Zidovudine (ZDV, Retrovir)

Updated: April 11, 2023
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Formulations

Syrup: 10 mg/mL

Capsule: 100 mg

Concentrate for Injection or Intravenous Infusion: 10 mg/mL (Retrovir)

Generic Formulations

- 100-mg capsule
- 10-mg/mL syrup
- 300-mg tablet

Fixed-Dose Combination (FDC) Tablets

- [Combivir and generic] Lamivudine 150 mg/zidovudine 300 mg (scored)
- [Trizivir and generic] Abacavir 300 mg/lamivudine 150 mg/zidovudine 300 mg

When using FDC tablets, refer to other sections of the Drug Appendix for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

Note: Zidovudine (ZDV) is frequently used in neonates to prevent perinatal transmission of HIV. See Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection and Table 12 for information about using ZDV to prevent perinatal transmission.

Recommended Neonatal Dose for Treatment of HIV by Gestational Age at Birth[a]

Gestational Age at Birth	Oral ZDV Dose
≥35 weeks	Birth to Age 4 Weeks • ZDV 4 mg/kg twice daily; *or* • Alternative simplified weight-band dosing Simplified Weight-Band Dosing for Infants With a **Gestational Age ≥35** Weeks at Birth Note: The doses in this table provide approximately ZDV 4 mg/kg twice daily from birth to age 4 weeks.

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 ZDV) and myositis

Special Instructions

- Give ZDV without regard to food.
- If substantial granulocytopenia or anemia develops in patients who are receiving ZDV, 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.

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<tr>
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<tr><th>Weight Band</th><th>Twice-Daily Volume of ZDV 10 mg/mL Syrup</th></tr>
<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>
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Aged >4 Weeks
• ZDV 12 mg/kg twice daily
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<tr>
<td>≥30 weeks to <35 weeks</td>
<td>Birth to Age 2 Weeks
• ZDV 2 mg/kg twice daily
Aged 2 Weeks to 6 Weeks
• ZDV 3 mg/kg twice daily
• Aged >6 Weeks ZDV 12 mg/kg twice daily</td>
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<tr>
<td><30 weeks</td>
<td>Birth to Age 4 Weeks
• ZDV 2 mg/kg twice daily
Aged 4 Weeks to 8 Weeks
• ZDV 3 mg/kg twice daily
Aged >8 Weeks
• ZDV 12 mg/kg twice daily</td>
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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

Weight-Based Dosing for Zidovudine

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

- ZDV 180 mg to 240 mg per m^2 of body surface area every 12 hours

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

- ZDV 300 mg twice daily

- Screen patients for hepatitis B virus (HBV) infection before using FDC products that contain lamivudine (3TC). Severe acute exacerbation of HBV infection can occur when 3TC is discontinued; therefore, hepatic function should be monitored for several months after patients with HBV infection stop taking 3TC.

Metabolism/Elimination

- ZDV is eliminated primarily by hepatic metabolism. The major metabolite is ZDV glucuronide, which is renally excreted.
- ZDV is phosphorylated intracellularly to active ZDV-triphosphate.

Zidovudine Dosing in **P**atients With Hepatic Impairment

- The dose of ZDV may need to be reduced in patients with hepatic impairment.
- Do not use FDC products (e.g., Combivir, Trizivir) in patients who have impaired hepatic function.

Zidovudine Dosing in Patients With Renal Impairment

- A dose adjustment is required for ZDV in patients with renal insufficiency.
- Do not use FDC products (e.g., Combivir, Trizivir) in patients with creatinine clearance <50 mL/min and patients who are on hemodialysis.

[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	

[a] For premature infants who receive an HIV diagnosis, the time to change to the continuation dose varies with post-gestational age and clinical status of the infant.

Drug Interactions

Additional information about drug interactions is available in 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 (ZDV).
- *Nucleoside analogues that affect DNA replication:* Nucleoside analogues—such as ribavirin—antagonize *in vitro* antiviral activity of ZDV.
- *Doxorubicin:* Simultaneous use of doxorubicin and ZDV **should be avoided.** Doxorubicin may inhibit the phosphorylation of ZDV 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 (3TC) and ZDV than in infants who are receiving only ZDV.[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 has been observed in patients receiving antiretroviral medications.
- *Rare:* Possible increased risk of cardiomyopathy.[2-4]

Resistance

The International Antiviral Society–USA maintains a list of HIV drug resistance mutations, and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

ZDV 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 (ABC) and 3TC.[5-8] Pediatric experience with ZDV both for treating HIV and for preventing perinatal transmission is extensive. However, the mitochondrial toxicity of ZDV leads many experts to favor the use of ABC 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 ZDV and 3TC has been extensively studied in children and has been a part of antiretroviral (ARV) regimens in many trials. The safety and efficacy of ZDV plus 3TC were compared to the safety and efficacy of ABC plus 3TC and stavudine (d4T) plus 3TC in children aged <5 years in the CHAPAS-3 (Children with HIV in Africa Pharmacokinetics and Adherence of Simple antiretroviral regimens) study. All regimens also included either nevirapine or efavirenz. All the NRTIs had low toxicity and produced good clinical, immunologic, and virologic responses.[9] A number of studies have evaluated the efficacy and toxicity of different dual-nucleoside reverse transcriptase inhibitor backbones used as part of combination ART.[10-12]

Infants with Perinatal HIV Exposure

The Pediatric AIDS Clinical Trials Group (PACTG) 076 clinical trial[13] demonstrated that administering ZDV to pregnant women and their infants could reduce the risk of perinatal HIV transmission by nearly 70%. See Antiretroviral Management of Newborns With Perinatal HIV Exposure or HIV Infection for further discussion on using ZDV to prevent perinatal transmission of HIV. A dose of approximately ZDV 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 ZDV (see Pharmacokinetics below). The rate-limiting step in the phosphorylation of ZDV to active ZDV triphosphate is the limited amount of thymidylate kinase. Increasing the dose of ZDV will lead to increased ZDV plasma concentrations and increased intracellular concentrations of ZDV monophosphate, but not ZDV diphosphate or ZDV triphosphate.

In 31 infants who received ZDV to prevent perinatal transmission, levels of intracellular ZDV metabolites were measured after delivery. Plasma ZDV and intracellular ZDV monophosphate decreased by roughly 50% between post-delivery Day 1 and Day 28, whereas ZDV diphosphate and ZDV triphosphate remained low throughout the sampling period.[14] ZDV dose is poorly correlated with the active form of ZDV that is 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 above). This approach should simplify the minor dose adjustments that are commonly made based on changes in infant weight during ZDC use in the first 4 weeks of life and will make it easier for caregivers to administer ZDV oral syrup to their infants. The changes in weight and the small differences in ZDV dose will have minor effects on the intracellular concentrations of ZDV triphosphate.

Infants With HIV Infection

The Early Infant Treatment Study in Botswana evaluated the safety and efficacy of initiation of antiretroviral therapy in the first week of life. Forty infants who tested positive for HIV within 96 hours of birth were started on ZDV, 3TC, and nevirapine (NVP) with successful transition to lopinavir/ritonavir (LPV/r) at 2 to 5 weeks after delivery. Early treatment was found to be safe and effective, with most infants achieving and maintaining viral suppression by 24 weeks of age.[15]

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

For premature infants who receive an HIV diagnosis, the time to increase the ZDV 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 ZDV PKs in premature infants, the Panel on Antiretroviral Therapy and Medical Management of Children Living With HIV recommends the following:

- For infants with HIV born at ≥30 weeks to <35 weeks, switch to a dose of ZDV 12 mg/kg twice daily at a post-gestational age of 6 weeks to 8 weeks.
- For infants born at <30 weeks, switch to ZDV 12 mg/kg twice daily at a post-gestational age of 8 weeks to 10 weeks.[16]

Clinicians should perform a careful clinical assessment of the infant, evaluate hepatic and renal function, and review concomitant medications before increasing the ZDV dose to the dose recommended for full-term infants.

Pharmacokinetics

ZDV undergoes intracellular metabolism to achieve its active form, ZDV triphosphate. Phosphorylation requires multiple steps: ZDV is phosphorylated by thymidine kinase to ZDV monophosphate, ZDV monophosphate is phosphorylated by thymidylate kinase to ZDV diphosphate, and ZDV diphosphate is phosphorylated by nucleoside diphosphate kinase to ZDV triphosphate. Overall, ZDV PKs in pediatric patients aged >3 months are like those seen in adults. Although the mean half-life of intracellular ZDV triphosphate (9.1 hours) is considerably longer than that of unmetabolized ZDV in plasma (1.5 hours), once-daily ZDV dosing is not recommended because of the low intracellular ZDV triphosphate concentrations seen with 600-mg, once-daily dosing in adolescents.[17] PK studies, such as PACTG 331, demonstrate that dose adjustments are necessary for premature infants because they have reduced clearance of ZDV compared with the clearance observed in term newborns of similar postnatal ages.[6] ZDV has good central nervous system (CNS) penetration (cerebrospinal fluid-to-plasma concentration ratio is 0.68), and ZDV has been used in children with HIV-related CNS disease.[8]

PK and safety of ZDV, 3TC, and LPV/r in children living with HIV and severe acute malnutrition (SAM) was studied in International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) P1092.[18] Steady-state PK, safety, and tolerability was compared in children with

HIV with and without SAM. Overall safety and tolerability did not differ between the two cohorts and similar area-under-the-curve values for ZDV, 3TC, and LPV/r were observed in these children who were dosed according to World Health Organization weight-band dosing recommendations.[18]

Toxicity

Several studies suggest that the adverse hematologic effects of ZDV may be concentration-dependent, with a higher risk of anemia and neutropenia in patients with higher mean plasma area-under-the-curve values for ZDV.[5,6,19] A significant reduction in the incidence of hematologic toxicity was observed during a retrospective analysis of infants who received a short course of ZDV (2 weeks) to prevent perinatal HIV transmission.[20] In this study, 137 infants received ZDV for 2 weeks, and 184 infants received ZDV for >2 weeks; of these infants, 168 (91.3%) received 4 weeks of ZDV prophylaxis. The risk of anemia (defined as a Division of AIDS [DAIDS] severity grade of mild or higher) was significantly lower in the short-course group at both age 1 month ($P < 0.001$) and age 3 months ($P < 0.001$).[20] Some national guidelines, including those from Germany/Austria and Great Britain, recommend a minimum of 2 weeks of post-exposure prophylaxis in infants at low risk or very low risk of HIV transmission.[20,21] Current U.S. guidelines recommend 4 weeks of prophylaxis for infants at low risk of HIV transmission. For infants who develop significant anemia while receiving ZDV for prevention of perinatal HIV transmission, early discontinuation may be considered for infants who are determined to be at a low risk of transmission after expert consultation. A recent study conducted in Thailand evaluated the safety of triple antiretroviral neonatal presumptive therapy with ZDV/3TC/nevirapine for 6 weeks in infants at high risk of acquisition of HIV compared with 4 weeks of monotherapy with ZDV in infants considered at low risk. No significant differences were observed in the incidence of neutropenia, hepatoxicity, or severe anemia between the triple antiretroviral and the ZDV monotherapy groups.[22]

Incidence of hematological toxicity was investigated in the ARROW study, which randomized ART-naive Ugandan and Zimbabwean children to receive either ZDV-containing regimens or ABC-containing regimens. The incidence of severe anemia was similar regardless of ZDV use, and this finding suggests that advanced HIV disease contributed to low hemoglobin values. ZDV use was associated with severe neutropenia in a small number of children.[23] In a retrospective study conducted in Ethiopia, an evaluation of predictors of anemia among children on ART[24] was conducted for the time period of 2007 to 2017. Study participants receiving ZDV-containing regimens were four times more likely to develop anemia than those children receiving ABC-containing regimens. Other predictors of anemia in addition to ZDV in this patient population included tuberculosis, severe immunosuppression, and undernutrition.

ZDV is associated with greater mitochondrial toxicity than ABC and tenofovir disoproxil fumarate, but it is associated with less mitochondrial toxicity than d4T.[25,26]

Although 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 ZDV may increase the risk.[2,4] Analysis of data from a U.S.-based multicenter prospective cohort study (PACTG 219/219C) found that ongoing ZDV exposure was independently associated with a higher rate of cardiomyopathy.[2] As part of the Pediatric HIV/AIDS Cohort Study (PHACS)/Adolescent Master Protocol (AMP) study, echocardiogram measurements were collected between 2008 and 2010 in 325 youth aged 7 to 16 years with perinatally acquired HIV infection. An association between ZDV use and increased end-systolic wall stress was observed in this study. The investigators speculate that alterations in cardiac structure in these children could progress to symptomatic cardiomyopathy later

in life.[3] A large cohort study to evaluate the prevalence of cardiac dysfunction in children and young adults <26 years of age was conducted in Kenya.[4] Approximately 28% of participants were found to have evidence of early cardiac dysfunction. Left ventricular ejection fraction negatively correlated with prior ZDV exposure, detectable HIV RNA, and elevated interleukin-6 concentrations.[4]

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