least two consecutive tests with HIV RNA levels <50 copies/mL obtained at least 4 weeks apart) for the remainder of the pregnancy **and** has HIV RNA <50 copies/mL at or after 36 weeks and within 4 weeks of delivery, **and** did not have acute HIV infection during pregnancy, **and** maternal ART adherence is not of concern (see Table 12). Infants born to individuals who do not meet the criteria above or criteria for high risk of transmission (see Table 12), but who have a viral load <50 copies/mL at or after 36 weeks, should receive ZDV alone for 4 to 6 weeks. In addition, all premature infants (<37 weeks gestation) should receive 4 to 6 weeks of ZDV unless they are at high risk of HIV acquisition. Dosing recommendations for ZDV are available for premature newborns, and an intravenous preparation of ZDV is available. Table 13. Antiretroviral Drug Dosing Recommendations for Newborns shows recommended neonatal ZDV dosing based on gestational age and birthweight.

ARV Prophylaxis for Newborns at Low Risk of Perinatal HIV Transmission Who Are Breastfed

Increasingly, individuals who have achieved and maintained *or* maintained viral suppression on ART are considering breastfeeding their infants. Individuals with HIV on ART with a consistently suppressed viral load during pregnancy (at a minimum during the third trimester) and at the time of delivery should be counseled on the options of formula feeding, banked donor human milk, or breastfeeding. The Panels recommend patient-centered, evidence-based counseling to support shared decision-making about infant feeding. See Infant Feeding for Individuals With HIV in the United States for more information on counseling, management, and monitoring.

There is no consensus on appropriate management of ARV prophylaxis for infants of individuals with sustained viral suppression who are breastfed. Available data to guide decisions are from studies in sub-Saharan Africa, where breastfeeding is recommended for all birthing parents with HIV infection. It is important to note that the World Health Organization (WHO) recommends six weeks of NVP for all infants who are breastfed by a parent who is receiving ART in resource-limited countries.[49] In the PROMISE study, among 1,219 infants of mothers on ART, there were 7 HIV transmissions reported. Among these, five mothers had documented detectable viral loads immediately prior to first report of the infant's positive HIV nucleic acid test (NAT); the remaining two mothers had elevated viral loads in subsequent testing.[17] Note that these two infants had their first detectable HIV NAT at weeks 13 and 38 of life, beyond 6 weeks of age where infant NVP was administered according to WHO guidelines. In the Breastfeeding, Antiretrovirals, and Nutrition

study, a sub-study of 31 infected infants and 232 uninfected infants and their mothers[18] demonstrated that there were no HIV transmissions when the mother consistently maintained a viral load less than 100 copies/mL. Bispo et al. have reported a meta-analysis of 11 studies of breastfeeding mothers with HIV who started ART before or during pregnancy and continued until at least 6 months postnatally.[19] The included studies were very heterogeneous and did not include viral load measurements or information about adherence. In addition, some studies included infants receiving NVP prophylaxis. Six of these studies provided estimates of postnatal transmission rates, excluding peripartum infections. In these six studies, the postnatal transmission rate was 1.08% (95% confidence interval: 0.32–1.85) at 6 months in infants who tested HIV negative at 4 to 6 weeks of age. In a *post-hoc* analysis of the HIV Prevention Trials Network (HPTN) 046 study, which showed <1% risk of postnatal HIV transmission in both the extended NVP and placebo arms, the addition of infant prophylaxis did not further reduce breastfeeding transmission in mothers who were receiving ART.[20] Taken together, these data support the efficacy of ART with documented sustained viral suppression to prevent postnatal transmission of HIV, suggesting that the recommended management consisting of 2 weeks of infant ZDV prophylaxis is appropriate for breastfed infants when their mothers have sustained viral suppression. This approach is currently recommended by the British HIV Association (BHIVA).[12]

The Panels could not reach a consensus on recommendations for infant prophylaxis while breastfeeding. Most Panel members agree on adopting the BHIVA recommendation of only 2 weeks of infant ZDV in this scenario. However, several Panel members prefer to extend the duration of ZDV prophylaxis to 4 to 6 weeks. Alternatively, some Panel members recommend 6 weeks of NVP, as currently recommended by WHO for breastfeeding infants at low risk of HIV transmission in resource limited countries. Some others opt to continue NVP dosing throughout breastfeeding. In infants who cannot tolerate ZDV or NVP, alternative regimens include daily lamivudine (3TC) or daily lopinavir/ritonavir (LPV/r).[21,22] If one of these alternative regimens is used, dosing recommendations for 3TC are included in Table 13 and dosing for LPV/r is available in Lopinavir/Ritonavir. LPV/r should not be used in infants before a postmenstrual age of 42 weeks and a postnatal age of 14 days.

Table 14. Infant Antiretroviral Prophylaxis for Newborns of Mothers With Sustained Viral Suppression Who Breastfeed

<table>
<tr><th colspan="2">Newborns at Low Risk of HIV Acquisition During Breastfeeding</th></tr>
<tr><th>Recommended Regimen</th><th>Recommended Duration</th></tr>
<tr><td>ZDV</td><td>ZDV administered for 2 weeks (see Table 13 for dosing)</td></tr>
<tr><th colspan="2">Optional Extended Postnatal Prophylaxis for Newborns at Low Risk of HIV Transmission During Breastfeeding</th></tr>
<tr><th>Optional Regimen</th><th>Optional Recommended Duration</th></tr>
<tr><td>ZDV</td><td>ZDV administered for 4 to 6 weeks (see Table11 for dosing)</td></tr>
<tr><td>NVP</td><td>Simplified Age-Based Dosing for Newborns ≥32 Weeks Gestation Receiving Extended NVP Prophylaxis During Breastfeeding[a]
<table>
<tr><th>Age</th><th>Volume of NVP 10 mg/mL Oral Syrup Daily</th></tr>
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</td></tr>
</table>

Table 14. Infant Antiretroviral Prophylaxis for Newborns of Mothers With Sustained Viral Suppression Who Breastfed

	Birth to 6 weeks	1.5 mL
	6 weeks to 6 months	2.0 mL
	6 months to 9 months	3.0 mL
	9 months to 1 to 4 weeks post-weaning	4.0 mL

[a] Extended NVP prophylaxis during breastfeeding recommendations are adapted from the Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring: Recommendations for a Public Health Approach. If prescribed, these simplified doses should start following confirmation of a negative infant NAT test and completion of a presumptive HIV therapy regimen in infants at high risk of HIV acquisition. For infants at low risk of transmission, these doses can be given from birth. Geneva: World Health Organization; 2021 Jul. Simplified Age-Based Dosing for Newborns ≥32 Weeks Gestation Receiving Extended NVP Prophylaxis During Breastfeeding in Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service delivery and Monitoring: Recommendations for a Public Health Approach

[b] For breastfeeding parents with viral resistance to NVP, alternative regimens for infant prophylaxis after completion of the 4 to 6 weeks of presumptive HIV therapy include daily 3TC or LPV/r; see Table 13. Antiretroviral Drug Dosing Recommendations for Newborns for dosing information.

Newborns Born to Mothers Who Received No Antepartum 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 Panels recommend that all newborns born to mothers who do not have viral suppression (defined as at least two consecutive tests with HIV RNA level <50 copies/mL obtained at least 4 weeks apart and a HIV RNA <50 copies/mL at or after 36 weeks and within 4 weeks prior to delivery), who received only intrapartum ARV drugs, or who received no ARV drugs during pregnancy are at high risk for HIV acquisition and **should receive presumptive HIV therapy**.[5,23-28] These infants should also have a HIV NAT test performed as soon as possible to determine HIV infection status. Primary or acute HIV infection during pregnancy also is associated with an increased risk of perinatal transmission of HIV. Infants born to people who acquired HIV during pregnancy **should receive presumptive HIV therapy** (see Early (Acute and Recent) HIV Infection).

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.[29-37] Because of these potential benefits of early ART, the Panels recommend a three-drug ARV presumptive HIV therapy regimen consisting of ZDV, 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. In the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) P1115, 438 neonates who were at least 34 weeks gestational age at birth and enrolled within 48 hours of birth received a presumptive HIV therapy regimen containing two nucleoside reverse transcriptase inhibitors (NRTIs) (97% received ZDV and 3TC) and NVP dosed at 6 mg/kg twice daily for term neonates (≥37 weeks gestational age) or 4 mg/kg twice daily for 1 week and 6 mg/kg twice daily therapy for preterm neonates (34 to <37 weeks gestational age). Among the

study participants, 7% reported Division of AIDS Grade 3 or 4 adverse events at least possibly related to ART. These Grade 3 or 4 events included 6% with neutropenia and 1% with anemia.[28] The Early Infant Treatment Study in Botswana initiated ART consisting of NVP 6 mg/kg twice daily, ZDV, and 3TC at <7 days gestational age in 40 infants who were ≥35 weeks gestational age and ≥2 kg at birth with HIV infection. Eighteen percent of these infants had Grade 3 or 4 hematologic toxicity, mostly neutropenia.[38] Similar findings have been reported from other studies of presumed HIV therapy or early treatment of confirmed HIV infection.[38-40] 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 than 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.[41] In a Madrid, Spain, cohort, 227 infants received prophylaxis containing two or more drugs (64% who received ZDV, 3TC, and NVP) and 1,002 infants received ZDV alone. Although there were more frequent reports of anemia and neutropenia among infants receiving prophylaxis with 2 or more drugs, there were no significant differences in grade 3 or 4 anemia or neutropenia between the two groups.[42] 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%; $P = 0.01$).[40]

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 at least 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.[43-48]

At this time, if a presumptive HIV therapy regimen is required, the Panels recommend using a combination of ZDV, 3TC, and NVP (treatment dose) or ZDV, 3TC, and RAL (see Table 12. Neonatal Antiretroviral Management According to Risk of HIV Infection in the Newborn, and Table 13. Antiretroviral Drug Dosing Recommendations for Newborns). The optimal duration of presumptive HIV therapy in newborns at high risk of perinatal HIV acquisition is unknown. Some Panel members opt to discontinue additional medications if infant birth 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, NVP should be replaced with an integrase strand transfer inhibitor or a boosted protease inhibitor at the appropriate infant age. Information about selecting an agent and recommended dosing can be found in What to Start: Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children and Appendix A: Pediatric Antiretroviral Drug Information in the Pediatric Antiretroviral Guidelines.

New dosing recommendations for abacavir (ABC) in neonates based on the IMPAACT P1106 trial and two observational European and African cohorts are now available from WHO.[49] ABC is not approved by the U.S. Food and Drug Administration (FDA) for use in neonates and infants aged <3 months. However, a 2-mg/kg-per-dose twice-daily dose has been modeled using PK simulation and is endorsed by WHO using weight-band dosing for full-term infants from birth through 1 month of age. Limited observational data suggested safety of ABC when initiated in neonates <1 month of age (see Abacavir in the Pediatric Antiretroviral Guidelines).[50,51] At this time, the Panels do not

recommend ABC as part of a presumptive HIV therapy regimen. However, in situations where ZDV is not available or the infant has ZDV-associated toxicity, ABC could be considered an alternative to ZDV. This substitution should be considered in circumstances where increased risk of ZDV toxicity may exist, such as in infants with anemia or neutropenia. It also is suggested that negative testing for HLA-B5701 allele be confirmed prior to administration of ABC. 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

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development–HIV Prevention Trials Network 040/Pediatric AIDS Clinical Trials Group 1043 (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 NRTI resistance in 3 of 53 participants (5.7%) with *in utero* infection who were treated with ZDV alone and in 6 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% of study participants.[52]

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 13.

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 people who received ARV drugs during pregnancy but who have a detectable viral load within 4 weeks prior to delivery, 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% and 0.3% when the mother had a viral load <50 copies/mL at delivery. Rates of transmission in these studies increased to 1.1% and 1.5 percent when viral load was 50 to 399 copies/mL and 2.8% and 4.1% when viral load was >400 copies/mL.[53,54] Although most Panel members would recommend initiating presumptive HIV therapy with any detectable level of viremia within 4 weeks prior to delivery, others may opt for a two-drug prophylaxis regimen if maternal viral load was less than 200 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 acquisition, 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 this section). 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 Perinatal HIV/AIDS hotline (1-888-448-8765) is recommended when selecting a regimen based on case-specific risk factors.

Breastfeeding in Newborns at High Risk of Perinatal HIV Acquisition

For people with HIV who are not on ART and/or have not achieved sustained viral suppression at the time of delivery, the Panels strongly advise against breastfeeding. Replacement feeding with formula or banked pasteurized donor human milk is recommended given the high risk of postnatal HIV transmission associated with viremia during breastfeeding (see Infant Feeding for Individuals With HIV in the United States).

If after counseling, the breastfeeding parent without a suppressed viral load chooses to continue to breastfeed, the parent and provider should remain engaged; the provider should offer guidance on ARV prophylaxis (see below) and testing for the infant and assist the parent to work with their primary provider to most rapidly regain and maintain virologic suppression. Diagnosis of HIV Infection in Infants and Children provides guidance about HIV diagnostic testing for infants who are being breastfed.

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.[22,55-58] Many of these studies were in mothers who were not receiving ART or, if receiving ART, did not have viral load routinely measured. If, despite the recommendation not to breastfeed, the infant is breastfed by a parent with unsuppressed viral load, the Panels recommend 6 weeks of presumptive HIV therapy followed by daily NVP throughout breastfeeding and for 1 to 4 weeks after weaning to minimize the risk of vertical transmission. Dosing recommendations are shown in Table 13. For breastfeeding parents with viral resistance to NVP, alternative regimens for infant prophylaxis after completion of the 6 weeks of presumptive HIV therapy include daily 3TC or LPV/r. Consultation with an expert in pediatric HIV infection is strongly recommended. Coordination with adult care providers (such as obstetric or infectious disease clinicians) can provide appropriate services to support adherence.

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

HIV testing is recommended during labor for people 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). HIV test results should be available within 60 minutes. If maternal or infant testing is positive, the newborn **should begin presumptive HIV therapy immediately** without waiting for the results of supplemental tests. HIV testing with quick turnaround times 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 infection until supplemental testing clarifies maternal and newborn HIV 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 breastfeeding parent 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 breastmilk can be recommended. If HIV is ruled out, breastfeeding can resume. If HIV is confirmed, breastfeeding should be discontinued permanently.[59]

Newborns Born to Mothers With Antiretroviral Drug-Resistant Virus

The optimal ARV regimen for newborns born to mothers 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,[60] perinatal transmission of multidrug-resistant virus does occur.[61-66] 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).[66] Maraviroc (MVC) was approved recently for infants ≥2 kg and may provide an additional treatment option for newborns of mothers carrying multidrug-resistant HIV-1 that remains CCR5-trophic.[67] However, the lack of data about MVC as prophylaxis or treatment in infants 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, ART initiation should not be delayed while waiting for the results of the confirmatory HIV NAT, given the low likelihood of a false-positive HIV NAT. A confirmatory specimen should be obtained prior to ART initiation. To date, 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 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.[68] 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.[38]

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).

For information about recommended ART regimens for newborns, please see What to Start: Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children in the Pediatric Antiretroviral Guidelines.

Newborns of Mothers Who Receive an HIV Diagnosis While Breastfeeding

People 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 breastfeeding parents 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. Given the high risk of HIV transmission when HIV is acquired or diagnosed during breastfeeding, the Panels advise against breastfeeding and recommend replacement feeding with formula or banked pasteurized donor human milk if HIV infection is confirmed in the breastfeeding parent.[69]

Other than discontinuing breastfeeding, optimal strategies for managing a newborn who was breastfed by a parent with HIV (often because the parent just learned of her own HIV diagnosis) have yet to be defined. Some Panel members would consider the use of post-exposure prophylaxis in newborns for 4 to 6 weeks after cessation of breastfeeding. Post-exposure 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 a single exposure to the virus.[70] 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 person with acute HIV infection who is breastfeeding, 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.[70] 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 Perinatal HIV/AIDS hotline (1-888-448-8765) can provide referrals to local or regional pediatric HIV specialists.

In the event that the parent does not stop breastfeeding, interventions similar to individuals with chronic HIV infection and detectable viral load who breastfeed should be followed. In these scenarios, 6 weeks of a presumptive HIV regimen followed by daily NVP throughout breastfeeding and for 1 to 4 weeks after weaning should be considered to minimize the risk of vertical transmission. See Breastfeeding in Newborns at High Risk of Perinatal HIV Acquisition, above, and Infant Feeding for Individuals with HIV in the United States. Again, consultation with a pediatric HIV specialist or the National Perinatal HIV hotline (1-888-448-8765) is recommended.

Newborns exposed to HIV during breastfeeding should be tested for HIV infection prior to initiating presumptive HIV therapy, as well as at specified time points after diagnosis of HIV infection in the breastfeeding person 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 and Table 13. Recommended Virologic Testing Schedule for Infants Who Were Exposed to HIV According to Risk of Perinatal HIV Acquisition At and After Birth). 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 1 week[26,71,72] 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% of newborns, and neutropenia was reported in 18% of newborns who were exposed to ZDV/3TC, with 2% of newborns requiring blood transfusion and 4% requiring treatment discontinuation for toxicity.[73] 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% and neutropenia seen in 13% of newborns.[74]

Recent data from the IMPAACT P1106 trial and two observational European and African cohorts provided reassuring data on the safety of ABC in infants when initiated at <3 months of age, including in infants with weight <3 kg.[75-77] See the Abacavir section of the Pediatric Antiretroviral Guidelines for additional information. At this time, the Panels suggest using ABC as an alternative to ZDV in certain situations and after negative HLA-B5701 allele testing.

Experience with other NRTI drugs for neonatal prophylaxis is more limited.[78,79] Hematologic and mitochondrial toxicity may be more common with exposure to multiple NRTI drugs than with exposure to a single NRTI.[73,80-83]

In rare cases, chronic multiple-dose NVP prophylaxis in pregnant women has been associated with severe and potentially life-threatening rash and hepatic toxicity.[84] 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.[5,55-58,85]

The FDA 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. PK modeling studies in infants with birthweight <2.5 kg with gestational age at birth ranging from 32.7 to 40 weeks suggests that prematurity reduces RAL clearance, and a modified dosing regimen may be needed to avoid elevated plasma RAL concentrations.[86] 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.[46] 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. Only one episode of Grade 4 neutropenia, possibly related to RAL, was reported. Among infants with RAL exposure (infants whose mothers received RAL within 2 to 24 hours before delivery), the first dose of RAL should be delayed for 24 to 48 hours after birth.[87] See the Raltegravir section of the Pediatric Antiretroviral Guidelines for additional information.

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