



**Recommendations for the Use of Antiretroviral Drugs in  
Pregnant Women with HIV Infection and Interventions to Reduce  
Perinatal HIV Transmission in the United States**

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## Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV (Last Updated December 7, 2018; last reviewed December 7, 2018)

### Panel's Recommendations

- All newborns perinatally exposed to HIV should receive postpartum antiretroviral (ARV) drugs to reduce the risk of perinatal transmission of HIV (**AI**).
- Newborn ARV regimens—at gestational-age-appropriate doses—should be initiated as close to the time of birth as possible, preferably within 6 to 12 hours of delivery (**AII**).
- The selection of a newborn ARV regimen should be determined based on maternal and infant factors that influence risk of perinatal transmission of HIV (**AIII**). 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.
  - **Empiric HIV Therapy:** The administration of a three-drug ARV regimen to newborns at highest risk of perinatal acquisition of HIV. Empiric HIV therapy is intended to be preliminary treatment for a newborn who is later documented to have HIV but 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 dosages (antiretroviral therapy [ART]) to newborns with documented HIV infection (see [Diagnosis of HIV Infection](#)).
- For newborns whose mothers have received ART during pregnancy with sustained viral suppression near delivery and for whom there are no concerns related to maternal adherence, a 4-week zidovudine ARV prophylaxis regimen can be used (**BII**).
- Newborns at higher risk of perinatal acquisition of HIV should receive a multi-drug ARV prophylaxis regimen or empiric HIV therapy based on clinician assessment of risk (see [Tables 8](#) and [9](#) for recommended regimens). **Newborns at higher 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 without viral suppression near delivery (**AII**), *or*
  - Have primary or acute HIV infection during pregnancy (**AII**), *or*
  - Have primary or acute HIV infection during breastfeeding (**AII**).
- Newborns of women with unknown HIV status who test HIV positive on expedited testing performed during labor or shortly after birth should initiate an ARV regimen (ARV prophylaxis or empiric HIV therapy based on clinician assessment of risk) (**AII**). If supplemental testing is negative, the ARV regimen can be discontinued (**AII**).
- For newborns with HIV infection, ART should be initiated (**AI**).
- The use of ARV drugs other than zidovudine, lamivudine, and nevirapine cannot be recommended for any indication in premature newborns (<37 weeks gestational age) because of lack of dosing and safety data (**BIII**).
- 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 in the neonatal period to reduce perinatal transmission of HIV, with selection of the appropriate ARV regimen guided by the level of transmission risk. The most important factors that influence the risk of HIV transmission to a newborn exposed to HIV are whether the mother has received antepartum/intrapartum antiretroviral therapy (ART) and her viral load. The risk of transmission is increased in the absence of maternal ART or if

maternal antepartum/intrapartum treatment was started after early pregnancy or was ineffective in producing virologic suppression; higher maternal viral load, especially in later pregnancy, correlates with higher risk of transmission. There is a spectrum of transmission risk that depends on these and other maternal and infant factors, including mode of delivery, gestational age at delivery, and maternal health status. HIV transmission can occur *in utero*, intrapartum, or during breastfeeding.

Historically, the use of ARV drugs in the newborn period was referred to as ARV prophylaxis since 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 empiric treatment of HIV. In this guideline, 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, as well as combinations of two or three ARV drugs.
- **Empiric HIV Therapy:** The administration of a three-drug ARV regimen to newborns at highest risk of HIV acquisition. Empiric HIV therapy is intended to be early treatment for a newborn who is later documented to have acquired HIV, but 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 treatment regimen to newborns with documented HIV (see [Diagnosis of HIV Infection](#)). HIV therapy is lifelong.

The terms ARV prophylaxis and empiric HIV therapy describe the clinician's intent in prescribing ARV drugs and may be overlapping. For example, an empiric HIV therapy regimen also provides ARV prophylaxis for a newborn. However, two-drug (and some three-drug) ARV prophylaxis regimens, notably those that use prophylactic rather than therapeutic dosages of nevirapine, are not considered empiric HIV therapy.

The interval during which newborn ARV prophylaxis or empiric HIV therapy can be initiated and still be beneficial is undefined; however, most studies support providing ARVs as early as possible after delivery.<sup>1-6</sup>

[Table 8](#) provides an overview of neonatal ARV management recommendations according to risk of perinatal transmission of HIV to the newborn and [Table 8](#) summarizes the dosing recommendations for ARV dosing in newborns. Additional information about dose selection for newborns, including premature infants (<37 weeks gestational age), can be found in [Pediatric Antiretroviral Drug Information](#). In addition, the [National Perinatal HIV Hotline](#) (888-448-8765) is a federally funded service providing free clinical consultation for difficult cases to providers caring for pregnant women living with HIV and their newborns, and can provide referral to local or regional pediatric HIV specialists.

**Table 8. Newborn 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 (888-448-8765).

Category	Description	Neonatal ARV Management
<b>Low Risk of Perinatal HIV Transmission</b>	<ul style="list-style-type: none"> <li>Mothers who received ART during pregnancy with sustained viral suppression near delivery and no concerns related to adherence</li> </ul>	ZDV for 4 weeks
<b>Higher Risk of Perinatal HIV Transmission<sup>a,b</sup></b>	<ul style="list-style-type: none"> <li>Mothers who received neither antepartum nor intrapartum ARV drugs</li> <li>Mothers who received only intrapartum ARV drugs</li> <li>Mothers who received antepartum and intrapartum ARV drugs but who have detectable viral load near delivery, particularly if delivery was vaginal</li> <li>Mothers with acute or primary HIV infection during pregnancy or breastfeeding (in which case, the mother should discontinue breastfeeding).<sup>c</sup></li> </ul>	2-drug ARV prophylaxis (NICHD-HPTN 040/PACTG 1043 regimen) with 6 weeks ZDV and 3 doses of NVP (prophylactic dosage, with doses given within 48 hours of birth, 48 hours after first dose, and 96 hours after second dose) or Empiric HIV therapy using either ZDV, 3TC, and NVP (treatment dosage) or ZDV, 3TC, and RAL administered from birth to age 6 weeks. <sup>d</sup>
<b>Presumed Newborn HIV Exposure</b>	<ul style="list-style-type: none"> <li>Mothers with unknown HIV status who test HIV positive at delivery or postpartum or whose newborns have a positive HIV antibody test</li> </ul>	ARV management as above (for higher risk of perinatal HIV transmission)  Infant ARVs should be discontinued immediately if supplemental testing confirms that the mother does not have HIV.
<b>Newborn with HIV<sup>e</sup></b>	<ul style="list-style-type: none"> <li>Positive newborn HIV virologic test/NAT</li> </ul>	3-drug ARV regimen using treatment dosages

<sup>a</sup> See text for evidence supporting a 2-drug ARV prophylaxis regimen and empiric HIV therapy.

<sup>b</sup> See the [Intrapartum Care](#) section 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.

<sup>c</sup> Most Panel members would opt to administer empiric 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, mother should stop breastfeeding.

<sup>d</sup> The optimal duration of empiric HIV therapy in newborns at higher risk of perinatal HIV transmission is unknown. Some Panel members opt to discontinue NVP, RAL, and/or 3TC when a birth NAT returns negative, while others would continue empiric HIV therapy for infants at highest risk of HIV acquisition for 6 weeks. In all cases, ZDV should be continued for 6 weeks. It is recommended that providers consult with an expert in pediatric HIV infection to determine therapy duration based on case-specific risk factors and interim HIV NAT results.

<sup>e</sup> Most Panel members do not recommend delaying the initiation of ART pending results of the confirmatory HIV NAT, given 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 to 12 hours of delivery. See [Table 9](#) for dosing specifics.

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

**Table 9. Antiretroviral Dosing Recommendations for Newborns (page 1 of 3)**

Newborns at Low Risk of Perinatal HIV Transmission	
<b>Recommended Regimen</b>	<b>Recommended Duration</b>
• ZDV	• ZDV administered for 4 weeks
Newborns at Higher Risk of Perinatal HIV Transmission	
<b>Recommended Regimen</b>	<b>Recommended Duration</b>
• 2-drug ARV prophylaxis with ZDV and 3 doses of NVP (NICHD-HPTN 040/PACTG 1043 regimen), or	• ZDV administered for 6 weeks; 3 doses of NVP during the first week of life
• Empiric HIV therapy with ZDV/3TC/NVP, or	• ZDV administered for 6 weeks; 3TC and NVP administered for 2–6 weeks, up to 6 weeks of age <sup>a</sup>
• Empiric HIV therapy with ZDV/3TC/RAL	• ZDV administered for 6 weeks; 3TC and RAL administered for 2–6 weeks, up to 6 weeks of age <sup>a</sup>
Newborns with HIV Infection	
<b>Recommended Regimen</b>	<b>Recommended Duration</b>
• HIV therapy with ZDV/3TC/NVP, or	• Lifelong therapy
• HIV therapy with ZDV/3TC/RAL	• Lifelong therapy

Drug	Indication			
	Low Risk Prophylaxis	Higher Risk Prophylaxis: 2-Drug	Higher Risk Prophylaxis: Empiric and HIV Therapy	
<b>ZDV</b> <b>Note:</b> For newborns unable to tolerate oral agents, the IV dose is 75% of the oral dose while maintaining the same dosing interval.	$\geq 35$ Weeks Gestation at Birth: • ZDV 4 mg/kg/dose orally twice daily <u>Simplified Weight-Band Dosing for Newborns <math>\geq 35</math> Weeks Gestation at Birth:</u>		$\geq 35$ Weeks Gestation at Birth <i>Birth–4 Weeks:</i> • ZDV 4 mg/kg/dose orally twice daily <i>Age &gt;4 Weeks:</i> • ZDV 12 mg/kg/dose orally twice daily <u>Simplified Weight-Band Dosing for Newborns Aged <math>\geq 35</math> Weeks Gestation from Birth to 4 Weeks:</u>	
	<b>Weight Band (kg)</b>	<b>Volume (mL) ZDV 10 mg/mL Oral Syrup Twice Daily</b>	<b>Weight Band (kg)</b>	<b>Volume (mL) ZDV 10 mg/mL Oral Syrup Twice Daily</b>
	2 to <3 kg	1 mL	2 to <3 kg	1 mL
	3 to <4 kg	1.5 mL	3 to <4 kg	1.5 mL
	4 to <5 kg	2 mL	4 to <5 kg	2 mL
	$\geq 30$ to <35 Weeks Gestation at Birth <i>Birth to Age 2 Weeks:</i> • ZDV 2 mg/kg/dose orally twice daily <i>Age 2 Weeks to 4–6 Weeks:</i> • ZDV 3 mg/kg/dose orally twice daily		$\geq 30$ to <35 Weeks Gestation at Birth <i>Birth to Age 2 Weeks:</i> • ZDV 2 mg/kg/dose orally twice daily <i>Age 2 Weeks to 6–8 Weeks:</i> • ZDV 3 mg/kg/dose orally twice daily <i>Age &gt;6–8 Weeks:</i> • ZDV 12 mg/kg/dose orally twice daily	
	<30 Weeks Gestation at Birth <i>Birth to Age 4–6 Weeks:</i> • ZDV 2 mg/kg/dose orally twice daily		<30 Weeks Gestation at Birth <i>Birth to Age 4 Weeks:</i> • ZDV 2 mg/kg/dose orally twice daily <i>Age 4 to 8–10 Weeks:</i> • ZDV 3 mg/kg/dose orally twice daily <i>Aged &gt;8–10 Weeks:</i> • ZDV 12 mg/kg/dose orally twice daily	

**Table 9. Antiretroviral Dosing Recommendations for Newborns (page 2 of 3)**

Indication																											
Drug	Low Risk Prophylaxis	Higher Risk Prophylaxis: 2-Drug	Higher Risk Prophylaxis: Empiric and HIV Therapy																								
<b>3TC</b>	N/A	N/A	<p>≥32 Weeks Gestation at Birth</p> <p><i>Birth to Age 4 Weeks:</i></p> <ul style="list-style-type: none"> <li>• 3TC 2 mg/kg/dose orally twice daily</li> </ul> <p><i>Age &gt;4 Weeks:</i></p> <ul style="list-style-type: none"> <li>• 3TC 4 mg/kg/dose orally twice daily</li> </ul>																								
<b>NVP</b>	N/A	<p>≥32 Weeks Gestation at Birth:</p> <ul style="list-style-type: none"> <li>• NVP in 3 doses given</li> <li>1. Within 48 hours of birth,</li> <li>2. 48 hours after the 1st dose, and</li> <li>3. 96 hours after the 2nd dose</li> </ul> <p><u>Birth Weight 1.5 to 2 kg:</u></p> <ul style="list-style-type: none"> <li>• NVP 8 mg per dose orally. <b>Note:</b> No calculation is required for this dose; <b>this is the actual dose, not a mg/kg dose.</b></li> </ul> <p><u>Birth Weight &gt;2 kg:</u></p> <ul style="list-style-type: none"> <li>• NVP 12 mg per dose orally. <b>Note:</b> No calculation is required for this dose; <b>this is the actual dose, not a mg/kg dose.</b></li> </ul>	<p>≥37 Weeks Gestation at Birth</p> <p><i>Birth to Age 4 Weeks:</i></p> <ul style="list-style-type: none"> <li>• NVP 6 mg/kg/dose orally twice daily<sup>b</sup></li> </ul> <p><i>Age &gt;4 Weeks:</i></p> <ul style="list-style-type: none"> <li>• NVP 200 mg/m<sup>2</sup> of BSA/dose orally twice daily</li> </ul> <p>34 to &lt;37 Weeks Gestation at Birth</p> <p><i>Birth to Age 1 Week:</i></p> <ul style="list-style-type: none"> <li>• NVP 4 mg/kg/dose orally twice daily</li> </ul> <p><i>Age 1 to 4 Weeks:</i></p> <ul style="list-style-type: none"> <li>• NVP 6 mg/kg/dose orally twice daily</li> </ul> <p><i>Age &gt;4 Weeks:</i></p> <ul style="list-style-type: none"> <li>• NVP 200 mg/m<sup>2</sup> of BSA/dose orally twice daily</li> </ul> <p><b>Note:</b> NVP dose adjustment at 4 weeks of age is optional for empiric HIV therapy.</p>																								
<b>RAL</b>	N/A	N/A	<p>≥37 Weeks Gestation at Birth and Weighing ≥2 kg<sup>c</sup></p> <p><i>Birth to Age 6 Weeks:</i></p> <table border="1"> <thead> <tr> <th>Body Weight (kg)</th> <th>Volume (Dose) of Suspension, RAL 10 mg/mL, to be Administered</th> </tr> </thead> <tbody> <tr> <td><b>Birth to 1 Week: Once Daily Dosing</b></td> <td><b>Approximately 1.5 mg/kg/dose</b></td> </tr> <tr> <td>2 to &lt;3 kg</td> <td>0.4 mL (4 mg) once daily</td> </tr> <tr> <td>3 to &lt;4 kg</td> <td>0.5 mL (5 mg) once daily</td> </tr> <tr> <td>4 to &lt;5 kg</td> <td>0.7 mL (7 mg) once daily</td> </tr> <tr> <td><b>1 to 4 Weeks: Twice Daily Dosing</b></td> <td><b>Approximately 3 mg/kg/dose</b></td> </tr> <tr> <td>2 to &lt;3 kg</td> <td>0.8 mL (8 mg) twice daily</td> </tr> <tr> <td>3 to &lt;4 kg</td> <td>1 mL (10 mg) twice daily</td> </tr> <tr> <td>4 to &lt;5 kg</td> <td>1.5 mL (15 mg) twice daily</td> </tr> <tr> <td><b>4 to 6 Weeks: Twice Daily Dosing</b></td> <td><b>Approximately 6 mg/kg/dose</b></td> </tr> <tr> <td>3 to &lt;4 kg</td> <td>2.5 mL (25 mg) twice daily</td> </tr> <tr> <td>4 to &lt;6 kg</td> <td>3 mL (30 mg) twice daily</td> </tr> </tbody> </table> <p><b>Note:</b> 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 birth; additional ARVs should be started as soon as possible.</p>	Body Weight (kg)	Volume (Dose) of Suspension, RAL 10 mg/mL, to be Administered	<b>Birth to 1 Week: Once Daily Dosing</b>	<b>Approximately 1.5 mg/kg/dose</b>	2 to <3 kg	0.4 mL (4 mg) once daily	3 to <4 kg	0.5 mL (5 mg) once daily	4 to <5 kg	0.7 mL (7 mg) once daily	<b>1 to 4 Weeks: Twice Daily Dosing</b>	<b>Approximately 3 mg/kg/dose</b>	2 to <3 kg	0.8 mL (8 mg) twice daily	3 to <4 kg	1 mL (10 mg) twice daily	4 to <5 kg	1.5 mL (15 mg) twice daily	<b>4 to 6 Weeks: Twice Daily Dosing</b>	<b>Approximately 6 mg/kg/dose</b>	3 to <4 kg	2.5 mL (25 mg) twice daily	4 to <6 kg	3 mL (30 mg) twice daily
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<sup>a</sup> The optimal duration of empiric HIV therapy in newborns at higher risk of perinatal HIV transmission is unknown. Some Panel members opt to discontinue NVP, RAL, and/or 3TC when birth NAT returns negative, while others would continue empiric HIV therapy for infants at the highest risk of HIV acquisition for 6 weeks. In all cases in which the newborn is at higher risk of HIV acquisition, ZDV should be continued for 6 weeks. Consultation with an expert in pediatric HIV to select a therapy duration based on case-specific risk factors and interim HIV NAT results is recommended.



**Table 9. Antiretroviral Dosing Recommendations for Newborns** (page 3 of 3)

<sup>b</sup> Investigational NVP treatment dose recommended by the Panel; FDA has not approved a dose of NVP for infants <1 month of age.

<sup>c</sup> 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 to 6 weeks of life. No dosing information is available for preterm or low birthweight infants.

**Key to Acronyms:** 3TC = lamivudine; ARV = antiretroviral; BSA = body surface area; FDA = Food and Drug Administration; IV = intravenous; N/A = no recommendation; 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; UGT1A1 = uridine diphosphate glucotransferase; ZDV = zidovudine

### ***Recommendations for Antiretrovirals in Specific Clinical Situations***

In the following sections 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 with effective viral suppression
- Are at higher risk of transmitting HIV to their newborns, including mothers who:
  - Received neither antepartum nor intrapartum ARV drugs
  - Received only intrapartum ARV drugs, *or*
  - Received antepartum and intrapartum ARV drugs but who had detectable viral load near delivery, particularly if delivery was vaginal
- Have acute or primary HIV infection during pregnancy or breastfeeding
- Have unknown HIV status
- Have known ARV drug-resistant virus

#### **Newborns Born to Mothers Who Received Antepartum/Intrapartum Antiretroviral Drugs with Effective Viral Suppression**

The risk of HIV acquisition in newborns born to women who received ART regimens during pregnancy and labor and had undetectable viral loads at delivery is <1%. In the PACTG 076 study, zidovudine alone was shown to effectively reduce perinatal HIV transmission and is recommended as prophylaxis for neonates whose mothers received ART that resulted in consistent virologic suppression during pregnancy. The optimal minimum duration of neonatal zidovudine prophylaxis has not been established in clinical trials. A 6-week newborn zidovudine regimen was studied in PACTG 076. However, in the United Kingdom and many other European countries, where a 4-week neonatal zidovudine prophylaxis regimen has been recommended for newborns born to mothers who have received ART regimens during pregnancy and have viral suppression, there has been no apparent increase in the overall HIV perinatal transmission rate.<sup>7,8</sup> Compared with the 6-week zidovudine regimen, a 4-week zidovudine regimen has been reported to allow earlier recovery from anemia in otherwise healthy newborns.<sup>9</sup>

Therefore, the Panel now recommends a 4-week neonatal zidovudine prophylaxis regimen for newborns if the mother has received ART during pregnancy with viral suppression (usually defined as confirmed HIV RNA level below the lower limits of detection of an ultrasensitive assay) at or after 36 weeks gestation, and there are no concerns related to maternal adherence. Dosing recommendations for zidovudine are available for premature newborns and an intravenous preparation is available. [Table 9](#) shows recommended neonatal zidovudine dosing based on gestational age and birthweight.

## **Newborns Born to Mothers Who Have Received No Antepartum or Intrapartum Antiretroviral Drugs, Who Have Received Intrapartum Antiretroviral Drugs Only, Who Have Received Antiretroviral Drugs and Do Not Have Viral Suppression Near Delivery, or Who Have Acquired HIV During Pregnancy or Breastfeeding**

All newborns born to mothers with detectable viral load at the time of delivery, who received only intrapartum ARV drugs, or who have received no ARV drugs during pregnancy or delivery, are at higher risk of HIV acquisition and **should receive a multi-drug ARV prophylaxis regimen or empiric HIV therapy**.<sup>5,10-14</sup> The experience with these regimens is described below. Currently, the optimal duration of an empiric HIV therapy regimen in newborns at higher risk of perinatal HIV transmission is unknown. **When birth HIV nucleic acid test (NAT) returns negative, some Panel members would opt to discontinue nevirapine, raltegravir, and/or lamivudine, while others would continue empiric HIV therapy for 6 weeks. In all cases in which the newborn is at higher risk of HIV acquisition, zidovudine should be continued for 6 weeks. Consultation with an expert in pediatric HIV is recommended to select a duration of therapy based on case-specific risk factors and interim HIV NAT results.**

For those women who received ARV drugs during pregnancy but have a detectable viral load near delivery **(on or after 36 weeks gestation)**, the level of maternal viremia that would trigger the use of **a multi-drug ARV prophylaxis regimen or empiric 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 viral load measurements <50 copies/mL at delivery. Rates of transmission in these studies increased to 1.1% and 1.5% when viral load measurements were 50 to 399 copies/mL and 2.8% and 4.1% when viral load measurements were >400 copies/mL.<sup>15,16</sup> However, there has been no study to compare the relative efficacy of **a multi-drug ARV prophylaxis regimen or empiric HIV therapy** to standard newborn prophylaxis at these different thresholds of maternal viremia. While some Panel members would recommend a multi-drug ARV prophylaxis regimen or empiric HIV therapy with any level of detectable viremia, others reserve **multi-drug ARV prophylaxis** regimens and empiric HIV therapy until higher levels of maternal viral load are documented. The decision whether to initiate a **multi-drug ARV prophylaxis** regimen or empiric HIV therapy should be made following discussion with the parents weighing the risks and benefits of the proposed regimen.

Primary or acute HIV infection during pregnancy is associated with an increased risk of perinatal transmission of HIV. **A multi-drug ARV prophylaxis regimen** or empiric HIV therapy should be administered to the infant until **maternal** HIV can be confirmed or ruled out. (see [Acute HIV Infection](#)).

In summary, in these scenarios where the infant is at higher risk of HIV transmission, the Panel recommends either **a multi-drug ARV prophylaxis regimen, specifically the NICHD-HPTN 040/PACTG 1043 regimen**, or empiric HIV therapy. The data supporting the use these regimens are summarized below. Choosing between these regimens will depend on clinician assessment of the likelihood of HIV transmission.

### **Multi-Drug Antiretroviral Prophylaxis**

There is a paucity of data from randomized clinical trials to guide the optimal selection of a newborn multi-ARV prophylaxis regimen. To date, the NICHD-HPTN 040/PACTG 1043 trial is the only randomized clinical trial of multi-ARV prophylaxis in newborns at higher risk of HIV acquisition. 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 1 of 3 newborn prophylaxis regimens: the standard 6-week zidovudine regimen; 6 weeks of zidovudine plus three doses of nevirapine given during the first week of life (first dose at birth–48 hours, second dose 48 hours after the first dose, and third dose 96 hours after the second dose); and 6 weeks of zidovudine plus 2 weeks of lamivudine/neftravir. Forty-one percent of the mothers received zidovudine during labor. The risk of intrapartum transmission was significantly lower in the 2- and 3-drug arms (2.2% and 2.5%, respectively, vs. 4.9% for 6 weeks of zidovudine alone;  $P = 0.046$  for each experimental arm vs. zidovudine alone).<sup>5</sup> The NICHD-HPTN 040/PACTG 1043 regimen was associated with nucleoside reverse transcriptase inhibitor (NRTI) resistance in 3 of 53 (5.7%) participants with *in utero* infection who were



treated with zidovudine alone, and in 6 of 33 (18.2%) participants treated with zidovudine plus nevirapine ( $P > 0.05$ ). In addition, the third drug in the three-arm regimen was nelfinavir, which has highly variable pharmacokinetics (PKs) in this age group and did not reach the **nelfinavir target plasma concentration** in 46% of study participants.<sup>17</sup> 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 zidovudine-alone regimen (27.5% vs. 15%,  $P < 0.0001$ ).

Data from Europe and the United States indicate increasing use of multi-drug ARV prophylaxis regimens in newborns exposed to HIV. In the United Kingdom and Ireland, use of the regimens increased from 9% of newborns exposed to HIV between 2001 to 2004 to 13% between 2005 to 2008 and, in a poll of 134 U.S.-based providers, 62% reported using multi-ARV prophylaxis regimens in high-risk newborns.<sup>18-20</sup> However, interpretation of these observational studies is complicated by the definition of ARV prophylaxis, use of prophylaxis versus treatment dosing of nevirapine, and combining multiple different ARV prophylaxis regimens to compare safety and efficacy with zidovudine monotherapy. Many studies include single-dose nevirapine **combined** with another ARV, usually zidovudine, as **two-drug HIV prophylaxis**. Most do not report whether nevirapine was administered at the recommended prophylaxis dose or at a higher dose as part of empiric HIV therapy. So, despite increasing use of various ARV prophylaxis regimens, comprehensive data on efficacy and safety are lacking. For newborns at higher risk of HIV acquisition ([Table 8](#)), the Panel recommends the NICHD-HPTN 040/PACTG 1043 2-drug regimen of 6 weeks of zidovudine plus 3 doses of nevirapine as an option for management.

### Empiric HIV Therapy

The other option that the Panel recommends for newborns at higher risk of perinatal acquisition of HIV is a three-drug ARV empiric HIV therapy regimen consisting of zidovudine, lamivudine, and either nevirapine (at treatment dosage) or raltegravir.

Enthusiasm for the three drug approach followed a case of a “functional cure” of HIV in an newborn reported in 2013.<sup>21</sup> The newborn was born by vaginal delivery at 35 weeks’ gestation to a woman who received no prenatal care and whose HIV infection was diagnosed by expedited testing during labor; delivery occurred before maternal intrapartum ARV drugs could be given. When the newborn was 30 hours old, a regimen of zidovudine, lamivudine, and nevirapine (the latter drug administered at a higher treatment dose rather than standard prophylactic dosing) was initiated. The newborn was found to have a positive HIV DNA polymerase chain reaction (PCR) in a sample obtained at age 30 hours and an HIV RNA level of 19,812 copies/mL on an HIV RNA PCR assay performed at age 31 hours. Based on these test results, the newborn was continued on treatment for HIV, thought to be acquired *in utero*. At age 18 months, the mother discontinued the child’s ART; levels of plasma RNA, proviral DNA, and HIV antibodies remained undetectable in the child for >2 years without ART. Unfortunately, virologic rebound was identified shortly before the child turned 4 years of age. Of interest is the subsequently reported case of an infant treated from birth and virologically suppressed for 4 years who had virologic rebound within days of ART discontinuation.<sup>22</sup>

Further support of empiric HIV therapy comes from Canadian investigators who have reported outcomes in 136 newborns considered at higher risk of HIV acquisition (i.e., born to women with HIV who had detectable viral loads and/or poor adherence to therapy prior to delivery) who received a triple-ARV regimen within 72 hours of birth. Of these 136 newborns, 12 (9%) were found to have acquired HIV and no major regimen-related toxicities were identified.<sup>23</sup> However, there was no control group to permit comparison of safety or efficacy of this approach relative to single-drug or two-drug regimens. Another Canadian study compared the safety of empiric HIV therapy in 148 newborns with high-risk exposure (i.e., incomplete maternal virologic suppression at delivery or, in the absence of maternal viral load results, a maternal history of incomplete adherence or non-adherence to ART, or late pregnancy initiation of ART) to zidovudine alone in 145 low-risk newborns in a control group. Thirteen newborns in the empiric HIV therapy group acquired HIV, including five with a positive HIV NAT within the first 48 hours of life, suggesting *in utero* infection. No newborn in the low-risk zidovudine-only group acquired HIV. Non-specific signs and symptoms (e.g., vomiting,

diarrhea, rash, jitteriness, irritability) potentially attributable to medication-related adverse effects were reported among the newborns receiving empiric HIV therapy but not among those receiving zidovudine only (10.2% vs. 0%,  $P < 0.001$ ). ARV drugs were also more likely to be discontinued prematurely in the newborns receiving empiric HIV therapy than in those receiving only zidovudine (9.5% vs. 2.1%,  $P = 0.01$ ).<sup>24</sup>

Empiric HIV therapy in newborns is consistent with the Centers for Disease Control and Prevention's recommendations for occupational and non-occupational HIV post-exposure prophylaxis in adults, circumstances in which the risk of infection is often lower than for newborns at higher risk of HIV acquisition.<sup>25,26</sup> **The use of empiric HIV therapy in newborns was limited until the availability of new PK and safety information about ARVs in the neonatal period.** Although the use of nevirapine to prevent perinatal transmission has been found to be safe in neonates and low-birthweight newborns, these prophylaxis-dose regimens target trough drug levels are  $\geq 10$ -fold lower than targeted therapeutic levels. **However recent studies of therapeutic dosages of nevirapine and raltegravir have established safe doses that achieve targeted PK parameters.**<sup>27-31</sup>

At this time, if an empiric HIV therapy regimen is selected, the Panel recommends a combination of zidovudine, lamivudine, and nevirapine (treatment dosage) **or zidovudine, lamivudine, and raltegravir** (see [Tables 8](#) and [9](#)). The optimal duration of empiric HIV therapy in newborns at higher risk of perinatal HIV transmission is unknown. **Some** Panel members opt to discontinue **additional medications if returned birth NAT** results are **negative, while others would continue empiric HIV therapy for 6 weeks depending on risk for HIV transmission. In all cases,** zidovudine should be continued for 6 weeks. **Consultation with an expert in pediatric HIV to select a therapy duration based on case-specific risk factors and interim HIV NAT results is recommended.**

### **Newborns Born to Mothers with Unknown HIV Status at Presentation in Labor**

Expedited HIV testing is recommended during labor for women with unknown HIV status and, if not performed during labor, as soon as possible after birth for the mothers and/or their newborns (see Identification of Perinatal Exposure). Expedited test results should be available within 60 minutes. If maternal or infant expedited testing is positive, the **newborn should be immediately initiated on a multi-drug ARV prophylaxis regimen or empiric HIV therapy,** 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, as there is variability in the HIV testing allowed without parental consent.

A nursing mother who is suspected of having HIV based on an initial positive antibody or antibody/antigen test result should stop breastfeeding 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.<sup>32</sup>

### **Newborns Born to Mothers with Antiretroviral Drug-Resistant Virus**

The optimal ARV regimen for newborns delivered by women with ARV drug-resistant virus is unknown. It is also unknown whether resistant virus in the mother increases the risk of HIV acquisition by the infant. 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](#) (888-448-8765). However, there is no evidence that neonatal prophylaxis regimens customized based on presence of maternal drug resistance are more effective than standard neonatal prophylaxis regimens.

Data from the WITS study suggest that, in women who have mixed zidovudine-resistant and zidovudine-sensitive viral populations, the zidovudine-sensitive virus may be preferentially transmitted.<sup>33,34</sup> Thus, the selection of the newborn ARV regimen should be based on other risk factors ([Table 8](#)).

Some studies have suggested that ARV drug-resistant virus may have decreased replicative capacity (reduced viral fitness) and transmissibility.<sup>34</sup> However, perinatal transmission of multidrug-resistant virus has been reported both in the United States and in international settings.<sup>35-39</sup>

### **Newborns with HIV Infection**

Until recently, neonatal ARV regimens were designed for prophylaxis against perinatal HIV transmission and to be as simple as possible for practical use. There was little reason to develop ARV regimens for treatment of neonates, as the long turnaround times to receive HIV NAT results meant that neonatal infections were generally not diagnosed in 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. 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 very early treatment (before age 2 weeks) will lead to prolonged remission or better outcomes in newborns with HIV is lacking. Earlier diagnosis of HIV in newborns and the increasing use of empiric HIV therapy in newborns at higher risk for HIV acquisition have necessitated investigation of dosing and safety of ARV drugs in term and preterm newborns. Although 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 [nevirapine](#) (see [Pediatric Antiretroviral Drug Information](#)).

Sufficient data exist to provide dosing recommendations appropriate for the treatment of HIV in neonates using the following medications (see [Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection](#)):

- From birth in term and preterm newborns: [zidovudine](#), [lamivudine](#), [nevirapine](#)
- From birth in term newborns: [emtricitabine](#), [raltegravir](#)
- From age 2 weeks in term newborns: [lopinavir/ritonavir](#) (LPV/r)

Dosing recommendations for *premature* newborns are available for zidovudine, lamivudine, and nevirapine only. Neonatal dosing advice, including for premature newborns, is summarized in [Table 9](#). For more detailed information about neonatal dosing recommendations and considerations of these drugs, please see the [Pediatric Antiretroviral Drug Information](#).

### **Newborns of Mothers Diagnosed with HIV while Breastfeeding**

Women with suspected HIV (e.g., a positive initial screening test) should stop breastfeeding 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 [Guidance for Counseling and Managing Women Living with HIV in the United States Who Desire to Breastfeed](#)).<sup>40</sup>

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.<sup>41</sup> Newborns of women who develop acute HIV while breastfeeding are at greater risk of acquiring HIV than are those whose mothers have chronic HIV infection<sup>42</sup> because acute HIV infection is accompanied by a rapid increase in viral load and a corresponding decrease in CD4 cell count.<sup>43</sup>

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 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 non-occupational exposures because the exposure to breast milk is likely to have occurred during a prolonged period rather than a single exposure to the virus.<sup>44</sup>

Several studies of newborns breastfed by women with chronic HIV infection in low-resource settings have shown that daily newborn nevirapine, lamivudine, LPV/r, or nevirapine plus zidovudine can reduce the risk of postnatal infection during breastfeeding.<sup>45-49</sup> No trials have evaluated the use of **multi-ARV** 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 would be to offer empiric HIV therapy until infant HIV status can be determined. If the infant's initial HIV NAT is negative, the optimal duration of empiric HIV therapy is unknown. A 28-day course may be reasonable based on current recommendations for non-occupational HIV exposure.<sup>44</sup> As in other situations, decisions regarding ARV management should be accompanied by consultation with a pediatric HIV specialist and maternal counseling on the potential risks and benefits of this approach. The [National Perinatal HIV Hotline](https://www.hiv.gov/national-perinatal-hiv-hotline) (888-448-8765) is a federally funded service providing free clinical consultation for difficult cases to providers caring for pregnant women living with HIV and their newborns, and can provide referral to local or regional pediatric HIV specialists.

Newborns should be tested for HIV prior to initiation of empiric HIV therapy, **4 to 6 weeks and 4 to 6 months after diagnosis of maternal HIV infection and cessation of breastfeeding to determine their HIV status. An additional virologic test should be performed 2 to 4 weeks after discontinuation of empiric HIV therapy** (see [Diagnosis](#) section). If a newborn is already receiving an ARV prophylaxis regimen other than empiric HIV therapy and is found to have HIV, prophylaxis should be discontinued and treatment for HIV initiated. Resistance testing should be performed, and the ART regimen modified if needed (see the [Pediatric Antiretroviral Guidelines](#)).

### ***Short-Term Antiretroviral Drug Safety***

Newborn prophylaxis with zidovudine has been associated with only minimal toxicity, consisting primarily of transient hematologic toxicity (mainly anemia), which generally resolves by age 12 weeks (see [Initial Postnatal Management](#)). Data on toxicities in newborns exposed to multiple ARV drugs are limited.

Other than zidovudine, lamivudine is the NRTI with the most experience in use for neonatal prophylaxis. In early studies, neonatal exposure to combination zidovudine/lamivudine was generally limited to 1<sup>13,50,51</sup> or 2 weeks.<sup>5</sup> Six weeks of newborn zidovudine/lamivudine exposure has also been reported. These studies suggest that hematologic toxicity may be greater with zidovudine/lamivudine than with zidovudine 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 severe anemia and neutropenia were observed in newborns exposed to 6 weeks of zidovudine/lamivudine for prophylaxis plus maternal antepartum zidovudine/lamivudine than in a historical cohort of newborns exposed only to maternal and newborn zidovudine. Anemia was reported in 15% and neutropenia in 18% of newborns exposed to zidovudine/lamivudine, with 2% of newborns requiring blood transfusion and 4% requiring treatment discontinuation for toxicity.<sup>52</sup> Similarly, in a Brazilian study of maternal antepartum and 6-week newborn zidovudine/lamivudine prophylaxis, neonatal hematologic toxicity was common, with anemia seen in 69% and neutropenia in 13% of newborns.<sup>53</sup>

Experience with other NRTI drugs for neonatal prophylaxis is more limited.<sup>54,55</sup> Hematologic and mitochondrial toxicity may be more common with exposure to multiple NRTI drugs than to a single NRTI.<sup>52,56-59</sup>

In rare cases, chronic multiple-dose nevirapine prophylaxis in pregnant women has been associated with



severe and potentially life-threatening rash and hepatic toxicity.<sup>60</sup> These toxicities have not been observed in newborns receiving prophylactic dosing with single-dose nevirapine, the two-drug zidovudine regimen plus three doses of nevirapine in the first week of life in NICHD-HPTN 040/PACTG 1043), or in breastfeeding newborns receiving nevirapine prophylaxis daily for 6 weeks to 18 months to prevent transmission of HIV via breast milk.<sup>5,45-47,49,61</sup>

The Food and Drug Administration (FDA) recently approved infant dosing of raltegravir for term neonates  $\geq 37$  weeks gestation at birth and weighing  $\geq 2$  kg. Dosing information is not available for preterm or low birthweight infants. Infant raltegravir dosing needs to be increased at 1 week and 4 weeks of age. Raltegravir is metabolized by UGT1A1, the same enzyme responsible for the elimination of bilirubin. UGT enzyme activity is low at birth, and raltegravir elimination is prolonged in neonates. In addition, bilirubin and raltegravir may compete for albumin binding sites, and extremely elevated neonatal plasma raltegravir concentrations could pose a risk of kernicterus.<sup>62</sup> IMPAACT P1110 is a Phase I, multicenter trial enrolling full-term neonates exposed to HIV and who are at risk of acquiring perinatal HIV-1-infection, with or without *in utero* raltegravir exposure. Daily raltegravir was safe and well tolerated during the first 6 weeks of life. Infants were treated for  $\leq 6$  weeks from birth and followed for 24 weeks. There were no drug-related clinical adverse reactions observed and only three laboratory adverse reactions: one case of Grade 4 transient neutropenia in an infant receiving zidovudine-containing regimen; and two cases of bilirubin elevations (one each, Grade 1 and Grade 2) that were considered non-serious and did not require specific therapy<sup>63</sup> (see [Pediatric Antiretroviral Drug Information](#) for additional information).

The safety and PK data about daily dosing from P1110 are from raltegravir-naïve infants whose mothers did not receive raltegravir; data collection from infants born to mothers who were receiving raltegravir is ongoing. However, the Panel believes that the FDA-approved dosing of raltegravir, delaying the first dose for infants born to mothers who received raltegravir, is reasonable based on current data about clearance of the drug in premature and raltegravir-exposed infants.

Of the protease inhibitors, pediatric drug formulations are available for LPV/r, ritonavir, darunavir, tipranavir, and fosamprenavir, but their use in neonates in the first weeks of life is not recommended given the lack of dosing and safety information. In addition, LPV/r oral solution contains 42.4% alcohol and 15.3% propylene glycol, and enzymes that metabolize these compounds are immature in neonates, particularly preterm newborns. Four premature newborns (two sets of twins) started on LPV/r from birth, developed heart block that resolved after drug discontinuation.<sup>64,65</sup> In studies of adults, both ritonavir and LPV/r cause dose-dependent prolongation of the PR interval, and cases of significant heart block, including complete heart block, have been reported. Elevation of 17-hydroxyprogesterone and dehydroepiandrosterone-sulfate has also been associated with administration of LPV/r in the neonatal period, an association not found with zidovudine. Levels of 17-hydroxyprogesterone were greater in newborns who were also exposed to LPV/r *in utero* than in those exposed only in 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.<sup>66</sup> On the basis of these and other post-marketing 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,<sup>67</sup> predominantly in preterm neonates, the FDA now recommends that LPV/r oral solution **not be administered** to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of  $\geq 14$  days.<sup>68</sup> However, a recent study (ANRS 12174) randomized 1,273 newborns, 615 assigned to LPV/r and 621 assigned to lamivudine, 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  $> 2$  kg were randomized. Clinical and biological severe adverse events did not differ between groups suggesting that LPV/r is safe in term newborns, 7 days of age and older.<sup>69</sup> 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  $\geq 14$  days.



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