Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

Downloaded from http://aidsinfo.nih.gov/guidelines on 2/21/2013 EST.

Zidovudine (ZDV, AZT, Retrovir) (Last updated November 1, 2012; last reviewed November 1, 2012)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Capsules: 100 mg

Tablets: 300 mg

Syrup: 10 mg/mL

Concentrate for injection or intravenous (IV) infusion: 10 mg/mL

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

Combination tablets:

- *With lamivudine (3TC):* 300 mg ZDV + 150 mg 3TC (Combivir, generic)
- *With 3TC + abacavir (ABC):* 300 mg ZDV + 150 mg 3TC + 300 mg ABC (Trizivir)

Dosing Recommendations

ZDV dose for neonates/infants (<6 weeks of age) for prevention of transmission or treatment (Note: standard neonate dose may be excessive in premature infants)**:**

Gestational Age (weeks)	ZDV Oral Dosing	ZDV Intravenous Dosing (if unable to tolerate oral agents)
≥35 weeks	4 mg/kg of body weight every 12 hours	3 mg/kg of body weight IV every 12 hours
≥30–<35 weeks	2 mg/kg of body weight every 12 hours during first 14 days of life; increased to 3 mg/kg every 12 hours aged ≥15 days	1.5 mg/kg of body weight IV every 12 hours during first 14 days of life; increased to 2.3 mg/kg every 12 hours aged ≥15 days
<30 weeks	2 mg/kg of body weight every 12 hours during first 4 weeks of life; increased to 3 mg/kg every 12 hours after age 4 weeks	1.5 mg/kg of body weight IV every 12 hours until 4 weeks of life; increased to 2.3 mg/kg every 12 hours after age 4 weeks

Selected Adverse Events

- Bone marrow suppression: macrocytic anemia or neutropenia
- Nausea, vomiting, headache, insomnia, asthenia
- Lactic acidosis/severe hepatomegaly with hepatic steatosis
- Nail pigmentation
- Hyperlipidemia
- Insulin resistance/diabetes mellitus
- Lipoatrophy
- Myopathy.

Special Instructions

- Give ZDV without regard to food.
- If substantial granulocytopenia or anemia develop in patients 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 and platelets.

Pediatric dose (6 weeks to <18 years of age):

- *Body surface area dosing:*
  Oral: 180–240 mg/m^2 of body surface area every 12 hours or 160 mg/m^2 every 8 hours.

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

*Three times daily dosing is approved but rarely used in clinical practice.

Adolescent (age ≥18 years)/adult dose:

- 300 mg twice daily.

Combivir

Adolescent (weight ≥30 kg)/adult dose:

- 1 tablet twice daily.

Trizivir

Adolescent (weight ≥40 kg)/adult dose:

- 1 tablet twice daily.

Metabolism

- Metabolized to AZT glucuronide, which is renally excreted.
- Dosing in patients with renal impairment: Dosage adjustment is required in renal insufficiency.
- Dosing in patients with hepatic impairment: Decreased dosing may be required in patients with hepatic impairment.
- Do not use Combivir and Trizivir (fixed-dose combination products) in patients with creatinine clearance (CrCl) <50 mL/min, patients on dialysis, or patients with impaired hepatic function.

Drug Interactions: (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*):

- *Other nucleoside reverse transcriptase inhibitors (NRTIs):* Zidovudine should not be administered in combination with stavudine because of virologic antagonism.
- *Bone marrow suppressive/cytotoxic agents including ganciclovir, interferon alpha, and ribavirin:* These agents may increase the hematologic toxicity of zidovudine.
- *Doxorubicin:* Simultaneous use of doxorubicin and zidovudine should be avoided.

Major Toxicities:

- *More common:* Hematologic toxicity, including granulocytopenia and anemia particularly in patients with advanced HIV-1 disease. Headache, malaise, nausea, vomiting, and anorexia. Incidence of neutropenia may be increased in infants receiving lamivudine.[1]
- *Less common (more severe):* Myopathy (associated with prolonged use), myositis, and liver toxicity. 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.[2]

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/ZDV.html).

Resistance mutations were shown to be present in 29% (5 of 17) of infants born to mothers who received zidovudine during pregnancy.[3]

Pediatric Use: Zidovudine is frequently included as a component of the NRTI backbone for antiretroviral therapy.[4-20] Pediatric experience with zidovudine both for treatment of HIV and for prevention of mother-to-child transmission (PMTCT) is extensive.

Perinatal trial PACTG 076 established that zidovudine prophylaxis given during pregnancy, labor, and delivery, and to the newborn reduced risk of perinatal transmission of HIV by nearly 70%[21] (see the Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States for further discussion on the use of zidovudine for PMTCT of HIV). Although the PACTG 076 study used a zidovudine regimen of 2 mg/kg every 6 hours, data from many international studies support twice daily oral infant dosing for prophylaxis. Zidovudine 4 mg/kg of body weight every 12 hours is now recommended for neonates/infants >35 weeks of gestation for prevention of transmission or treatment (see *Perinatal Guidelines*).

Overall, zidovudine pharmacokinetics (PKs) in pediatric patients aged >3 months are similar to those 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 low intracellular zidovudine triphosphate concentrations seen with 600-mg once-daily dosing in adolescents.[22] PK studies, such as PACTG 331, demonstrate that dose adjustments are necessary for premature infants because they have reduced clearance of zidovudine compared with term newborns of similar postnatal age.[5] 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.[23]

References

1. Nielsen-Saines K, Watts DH, Gonçalves Veloso, V Bryson Y, Joao E, Pilotto JH, Gray G, Theron G, Bethel J, Mofenson L, and NICHD/HPTN 040 Study Group. Phase III Randomized Trial of the Safety and Efficacy of 3 Neonatal ARV Regimens for Prevention of Intrapartum HIV-1 Transmission: NICHD HPTN 040/PACTG 1043. Paper presented at: 18th Conference on Retroviruses and Oportunisitic Infections; Abstract 124LB; 2011; Boston, MA,
2. Watts DH, Li D, Handelsman E, et al. Assessment of birth defects according to maternal therapy among infants in the Women and Infants Transmission Study. *J Acquir Immune Defic Syndr*. Mar 1 2007;44(3):299-305. Available at http://www.ncbi.nlm.nih.gov/pubmed/17159659.
3. Kovacs A, Cowles MK, Britto P, et al. Pharmacokinetics of didanosine and drug resistance mutations in infants exposed to zidovudine during gestation or postnatally and treated with didanosine or zidovudine in the first three months of life. *Pediatr Infect Dis J*. Jun 2005;24(6):503-509. Available at http://www.ncbi.nlm.nih.gov/pubmed/15933559.
4. Balis FM, Pizzo PA, Murphy RF, et al. The pharmacokinetics of zidovudine administered by continuous infusion in children. *Ann Intern Med*. Feb 15 1989;110(4):279-285. Available at http://www.ncbi.nlm.nih.gov/pubmed/2643914.
5. Capparelli EV, Mirochnick M, Dankner WM, et al. Pharmacokinetics and tolerance of zidovudine in preterm infants. *J Pediatr.* Jan 2003;142(1):47-52. Available at http://www.ncbi.nlm.nih.gov/pubmed/12520254.

6. Chadwick EG, Rodman JH, Britto P, et al. Ritonavir-based highly active antiretroviral therapy in human immunodeficiency virus type 1-infected infants younger than 24 months of age. *Pediatr Infect Dis J*. Sep 2005;24(9):793-800. Available at http://www.ncbi.nlm.nih.gov/pubmed/16148846.
7. Englund JA, Baker CJ, Raskino C, et al. Zidovudine, didanosine, or both as the initial treatment for symptomatic HIV-infected children. AIDS Clinical Trials Group (ACTG) Study 152 Team. *N Engl J Med*. Jun 12 1997;336(24):1704-1712. Available at http://www.ncbi.nlm.nih.gov/pubmed/9182213.
8. Jankelevich S, Mueller BU, Mackall CL, et al. Long-term virologic and immunologic responses in human immunodeficiency virus type 1-infected children treated with indinavir, zidovudine, and lamivudine. *J Infect Dis*. Apr 1 2001;183(7):1116-1120. Available at http://www.ncbi.nlm.nih.gov/pubmed/11237839.
9. King JR, Kimberlin DW, Aldrovandi GM, Acosta EP. Antiretroviral pharmacokinetics in the paediatric population: A review. *Clinical pharmacokinetics*. 2002;41(14):1115-1133. Available at http://www.ncbi.nlm.nih.gov/pubmed/12405863.
10. Luzuriaga K, Bryson Y, Krogstad P, et al. Combination treatment with zidovudine, didanosine, and nevirapine in infants with human immunodeficiency virus type 1 infection. *N Engl J Med*. May 8 1997;336(19):1343-1349. Available at http://www.ncbi.nlm.nih.gov/pubmed/9134874.
11. McKinney RE Jr, Maha MA, Connor EM, et al. A multicenter trial of oral zidovudine in children with advanced human immunodeficiency virus disease. The Protocol 043 Study Group. *N Engl J Med*. Apr 11 1991;324(15):1018-1025. Available at http://www.ncbi.nlm.nih.gov/pubmed/1672443.
12. McKinney RE Jr, Johnson GM, Stanley K, et al. A randomized study of combined zidovudine-lamivudine versus didanosine monotherapy in children with symptomatic therapy-naive HIV-1 infection. The Pediatric AIDS Clinical Trials Group Protocol 300 Study Team. *J Pediatr*. Oct 1998;133(4):500-508. Available at http://www.ncbi.nlm.nih.gov/pubmed/9787687.
13. Mueller BU, Nelson RP Jr, Sleasman J, et al. A phase I/II study of the protease inhibitor ritonavir in children with human immunodeficiency virus infection. *Pediatrics*. 1998;101(3 Pt 1):335-343. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9480994&dopt=Abstract.
14. Mueller BU, Sleasman J, Nelson RP Jr, et al. A phase I/II study of the protease inhibitor indinavir in children with HIV infection. *Pediatrics*. Jul 1998;102(1 Pt 1):101-109. Available at http://www.ncbi.nlm.nih.gov/pubmed/9651421.
15. Nachman SA, Stanley K, Yogev R, et al. Nucleoside analogs plus ritonavir in stable antiretroviral therapy-experienced HIV-infected children: a randomized controlled trial. Pediatric AIDS Clinical Trials Group 338 Study Team. *JAMA*. Jan 26 2000;283(4):492-498. Available at http://www.ncbi.nlm.nih.gov/pubmed/10659875.
16. Palacios GC, Palafox VL, Alvarez-Munoz MT, et al. Response to two consecutive protease inhibitor combination therapy regimens in a cohort of HIV-1-infected children. *Scand J Infect Dis*. 2002;34(1):41-44. Available at http://www.ncbi.nlm.nih.gov/pubmed/11874163.
17. Pizzo PA, Eddy J, Falloon J, et al. Effect of continuous intravenous infusion of zidovudine (AZT) in children with symptomatic HIV infection. *N Engl J Med*. Oct 6 1988;319(14):889-896. Available at http://www.ncbi.nlm.nih.gov/pubmed/3166511.
18. Saez-Llorens X, Nelson RP Jr, Emmanuel P, et al. A randomized, double-blind study of triple nucleoside therapy of abacavir, lamivudine, and zidovudine versus lamivudine and zidovudine in previously treated human immunodeficiency virus type 1-infected children. The CNAA3006 Study Team. *Pediatrics*. Jan 2001;107(1):E4. Available at http://www.ncbi.nlm.nih.gov/pubmed/11134468.
19. van Rossum AM, Geelen SP, Hartwig NG, et al. Results of 2 years of treatment with protease-inhibitor-containing antiretroviral therapy in dutch children infected with human immunodeficiency virus type 1. *Clin Infect Dis*. Apr 1 2002;34(7):1008-1016. Available at http://www.ncbi.nlm.nih.gov/pubmed/11880968.

20. Bergshoeff AS, Fraaij PL, Verweij C, et al. Plasma levels of zidovudine twice daily compared with three times daily in six HIV-1-infected children. *J Antimicrob Chemother.* Dec 2004;54(6):1152-1154. Available at http://www.ncbi.nlm.nih.gov/pubmed/15537694.
21. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med*. Nov 3 1994;331(18):1173-1180. Available at http://www.ncbi.nlm.nih.gov/pubmed/7935654.
22. Flynn PM, Rodman J, Lindsey JC, et al. Intracellular pharmacokinetics of once versus twice daily zidovudine and lamivudine in adolescents. *Antimicrob Agents Chemother*. Oct 2007;51(10):3516-3522. Available at http://www.ncbi.nlm.nih.gov/pubmed/17664328.
23. Pizzo PA, Eddy J, Falloon J, et al. Effect of continuous intravenous infusion of zidovudine (AZT) in children with symptomatic HIV infection. *N Engl J Med*. 1988;319(14):889-896. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3166511&dopt=Abstract.