



## **Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection**

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# Zidovudine (ZDV, AZT, Retrovir) (Last updated May 22, 2018; last reviewed May 22, 2018)

For additional information see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf/>

## Formulations

**Capsules:** 100 mg

**Tablets:** 300 mg

**Syrup:** 10 mg/mL

**Concentrate for Injection or Intravenous Infusion:** 10 mg/mL

### Generic Formulations:

Zidovudine capsules, tablets, syrup, and injection are approved by the Food and Drug Administration for manufacture and distribution in the United States.

### Fixed-Dose Combination Tablets:

- [*Combivir and Generic*] Lamivudine 150 mg plus zidovudine 300 mg (scored)
- [*Trizivir*] Abacavir 300 mg plus lamivudine 150 mg plus zidovudine 300 mg

## Dosing Recommendations

**Note:** See [Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV](#) and [Table 12](#) for information about using zidovudine to prevent perinatal transmission.

### Recommended Neonatal Dose for Treatment of HIV by Gestational Age (Weeks) at Birth<sup>a</sup>

Gestational Age at Birth	Oral Zidovudine Dose								
≥35 Weeks	Birth to Age 4 Weeks: <ul style="list-style-type: none"><li>• 4 mg/kg orally twice daily or alternative simplified weight band dosing</li></ul>								
	Simplified Weight Band Dosing for Infants with a Gestational Age ≥35 Weeks at Birth: <b>Note:</b> The doses in this table provide approximately 4 mg/kg orally twice daily from birth to age 4 weeks.								
	<table border="1"><thead><tr><th>Weight Band</th><th>Volume Zidovudine 10 mg/mL Oral Syrup Twice Daily</th></tr></thead><tbody><tr><td>2 kg to &lt;3 kg</td><td>1 mL</td></tr><tr><td>3 kg to &lt;4 kg</td><td>1.5 mL</td></tr><tr><td>4 kg to &lt;5 kg</td><td>2 mL</td></tr></tbody></table>	Weight Band	Volume Zidovudine 10 mg/mL Oral Syrup Twice Daily	2 kg to <3 kg	1 mL	3 kg to <4 kg	1.5 mL	4 kg to <5 kg	2 mL
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	2 kg to <3 kg	1 mL							
3 kg to <4 kg	1.5 mL								
4 kg to <5 kg	2 mL								
Aged >4 Weeks: <ul style="list-style-type: none"><li>• 12 mg/kg orally twice daily</li></ul>									

## Selected Adverse Events

- Bone marrow suppression: macrocytosis with or without anemia, neutropenia
- Nausea, vomiting, headache, insomnia, asthenia
- Lactic acidosis/severe hepatomegaly with hepatic steatosis
- Lipodystrophy and lipoatrophy
- Myopathy (associated with prolonged use of zidovudine) and myositis

## Special Instructions

- Give zidovudine without regard to food.
- If substantial granulocytopenia or anemia develops in patients receiving zidovudine, it may be necessary to discontinue therapy until bone marrow recovery is observed. In this setting, some patients may require erythropoietin or filgrastim injections or transfusions of red blood cells.
- For infants unable to tolerate oral agents, the intravenous (IV) dose should be 75% of the oral dose, but the dosing interval should remain the same.
- When using fixed-dose combination (FDC) tablets that contain zidovudine, see other sections of the [Drug Appendix](#) for special instructions and additional information about the individual components of the FDC.

Gestational Age at Birth	Oral Zidovudine Dose
≥30 to <35 Weeks	<p>Birth to Age 2 Weeks:</p> <ul style="list-style-type: none"> <li>• 2 mg/kg orally twice daily</li> </ul> <p>Aged 2 Weeks to 6 to 8 Weeks:</p> <ul style="list-style-type: none"> <li>• 3 mg/kg orally twice daily</li> </ul> <p>Aged &gt;6 to 8 Weeks:</p> <ul style="list-style-type: none"> <li>• 12 mg/kg orally twice daily</li> </ul>
<30 Weeks	<p>Birth to Age 4 Weeks:</p> <ul style="list-style-type: none"> <li>• 2 mg/kg orally twice daily</li> </ul> <p>Aged 4 Weeks to 8 to 10 Weeks:</p> <ul style="list-style-type: none"> <li>• 3 mg/kg orally twice daily</li> </ul> <p>Aged &gt;8 to 10 Weeks:</p> <ul style="list-style-type: none"> <li>• 12 mg/kg orally twice daily</li> </ul>

<sup>a</sup> For premature infants who are diagnosed with HIV, the time to change the dose to continuation dose varies with postgestational age and clinical status of the neonate (see the Special Issues for Neonates section below).

**Note:** For infants who are unable to tolerate oral agents, the intravenous (IV) dose should be 75% of the oral dose, but the dosing interval should remain the same.

### Infant (Aged ≥35 Weeks Post-Conception and ≥4 Weeks Post-Delivery, Weighing ≥4 kg) and Child Dose

#### Zidovudine Weight-Based Dosing

Body Weight	Twice-Daily Dosing
4 kg to <9 kg	12 mg/kg
9 kg to <30 kg	9 mg/kg
≥30 kg	300 mg

#### Alternative Body Surface Area Dosing

- Oral: 180–240 mg/m<sup>2</sup> body surface area every 12 hours

#### Adolescent (Aged ≥18 Years) and Adult Dose:

- 300 mg twice daily

#### [Combivir and Generic] Lamivudine plus Zidovudine

Adolescent (Weighing ≥30 kg) and Adult Dose:

- 1 tablet twice daily

#### [Trizivir] Abacavir plus Lamivudine plus Zidovudine

Adolescent (Weighing ≥40 kg) and Adult Dose:

- 1 tablet twice daily

## Metabolism/Elimination

- Metabolized primarily in the liver to zidovudine glucuronide, which is renally excreted.
- Zidovudine is phosphorylated intracellularly to active zidovudine-triphosphate.

#### Zidovudine Dosing in Patients with Renal Impairment:

- Dose adjustment is required in renal insufficiency.

#### Zidovudine Dosing in Patients with Hepatic Impairment:

- Dose may need to be reduced in patients with hepatic impairment.
- Do not use FDC products (e.g., Combivir, Trizivir) in patients with creatinine clearance <50 mL/min or in patients who are on dialysis or who have impaired hepatic function.

**Drug Interactions** (see also the [Adult and Adolescent Guidelines](#) and the [HIV Drug Interaction Checker](#))

- *Other nucleoside reverse transcriptase inhibitors (NRTIs):* Zidovudine **should not be administered in combination** with stavudine because of *in vitro* virologic antagonism.
- *Bone marrow suppressive/cytotoxic agents, including ganciclovir, valganciclovir, interferon alfa, and ribavirin:* These agents may increase the hematologic toxicity of zidovudine.
- *Nucleoside analogues that affect DNA replication:* Nucleoside analogues, such as ribavirin, antagonize *in vitro* antiviral activity of zidovudine.
- *Doxorubicin:* Simultaneous use of doxorubicin and zidovudine should be avoided. Doxorubicin may inhibit the phosphorylation of zidovudine to its active form.

### **Major Toxicities**

- *More common:* Hematologic toxicity, including granulocytopenia and anemia, particularly in patients with advanced HIV-1 disease. Headache, malaise, nausea, vomiting, and anorexia. Neutropenia may occur more frequently in infants receiving both lamivudine and zidovudine than in infants receiving only zidovudine.<sup>1</sup>
- *Less common (more severe):* Myopathy (associated with prolonged use), myositis, and liver toxicity. Cases of lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Fat maldistribution.
- *Rare:* Increased risk of hypospadias after first-trimester exposure to zidovudine observed in one cohort study.<sup>2</sup> Possible increased risk of cardiomyopathy.<sup>3</sup> Possible association between first-trimester exposure to zidovudine and congenital heart defects (see [Teratogenicity](#) in the [Perinatal Guidelines](#)).<sup>4-6</sup>

### **Resistance**

The International Antiviral Society-USA (IAS-USA) maintains a [list of updated resistance mutations](#) and the [Stanford University HIV Drug Resistance Database](#) offers a discussion of each mutation.

### **Pediatric Use**

#### *Approval*

Zidovudine is frequently included as a component of the NRTI backbone for antiretroviral therapy (ART) and has been studied in children in combination with **other NRTIs, including** abacavir and lamivudine.<sup>7-23</sup> Pediatric experience with zidovudine both for treating HIV and for preventing perinatal transmission is extensive. **However, the mitochondrial toxicity of zidovudine leads many experts to favor the use of abacavir or tenofovir alafenamide in cases where patient age and the results of viral resistance testing do not restrict the use of these drugs.**

#### *Efficacy in Clinical Trials*

#### **Zidovudine in Combination with Other NRTIs**

- Zidovudine with lamivudine has been extensively studied in children and has been a part of ART regimens in many trials.
- Safety and efficacy of zidovudine combined with lamivudine was compared to abacavir/lamivudine and stavudine/lamivudine in children aged <5 years in the CHAPAS-3 study. All regimens also contained either nevirapine or efavirenz. All NRTIs had low toxicity and good clinical, immunologic, and virologic responses.<sup>24</sup>
- Zidovudine/abacavir and zidovudine/lamivudine had lower rates of viral suppression and more toxicity leading to drug modification than did abacavir/lamivudine in a European pediatric study.<sup>25,26</sup>

#### *Special Issues in Neonates*

Perinatal trial PACTG 076 established that zidovudine prophylaxis given to the mother during pregnancy, labor, and delivery, and given to the newborn reduced the risk of perinatal transmission of HIV by nearly 70%<sup>27</sup> (see [Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV](#) for further discussion

on the use of zidovudine for the prevention of perinatal transmission of HIV). Zidovudine 4 mg/kg body weight every 12 hours is recommended for neonates and infants with  $\geq 35$  weeks' gestation for prevention of perinatal HIV transmission. Infants who are HIV-exposed but uninfected should continue on the prophylactic dose for 4 to 6 weeks, depending on the assessment of risk for perinatal transmission and gestational age at time of delivery.

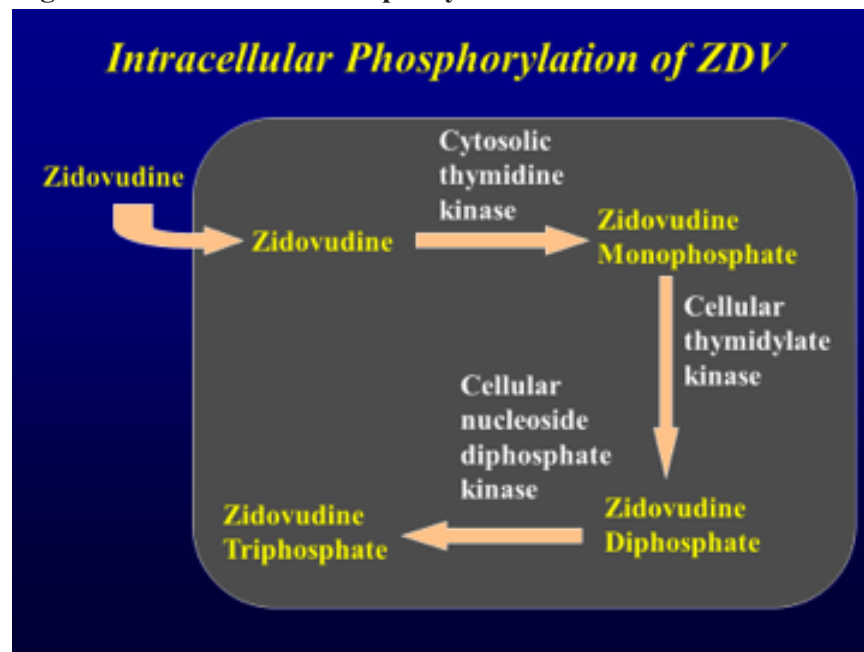
For full-term neonates who receive an HIV diagnosis, the zidovudine dose should be increased at age 4 weeks to the continuation dose (see dosing table). The activity of the enzymes responsible for glucuronidation is low at birth and increases dramatically over the first 4 to 6 weeks of life in full-term neonates.

For premature infants who are diagnosed with HIV infection, the time to increase the dose from the initial dose varies with postgestational age and the clinical status of the neonate. On the basis of modeling and the pharmacokinetics (PK) of zidovudine in premature infants, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends switching to a dose of zidovudine 12 mg/kg twice daily at postgestational age 6 to 8 weeks in infants born at  $\geq 30$  to  $< 35$  weeks. For infants who are born at  $< 30$  weeks, change to zidovudine 12 mg/kg twice daily at a postgestational age of 8 to 10 weeks.<sup>28</sup> Careful clinical assessment of the infant, evaluation of hepatic and renal function, and review of concomitant medications should be performed prior to increasing the zidovudine dose to that recommended for full-term infants.

### Pharmacokinetics

Overall, zidovudine PK in pediatric patients aged  $> 3$  months are similar to those seen in adults. Zidovudine undergoes intracellular metabolism to its active form, zidovudine triphosphate. Although the mean half-life of intracellular zidovudine triphosphate (9.1 hours) is considerably longer than that of unmetabolized zidovudine in plasma (1.5 hours), once-daily zidovudine dosing **is not recommended** because of the low intracellular zidovudine triphosphate concentrations seen with 600-mg, once-daily dosing in adolescents.<sup>29</sup> PK studies such as PACTG 331 demonstrate that dose adjustments are necessary for premature infants because they have reduced clearance of zidovudine compared with the clearance observed in term newborns of similar postnatal age.<sup>8</sup> Zidovudine has good central nervous system (CNS) penetration (cerebrospinal fluid-to-plasma concentration ratio = 0.68) and has been used in children with HIV-related CNS disease.<sup>19</sup>

**Figure A: Intracellular Phosphorylation of Zidovudine**



Source: Mirochnick, M. Antiretroviral pharmacology in pregnant women and their newborns. Presented at: Advances in Pediatric AIDS. 1999. Montreal, CA.

The rate-limiting step in phosphorylation of zidovudine to active zidovudine triphosphate is the limited amount of thymidylate kinase. Increasing doses of zidovudine will lead to increased zidovudine plasma concentrations

and increased intracellular concentrations of zidovudine monophosphate but not zidovudine diphosphate or zidovudine triphosphate. In 31 infants receiving zidovudine for prevention of perinatal transmission, intracellular zidovudine metabolites were measured after delivery. Plasma zidovudine and intracellular zidovudine monophosphate decreased by roughly 50% between postdelivery Day 1 and Day 28, whereas zidovudine diphosphate and zidovudine triphosphate remained low throughout the sampling period.<sup>30</sup> On the basis of poor correlation between zidovudine dose and intracellular zidovudine triphosphate concentrations, a simplified dosing approach can be used for infants  $\geq 35$  weeks gestation receiving approximately zidovudine 4 mg/kg twice daily oral dosing for the first 4 weeks of life (see the [dosing table](#)). These volumes provide approximately zidovudine 4 mg/kg per dose using the 10 mg/mL oral syrup. This approach should simplify the minor dose adjustments that are commonly made based on changes in infant weight during zidovudine use in the first 4 weeks of life. These changes in weight and small differences in zidovudine dose will have minor effects on the intracellular concentrations of zidovudine triphosphate. This approach should make it easier for caregivers to administer zidovudine oral syrup to their infants.

### **Toxicity**

Several studies suggest that the adverse hematologic effects of zidovudine may be concentration-dependent, with a higher risk of anemia and neutropenia in patients with higher mean area under the curve.<sup>7,8,31</sup>

Incidence of hematological toxicity was investigated in the ARROW study, which randomized Ugandan/Zimbabwean treatment-naïve children to receive either zidovudine-containing regimens or abacavir-containing regimens. The incidence of severe anemia was similar regardless of zidovudine use, and this finding suggests that advanced HIV disease contributed to low hemoglobin values. Zidovudine use was associated with severe neutropenia in a small number of children.<sup>32</sup>

Zidovudine is associated with greater mitochondrial toxicity when compared to abacavir and tenofovir disoproxil fumarate but less than stavudine.<sup>33,34</sup>

While the incidence of cardiomyopathy associated with perinatal HIV infection has decreased dramatically since use of ART became routine, a regimen containing zidovudine may increase the risk.<sup>3</sup> Recent analysis of data from a U.S.-based, multicenter, prospective cohort study (PACTG 219/219C) found that ongoing zidovudine exposure was independently associated with a higher rate of cardiomyopathy.<sup>3</sup>

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