



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Stavudine (d4T, Zerit) (Last updated April 27, 2017; last reviewed April 27, 2017)

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

Formulations

Powder for Oral Solution: 1 mg/mL

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

Generic Formulations:

Powder for Oral Solution: 1 mg/mL

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

Dosing Recommendations

Neonate/Infant Dose (Birth to 13 Days):

- 0.5 mg/kg per dose twice daily

Pediatric Dose (Aged ≥ 14 Days and Weighing < 30 kg):

- 1 mg/kg per dose twice daily

Adolescent (≥ 30 kg)/Adult Dose:

- 30 mg per dose twice daily

Selected Adverse Events

- Mitochondrial toxicity, highest risk of all NRTI drugs
- Peripheral neuropathy is dose-related and occurs more frequently in patients with advanced HIV disease, a history of peripheral neuropathy, and in patients receiving other drugs associated with neuropathy.
- Facial/peripheral lipoatrophy
- Pancreatitis
- Lactic acidosis/severe hepatomegaly with hepatic steatosis (higher incidence than with other nucleoside reverse transcriptase inhibitors). The risk is increased when used in combination with didanosine.
- Dyslipidemia
- Insulin resistance, asymptomatic hyperglycemia
- Rapidly progressive ascending neuromuscular weakness (rare)

Special Instructions

- Stavudine can be given without regard to food.
- Shake stavudine oral solution well before use. Keep refrigerated; the solution is stable for 30 days.

Metabolism/Elimination

- Renal excretion 50%. Decrease dose in renal dysfunction.
- Stavudine is phosphorylated intracellularly to the active metabolite stavudine triphosphate.

Drug Interactions (see also the [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents](#) and <http://www.hiv-druginteractions.org/>)

- *Renal elimination:* Drugs that decrease renal function could decrease stavudine clearance.
- *Other nucleoside reverse transcriptase inhibitors (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 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 patients with HIV/hepatitis C virus co-infection receiving combination antiretroviral therapy (ART), interferon, and ribavirin.
- *Doxorubicin:* Simultaneous use of doxorubicin and stavudine should be avoided. Doxorubicin may inhibit the phosphorylation of stavudine to its active form.

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 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. **Non-cirrhotic portal hypertension with prolonged exposure.**

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10), and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see <http://hivdb.stanford.edu/DR/>).

Pediatric Use

Approval

Although stavudine is Food and Drug Administration (FDA)-approved for use in **infants and children, it is not recommended for use by the Panel** because it carries a higher risk of adverse effects associated with mitochondrial toxicity and a higher incidence of lipoatrophy than other NRTIs.

Efficacy

Data from multiple pediatric studies of stavudine alone or in combination with other antiretroviral (ARV) agents demonstrate that stavudine is associated with clinical and virologic response.²⁻⁸ In resource-limited countries, stavudine is frequently a component of initial ART 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 (CD4) cell count and complete viral suppression in 50% to 80% of treatment-naïve 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 TMP-SMX prophylaxis.¹³ Short-term use of stavudine in certain settings where access to other ARVs may be limited remains an important strategy for treatment of children.^{14,15}

Toxicity

Stavudine is associated with a higher rate of adverse events than zidovudine in adults and children receiving ART.^{16,17} 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.¹⁷ Peripheral neuropathy is an important toxicity associated with stavudine but appears to be less common in children than in adults.^{3,18}

Lipodystrophy and Metabolic Abnormalities

Lipodystrophy syndrome (LS), and specifically lipoatrophy (loss of subcutaneous fat), are toxicities associated with NRTIs, particularly stavudine, in adults and children.¹⁹⁻²² Children with metabolic disorders and abnormalities in body fat distribution, including fat loss and central fat accumulation, may be at increased risk of cardiovascular disease in early adulthood.^{23,24} Stavudine use has consistently been associated with a higher risk of lipodystrophy and other metabolic abnormalities (e.g., insulin resistance) in multiple pediatric studies involving children.²³⁻³⁰ Lipodystrophy developed in 27% to 66% of children, with lipoatrophy being the most common form of lipodystrophy. While ever- or current-stavudine use has consistently been associated with a higher risk of LS, additional factors include older age and duration on ARVs.^{26,27} Improvements in (or resolution of) lipodystrophy were reported in 22.9% to 73% of cases after discontinuation of stavudine in two separate studies.^{28,31}

Lactic acidosis with hepatic steatosis, including fatal cases, has been reported with use of nucleoside analogues, including stavudine, alone or in combination with didanosine.³²⁻³⁴

Mechanism

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.^{32,35-37} In a recent analysis involving a large cohort of pediatric patients (PACTG protocols 219 and 219C), possible mitochondrial dysfunction was associated with NRTI use, especially in children receiving stavudine and/or lamivudine.³⁸

World Health Organization Recommendations

The World Health Organization (WHO) strongly recommends 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.^{39,40} Studies comparing the efficacy and toxicity of the two doses **have consistently shown** that the 30-mg dose is associated with similar efficacy and lower toxicity than the 40-mg dose but the overall incidence of toxicity is considered to be unacceptably high.⁴¹⁻⁴⁵ WHO recommends that stavudine be phased out of use in all patients because of concerns about unacceptable toxicity, even at the lower dose, since safer alternative agents can be prescribed.

Pharmacokinetics

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.⁴⁶ Although WHO has recommended a reduced dose in adults, a similar dose reduction has not been suggested in children. A reduced pediatric dose has been proposed based on PK modeling, but clinical data on intracellular concentrations of the active stavudine triphosphate are lacking.^{47,48}

Formulations

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, with 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.⁴⁹

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