Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Stavudine (d4T, Zerit) (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

Powder for Oral Solution: 1 mg/mL

Capsules: 15 mg, 20 mg, 30 mg, 40 mg

Generic: d4T capsules and solution have been approved by the Food and Drug Administration (FDA) for manufacture and distribution in the United States.

Dosing Recommendations

Neonate/infant dose (birth to 13 days):

- 0.5 mg/kg twice daily.

Pediatric dose (at least 14 days old and weighing <30 kg):

- 1 mg/kg twice daily

Adolescent (≥30 kg)/adult dose:

- 30 mg twice daily.

Selected Adverse Events

- Mitochondrial toxicity
- Peripheral neuropathy
- Lipoatrophy
- Pancreatitis
- Lactic acidosis/severe hepatomegaly with hepatic steatosis (higher incidence than with other nucleoside reverse transcriptase inhibitors [NRTIs]). The risk is increased when used in combination with ddI.
- Hyperlipidemia
- Insulin resistance/diabetes mellitus
- Rapidly progressive ascending neuromuscular weakness (rare)

Special Instructions

- d4T can be given without regard to food.
- Shake d4T oral solution well before use. Keep refrigerated; the solution will remain stable for 30 days.

Metabolism

- Renal excretion 50%. Decrease dose in renal dysfunction.

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

- *Renal elimination:* Drugs that decrease renal function could decrease stavudine clearance.
- *Other NRTIs:* Stavudine should not be administered in combination with zidovudine because of virologic antagonism.

- *Overlapping toxicities:* The combination of stavudine and didanosine is not recommended for initial therapy because of overlapping toxicities. Reported toxicities are more often reported in adults and include serious, even fatal, cases of lactic acidosis with hepatic steatosis with or without pancreatitis in pregnant women.
- *Ribavirin and interferon:* Hepatic decompensation (sometimes fatal) has occurred in HIV/hepatitis C virus co-infected patients receiving combination antiretroviral therapy (ART), interferon, and ribavirin.

Major Toxicities:

- *More common:* Headache, gastrointestinal disturbances, skin rashes, hyperlipidemia, and fat maldistribution.
- *Less common (more severe):* Peripheral sensory neuropathy is dose-related and occurs more frequently in patients with advanced HIV disease, a history of peripheral neuropathy, and in those patients receiving other drugs associated with neuropathy. Pancreatitis. Lactic acidosis and severe hepatomegaly with hepatic steatosis, including fatal cases, have been reported. The combination of stavudine with didanosine may result in enhanced toxicity (increased risk of fatal and nonfatal cases of lactic acidosis, pancreatitis, peripheral neuropathy, and hepatotoxicity), particularly in adults, including pregnant women. This combination should not be used for initial therapy. Risk factors found to be associated with lactic acidosis in adults include female gender, obesity, and prolonged nucleoside exposure.[1]
- *Rare:* Increased liver enzymes and hepatic toxicity which may be severe or fatal. Neurologic symptoms including rapidly progressive ascending neuromuscular weakness are most often seen in the setting of lactic acidosis.

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/d4T.html).

Pediatric Use: Although stavudine is FDA-approved for use in children, its use is limited because it carries a higher risk of side effects associated with mitochondrial toxicity and a higher incidence of lipoatrophy than other NRTIs.

Data from multiple pediatric studies of stavudine alone or in combination with other antiretroviral agents demonstrate that stavudine appears safe and is associated with clinical and virologic response.[2-8] In resource-limited countries, stavudine is frequently a component of initial ART therapy with lamivudine and nevirapine in children, often as a component of fixed-dose combinations not available in the United States. In this setting, reported outcomes from observational studies are good; data show substantial increases in the CD4 T lymphocyte count and complete viral suppression in 50% to 80% of treatment-naive children.[9-12] In such a setting, where pediatric patients are already predisposed to anemia because of malnutrition, parasitic infestations, or sickle cell anemia, stavudine carries a lower risk of hematologic toxicity than zidovudine, especially in patients receiving cotrimoxazole prophylaxis.[13]

Stavudine is associated with a higher rate of adverse events than zidovudine in adults and children receiving ART.[14, 15] In a large pediatric natural history study (PACTG 219C), stavudine-containing regimens had a modest but significantly higher rate of clinical and laboratory toxicities than those containing zidovudine, with pancreatitis, peripheral neuropathy, and lipodystrophy/lipoatrophy (fat maldistribution) associated more often with stavudine use.[15] Peripheral neuropathy is an important

toxicity associated with stavudine but appears to be less common in children than in adults.[3, 16] In PACTG 219C, peripheral neuropathy was recognized in 0.9% of children.[15] Lipodystrophy, and specifically lipoatrophy (loss of subcutaneous fat), are toxicities associated with NRTIs, particularly stavudine, in adults and children.[17-20] Lipodystrophy developed in 28% of 39 children receiving stavudine, lamivudine, and nelfinavir after a median of 49 months of therapy, with 9 children demonstrating lipoatrophy.[21] Among 90 children receiving stavudine, lamivudine, and either nevirapine or efavirenz, 65% developed lipodystrophy by 33 months.[22] Among 100 pre-pubertal African children, the prevalence of lipoatrophy was found to be 37% with a strong correlation with duration on stavudine therapy.[23] Improvements in lipodystrophy were observed among Thai children after substitution of stavudine with zidovudine.[24]

Lactic acidosis with hepatic steatosis, including fatal cases, has been reported with use of nucleoside analogues, including stavudine, alone or in combination with didanosine (ddI).[25-27] In adults, female gender, higher body mass index (BMI), and lower initial CD4 cell count are risk factors for developing lactic acidosis and hyperlactatemia.[1] The combination of stavudine and didanosine in pregnant women has been associated with fatal lactic acidosis and should be used during pregnancy only if no other alternatives are available.[28] (For additional information on lactic acidosis see Table 17. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations.)

Many of the above-mentioned adverse events are believed to be due to mitochondrial toxicity resulting from inhibition of mitochondrial DNA polymerase gamma, with depletion of mitochondrial DNA in fat, muscle, peripheral blood mononuclear cells, and other tissues.[25, 29-31] In a recent analysis involving a large cohort of pediatric patients (Pediatric AIDS Clinical Trials Group protocols 219 and 219C), possible mitochondrial dysfunction was associated with NRTI use, especially in children receiving stavudine and/or lamivudine.[32]

The World Health Organization recommends that stavudine be phased out of use because of unacceptable toxicity, with a strong recommendation that a maximum stavudine dose of 30 mg twice daily be used instead of the FDA-recommended 40 mg twice daily in patients weighing 60 kg or more.[33, 34] Several studies have compared the efficacy and toxicity of the two doses: HIV suppression was found to be similar in adults treated in South Africa with either the 30-mg or 40-mg dose;[35] in adults treated in South Africa, incidence of peripheral neuropathy was significantly lower in the 30-mg than in the 40-mg group, but the overall incidence was considered to be unacceptably high.[36] Lipoatrophy and peripheral neuropathy are more likely to occur with higher doses but the risk of lactic acidosis is associated with female gender and a high BMI.[33] Efficacy data are limited comparing the 30-mg and 40-mg doses given twice daily, but incidence of lipoatrophy and peripheral neuropathy are reduced when the lower doses are used.

Current pediatric dosing recommendations are based on early pharmacokinetic (PK) studies designed to achieve exposure (area under the curve) in children similar to that found in adults receiving a dose with proven efficacy.[37] These early studies were conducted at a time when treatment options were limited and many children had failure to thrive. The authors in this early PK study state that stavudine distributes in total body water and because total body weight correlates well with lean body mass (or weight) stavudine dosages in obese children should be based on lean body weight.[37]

The pediatric formulation for stavudine oral solution requires refrigeration and has limited stability once reconstituted. As an alternative dosing method for children, capsules can be opened and dispersed in a small amount of water, the appropriate dose drawn up into an oral syringe, and administered immediately. Because plasma exposure is equivalent with stavudine administered in an intact or a dispersed capsule, dosing with the dispersal method can be used as an alternative to the oral solution.[38]

References

1. Matthews LT, Giddy J, Ghebremichael M, et al. A risk-factor guided approach to reducing lactic acidosis and hyperlactatemia in patients on antiretroviral therapy. *PLoS One*. 2011;6(4):e18736. Available at http://www.ncbi.nlm.nih.gov/pubmed/21494566.
2. Aboulker JP, Babiker A, Chaix ML, et al. Highly active antiretroviral therapy started in infants under 3 months of age: 72-week follow-up for CD4 cell count, viral load and drug resistance outcome. *AIDS*. Jan 23 2004;18(2):237-245. Available at http://www.ncbi.nlm.nih.gov/pubmed/15075541.
3. Kline MW, Dunkle LM, Church JA, et al. A phase I/II evaluation of stavudine (d4T) in children with human immunodeficiency virus infection. *Pediatrics*. Aug 1995;96(2 Pt 1):247-252. Available at http://www.ncbi.nlm.nih.gov/pubmed/7630678.
4. Kline MW, Fletcher CV, Federici ME, et al. Combination therapy with stavudine and didanosine in children with advanced human immunodeficiency virus infection: pharmacokinetic properties, safety, and immunologic and virologic effects. *Pediatrics*. 1996;97(6 Pt 1):886-890. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8657531&dopt=Abstract.
5. Kline MW, van Dyke RB, Lindsey J, et al. Combination therapy with stavudine (d4T) plus didanosine (ddI) in children with human immunodeficiency virus infection. The Pediatric AIDS Clinical Trials Group 327 Team. *Pediatrics*. 1999;103(5):e62. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10224206&dopt=Abstract.
6. Krogstad P, Lee S, Johnson G, et al. Nucleoside-analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir for pretreated children infected with human immunodeficiency virus type 1. *Clin Infect Dis*. 2002;34(7):991-1001. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11880966&dopt=Abstract.
7. 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.
8. Yogev R, Lee S, Wiznia A, et al. Stavudine, nevirapine and ritonavir in stable antiretroviral therapy-experienced children with human immunodeficiency virus infection. *Pediatr Infect Dis J*. Feb 2002;21(2):119-125. Available at http://www.ncbi.nlm.nih.gov/pubmed/11840078.
9. Bolton-Moore C, Mubiana-Mbewe M, Cantrell RA, et al. Clinical outcomes and CD4 cell response in children receiving antiretroviral therapy at primary health care facilities in Zambia. *JAMA*. Oct 24 2007;298(16):1888-1899. Available at http://www.ncbi.nlm.nih.gov/pubmed/17954540.
10. Janssens B, Raleigh B, Soeung S, et al. Effectiveness of highly active antiretroviral therapy in HIV-positive children: evaluation at 12 months in a routine program in Cambodia. *Pediatrics*. Nov 2007;120(5):e1134-1140. Available at http://www.ncbi.nlm.nih.gov/pubmed/17954553.
11. Kamya MR, Mayanja-Kizza H, Kambugu A, et al. Predictors of long-term viral failure among ugandan children and adults treated with antiretroviral therapy. *J Acquir Immune Defic Syndr*. Oct 1 2007;46(2):187-193. Available at http://www.ncbi.nlm.nih.gov/pubmed/17693883.
12. Zhang F, Haberer JE, Zhao Y, et al. Chinese pediatric highly active antiretroviral therapy observational cohort: a 1-year analysis of clinical, immunologic, and virologic outcomes. *J Acquir Immune Defic Syndr*. Dec 15 2007;46(5):594-598. Available at http://www.ncbi.nlm.nih.gov/pubmed/18043313.
13. Okechukwu AA, Gambo D, Okechukwu IO. Prevalence of anaemia in HIV-infected children at the University of Abuja Teaching Hospital, Gwagwalada. *Niger J Med*. Jan-Mar 2010;19(1):50-57. Available at http://www.ncbi.nlm.nih.gov/pubmed/20232757.

14. Robbins GK, De Gruttola V, Shafer RW, et al. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med*. Dec 11 2003;349(24):2293-2303. Available at http://www.ncbi.nlm.nih.gov/pubmed/14668455.

15. Van Dyke RB, Wang L, Williams PL, Pediatric ACTGCT. Toxicities associated with dual nucleoside reverse-transcriptase inhibitor regimens in HIV-infected children. *J Infect Dis*. Dec 1 2008;198(11):1599-1608. Available at http://www.ncbi.nlm.nih.gov/pubmed/19000014.

16. Kline MW, Fletcher CV, Harris AT, et al. A pilot study of combination therapy with indinavir, stavudine (d4T), and didanosine (ddI) in children infected with the human immunodeficiency virus. *J Pediatr*. Mar 1998;132(3 Pt 1):543-546. Available at http://www.ncbi.nlm.nih.gov/pubmed/9544920.

17. Joly V, Flandre P, Meiffredy V, et al. Increased risk of lipoatrophy under stavudine in HIV-1-infected patients: results of a substudy from a comparative trial. *AIDS*. 2002;16(18):2447-2454. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12461419&query_hl=62.

18. European Paediatric Lipodystrophy Group. Antiretroviral therapy, fat redistribution and hyperlipidaemia in HIV-infected children in Europe. *AIDS*. 2004;18(10):1443-1451. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15199321&query_hl=60.

19. Ene L, Goetghebuer T, Hainaut M, Peltier A, Toppet V, Levy J. Prevalence of lipodystrophy in HIV-infected children: a cross-sectional study. *Eur J Pediatr*. Jan 2007;166(1):13-21. Available at http://www.ncbi.nlm.nih.gov/pubmed/16896646.

20. Haubrich RH, Riddler SA, DiRienzo AG, et al. Metabolic outcomes in a randomized trial of nucleoside, nonnucleoside and protease inhibitor-sparing regimens for initial HIV treatment. *AIDS*. Jun 1 2009;23(9):1109-1118. Available at http://www.ncbi.nlm.nih.gov/pubmed/19417580.

21. Scherpbier HJ, Bekker V, van Leth F, Jurriaans S, Lange JM, Kuijpers TW. Long-term experience with combination antiretroviral therapy that contains nelfinavir for up to 7 years in a pediatric cohort. *Pediatrics*. Mar 2006;117(3):e528-536. Available at http://www.ncbi.nlm.nih.gov/pubmed/16481448.

22. Aurpibul L, Puthanakit T, Lee B, Mangklabruks A, Sirisanthana T, Sirisanthana V. Lipodystrophy and metabolic changes in HIV-infected children on non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy. *Antivir Ther*. 2007;12(8):1247-1254. Available at http://www.ncbi.nlm.nih.gov/pubmed/18240864.

23. Innes S, van Niekerk M, Rabie H, et al. Prevalence and risk factors for lipoatrophy among pre-pubertal African children on HAART, Abstract #CDB430. 6th IAS Conference on HIV Pathogensesis, Treatment and Prevention; 17-20 July 2011, 2011; Rome, Italy.

24. Aurpibul L, Puthanakit T, Taejaroenkul S, et al. Improvement of lipodystropy in children after substitution of stavudine with zidovudine in NNRTI-based antiretroviral therapy, Abstract #CDB437. 6th IAS Conference on HIV Pathogenesis Treatment and Prevention; 17-20 July 2011, 2011; Rome, Italy.

25. Haugaard SB, Andersen O, Pedersen SB, et al. Depleted skeletal muscle mitochondrial DNA, hyperlactatemia, and decreased oxidative capacity in HIV-infected patients on highly active antiretroviral therapy. *J Med Virol*. Sep 2005;77(1):29-38. Available at http://www.ncbi.nlm.nih.gov/pubmed/16032748.

26. Koh MT. Unrecognized near-fatal hyperlactatemia in an HIV-infected infant exposed to nucleoside reverse transcriptase inhibitors. *Int J Infect Dis*. Jan 2007;11(1):85-86. Available at http://www.ncbi.nlm.nih.gov/pubmed/16581278.

27. Hernandez Perez E, Dawood H. Stavudine-induced hyperlactatemia/lactic acidosis at a tertiary communicable diseases clinic in South Africa. *J Int Assoc Physicians AIDS Care (Chic)*. Mar-Apr 2010;9(2):109-112. Available at http://www.ncbi.nlm.nih.gov/pubmed/20484736.

28. Sarner L, Fakoya A. Acute onset lactic acidosis and pancreatitis in the third trimester of pregnancy in HIV-1 positive women taking antiretroviral medication. *Sex Transm Infect*. Feb 2002;78(1):58-59. Available at http://www.ncbi.nlm.nih.gov/pubmed/11872862.

29. Blanco F, Garcia-Benayas T, Jose de la Cruz J, Gonzalez-Lahoz J, Soriano V. First-line therapy and mitochondrial

damage: different nucleosides, different findings. *HIV Clin Trials*. Jan-Feb 2003;4(1):11-19. Available at http://www.ncbi.nlm.nih.gov/pubmed/12577192.

30. Cherry CL, Gahan ME, McArthur JC, et al. Exposure to dideoxynucleosides is reflected in lowered mitochondrial DNA in subcutaneous fat. *J Acquir Immune Defic Syndr*. 2002;30(3):271-277. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12131563.
31. Sanchez-Conde M, de Mendoza C, Jimenez-Nacher I, Barreiro P, Gonzalez-Lahoz J, Soriano V. Reductions in stavudine dose might ameliorate mitochondrial-associated complications without compromising antiviral activity. *HIV Clin Trials*. Jul-Aug 2005;6(4):197-202. Available at http://www.ncbi.nlm.nih.gov/pubmed/16214736.
32. Crain MJ, Chernoff MC, Oleske JM, et al. Possible mitochondrial dysfunction and its association with antiretroviral therapy use in children perinatally infected with HIV. *J Infect Dis*. Jul 15 2010;202(2):291-301. Available at http://www.ncbi.nlm.nih.gov/pubmed/20533872.
33. World Health Organization. Toxicity of reduced and standard doses of d4T, http://www.who.int/hiv/pub/arv/rapid_advice_art.pdf. 2009.
34. World Health Organization. Rapid advice. Antiretroviral therapy for HIV infection in adults and adolescents, http://www.who.int/hiv/pub/arv/rapid_advice_art.pdf. 2009.
35. Hoffmann CJ, Charalambous S, Fielding KL, et al. HIV suppression with stavudine 30 mg versus 40 mg in adults over 60 kg on antiretroviral therapy in South Africa. *AIDS*. Aug 24 2009;23(13):1784-1786. Available at http://www.ncbi.nlm.nih.gov/pubmed/19491652.
36. Pahuja MG, Glesby MJ, Grobler A, et al. Effects of a reduced dose of stavudine (d4T) on the incidence and severity of peripheral neuropathy in PLHIV in South Africa. IAS-AIDS 2010. Abstract #WEPE0149. 2010.
37. Kaul S, Kline MW, Church JA, Dunkle LM. Determination of dosing guidelines for stavudine (2',3'-didehydro-3'-deoxythymidine) in children with human immunodeficiency virus infection. *Antimicrob Agents Chemother*. Mar 2001;45(3):758-763. Available at http://www.ncbi.nlm.nih.gov/pubmed/11181356.
38. Innes S, Norman J, Smith P, et al. Bioequivalence of dispersed stavudine: opened versus closed capsule dosing. *Antivir Ther*. 2011;16(7):1131-1134. Available at http://www.ncbi.nlm.nih.gov/pubmed/22024529.