



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Zidovudine (ZDV, Retrovir) (Last updated April 16, 2019; last reviewed April 16, 2019)

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

Formulations

Capsule: 100 mg

Tablet: 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/zidovudine 300 mg (scored)
- [*Trizivir and Generic*] Abacavir 300 mg/lamivudine 150 mg/zidovudine 300 mg

Dosing Recommendations

Note: Zidovudine is frequently used in neonates to prevent perinatal transmission of HIV. 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 at Birth^a

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

Selected Adverse Events

- Bone marrow suppression leading to anemia and neutropenia; macrocytosis with or without anemia
- 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.
- 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.

Metabolism/Elimination

- Zidovudine is eliminated primarily by

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

Note: For infants who are unable to tolerate oral agents, the intravenous 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:

- Zidovudine 180 mg to 240 mg per m² of body surface area every 12 hours

Adolescent (Aged ≥18 Years) and Adult Dose:

- Zidovudine 300 mg twice daily

[Combivir and Generic] Lamivudine/Zidovudine

Child and Adolescent (Weighing ≥30 kg) and Adult Dose:

- One tablet twice daily

[Trizivir and Generic] Abacavir/Lamivudine/Zidovudine

Child and Adolescent (Weighing ≥30 kg) and Adult Dose:

- One tablet twice daily

hepatic metabolism. The major metabolite is zidovudine glucuronide, which is renally excreted.

- Zidovudine is phosphorylated intracellularly to active zidovudine-triphosphate.

Zidovudine Dosing in Patients with Renal Impairment:

- A zidovudine dose adjustment is required in patients with renal insufficiency.

Zidovudine Dosing in Patients with Hepatic Impairment:

- The dose of zidovudine 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.

^a For premature infants who are diagnosed with HIV infection, the time to change to the continuation dose varies with post-gestational age and clinical status of the infant.

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

- *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 neutropenia and anemia, particularly in patients with advanced HIV disease. Headache, malaise, nausea, vomiting, and anorexia. Neutropenia may occur more frequently in infants who are receiving both lamivudine and zidovudine than in infants who are receiving only zidovudine.¹
- *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:* There is a possible increased risk of cardiomyopathy.²

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 nucleoside reverse transcriptase inhibitor (NRTI) backbone for antiretroviral therapy (ART), and it has been studied in children in combination with other NRTIs, including abacavir and lamivudine.³⁻¹⁹ 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 the patient's age and the results of viral resistance testing do not restrict the use of these drugs.

Efficacy in Clinical Trials

The combination of zidovudine and lamivudine has been extensively studied in children and has been a part of ART regimens in many trials. The safety and efficacy of zidovudine plus lamivudine were compared to the safety and efficacy of abacavir plus lamivudine and stavudine plus lamivudine in children aged <5 years in the CHAPAS-3 study. All regimens also included either nevirapine or efavirenz. All the NRTIs had low toxicity and produced good clinical, immunologic, and virologic responses.²⁰ Pediatric patients who received zidovudine plus abacavir or zidovudine plus lamivudine had lower rates of viral suppression and experienced more adverse events that required regimen modification than patients who received abacavir/lamivudine.^{21,22}

Infants with Perinatal HIV Exposure

The PACTG 076 clinical trial demonstrated that administering zidovudine to pregnant women and their infants could reduce the risk of perinatal transmission by nearly 70%.²³ See [Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV](#) for further discussion of the use of zidovudine for the prevention of perinatal transmission of HIV. A dose of approximately zidovudine 4 mg/kg of body weight every 12 hours is recommended for prevention of perinatal HIV transmission in neonates and infants with gestational ages ≥ 35 weeks. Infants who have been exposed to HIV but who are uninfected should continue

on the prophylactic dose for 4 weeks to 6 weeks, depending on their gestational age at time of delivery and the risk assessment for perinatal transmission.

Simplified, alternative weight-band dosing has also been developed, and the rationale for these doses is based on the intracellular metabolism of zidovudine (see Pharmacokinetics below). The rate-limiting step in the 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 who received zidovudine to prevent perinatal transmission, levels of intracellular zidovudine metabolites were measured after delivery. Plasma zidovudine and intracellular zidovudine monophosphate decreased by roughly 50% between post-delivery Day 1 and Day 28, whereas zidovudine diphosphate and zidovudine triphosphate remained low throughout the sampling period.²⁴ Zidovudine dose is poorly correlated with the active form of zidovudine found intracellularly. Because of this, a simplified weight-band dosing approach can be used for the first 4 weeks of life in infants with gestational ages ≥ 35 weeks (see the dosing table). 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 and will make it easier for caregivers to administer zidovudine oral syrup to their infants. The changes in weight and the small differences in zidovudine dose will have minor effects on the intracellular concentrations of zidovudine triphosphate.

Infants with HIV Infection

For full-term neonates who are diagnosed with HIV infection during the first days to weeks of life, the zidovudine dose should be increased at age 4 weeks to the continuation dose (see the dosing table). The activity of the enzymes responsible for glucuronidation is low at birth and increases dramatically during the first 4 weeks to 6 weeks of life in full-term neonates. **This increase in metabolizing enzyme activity leads to an increased clearance of plasma zidovudine, and the dose of zidovudine should be adjusted when zidovudine is used to treat HIV after the first 4 weeks in full-term infants.**

For premature infants who are diagnosed with HIV infection, the time to increase the zidovudine dose from the initial dose varies with post-gestational age and the clinical status of the neonate. On the basis of population pharmacokinetic (PK) modeling and simulations and data from studies that have evaluated zidovudine PK in premature infants, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends the following: in infants with HIV who were born at ≥ 30 weeks to < 35 week switch to a dose of zidovudine 12 mg/kg twice daily at a post-gestational age of 6 weeks to 8 weeks; for infants who are born at < 30 weeks, switch to zidovudine 12 mg/kg twice daily at a post-gestational age of 8 weeks to 10 weeks.²⁵ 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

Zidovudine undergoes intracellular metabolism to achieve its active form, zidovudine triphosphate. Phosphorylation requires multiple steps: zidovudine is phosphorylated by thymidine kinase to zidovudine monophosphate; zidovudine monophosphate is phosphorylated by thymidylate kinase to zidovudine diphosphate; and zidovudine diphosphate is phosphorylated by nucleoside diphosphate kinase to zidovudine triphosphate. Overall, zidovudine PKs in pediatric patients aged > 3 months are similar to those seen in adults. 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.²⁶ 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 ages.⁴ 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.¹⁵

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 plasma area under the curve values for zidovudine.^{3,4,27}

Incidence of hematological toxicity was investigated in the ARROW study, which randomized treatment-naïve Ugandan/Zimbabwean 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.²⁸

Zidovudine is associated with greater mitochondrial toxicity than abacavir and tenofovir disoproxil fumarate, but it is associated with less mitochondrial toxicity than stavudine.^{29,30}

While the incidence of cardiomyopathy associated with perinatal HIV infection has decreased dramatically since the use of ART became routine, the use of a regimen that contains zidovudine may increase the risk.² 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.²

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