Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Didanosine (ddI, Videx) (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

Videx pediatric powder for oral solution: reconstituted 10 mg/mL

Videx enteric-coated (EC) delayed-release capsules (EC beadlets): 125 mg, 200 mg, 250 mg, and 400 mg

Generic ddI delayed-release capsules: 200 mg, 250 mg, and 400 mg

Dosing Recommendations

Neonate/infant dose (aged 2 weeks to <3 months):

- 50 mg/m^2 of body surface area every 12 hours.
- Manufacturer recommends 100 mg/m^2 of body surface area every 12 hours in this age range. Panel members interpret pharmacokinetic data as suggesting potential increased toxicity at that dose in this age group and many would use 50 mg/m^2 of body surface area every 12 hours.

Infant dose (aged ≥3 months to 8 months):

- 100 mg/m^2 of body surface area every 12 hours.

Pediatric dose of oral solution (age >8 months):

- 120 mg/m^2 of body surface area every 12 hours.

  (Dose range: 90–150 mg/m^2 of body surface area every 12 hours; maximum dose 200 mg/dose twice daily.)

Pediatric dose of Videx EC or generic capsules (aged 6–18 years and body weight ≥20 kg):

Body Weight (kg)	Dose (mg)
20 kg to <25 kg	200 mg once daily
25 kg to <60 kg	250 mg once daily
≥60 kg	400 mg once daily

In treatment-naive children aged 3–21 years, 240 mg/m^2 of body surface area once daily (oral solution or capsules) has been used with effective viral suppression.

Selected Adverse Events

- Peripheral neuropathy
- Electrolyte abnormalities
- Diarrhea, abdominal pain, nausea, and vomiting
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported in adults. (The risk is increased when ddI is used in combination with stavudine [d4T].)
- Pancreatitis (less common in children than in adults, more common in adults when ddI is used in combination with tenofovir [TDF] or d4T)
- Non-cirrhotic portal hypertension
- Retinal changes, optic neuritis
- Insulin resistance/diabetes mellitus

Special Instructions

- Because food decreases absorption of ddI, administration of ddI on an empty stomach (30 minutes before or 2 hours after a meal) generally is recommended. To improve adherence, some practitioners administer ddI without regard to timing of meals (see text below).
- ddI oral solution contains antacids that may interfere with the absorption of other medications, including protease inhibitors (PIs). See individual protease inhibitor for instructions on timing of administration. This interaction is more pronounced for the buffered (solution) formulation of ddI, than for the enteric coated formulation.

Adolescent/adult dose:

Body Weight (kg)	Dose (mg)
<60 kg	250 mg once daily
≥60 kg	400 mg once daily

ddI in combination with TDF:

- This combination should be avoided, if possible, because of enhanced ddI toxicity.

Pediatric/adolescent dose of ddI when combined with TDF:

- No data on this combination in children or adolescents aged <18 years, but decrease in ddI dose is recommended as in adults.

Adult dose of ddI when combined with TDF:

Body Weight (kg)	Dose (mg)
<60 kg (limited data in adults)	200 mg once daily
≥60 kg	250 mg once daily

- Shake ddI oral solution well before use. Keep refrigerated; solution is stable for 30 days.

Metabolism

- Renal excretion 50%.
- Dosing of ddI in patients with renal insufficiency: Decreased dosage should be used in patients with impaired renal function. Consult manufacturer's prescribing information for adjustment of dosage in accordance with creatinine clearance.

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

- *Absorption:* The presence of antacids in didanosine suspension has the potential to decrease the absorption of a number of medications if given at the same time. Many of these interactions can be avoided by timing doses to avoid giving other medications concurrently with didanosine suspension.
- *Mechanism unknown:* Didanosine serum concentrations are increased when didanosine is co-administered with tenofovir and this combination should be avoided if possible.
- *Renal elimination:* Drugs that decrease renal function can decrease didanosine clearance.
- *Enhanced toxicity:* Didanosine mitochondrial toxicity is enhanced by ribavirin.
- *Overlapping toxicities:* Risk of pancreatitis and peripheral neuropathy is increased with use of some nucleoside reverse transcriptase inhibitors (NRTIs) (such as stavudine). The combination of stavudine and didanosine is not recommended (unless the benefits clearly outweigh the risks) because of overlapping toxicities and reports of serious, even fatal, cases of lactic acidosis with hepatic steatosis with or without pancreatitis in pregnant women.

Major Toxicities:

- *More common:* Diarrhea, abdominal pain, nausea, and vomiting.
- *Less common (more severe):* Peripheral neuropathy, electrolyte abnormalities, and hyperuricemia. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported.

Pancreatitis (less common in children than in adults, more common in adults when used in combination with tenofovir or stavudine), increased liver enzymes, and retinal depigmentation and optic neuritis have been reported. The combination of stavudine with didanosine may result in enhanced toxicity (increased risk of fatal and nonfatal cases of lactic acidosis or pancreatitis); this combination should not be used unless the potential benefit clearly outweighs the potential risk.

- *Rare:* Non-cirrhotic portal hypertension, presenting clinically with hematemesis, esophageal varices, ascites, and splenomegaly, and associated with increased transaminases, increased alkaline phosphatase, and thrombocytopenia, has been associated with long-term didanosine use in adults.[1-3] In adults, use of didanosine may be associated with increased risk of myocardial infarction.[4]

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/ddI.html).

Pediatric Use: Didanosine is Food and Drug Administration (FDA) approved for use in children as part of a dual-NRTI backbone in combination antiretroviral therapy (cART).

Recommended doses of didanosine oral solution in children have traditionally been 90 to 150 mg/m^2 body surface area per dose twice daily. Doses higher than 180 mg/m^2 body surface area twice daily are associated with increased toxicity.[5] The pharmacokinetic (PK) variable of greatest pharmacodynamic significance is the area under the curve (AUC), with virologic response best when didanosine AUC ≥0.60 mg*h/L.[6, 7] In a simulation based on didanosine concentration data from 16 children, a dose of 90 mg/m^2 body surface area twice daily was predicted to result in adequate drug exposure in only 57% of pediatric patients, compared with adequate exposure predicted in 88% of patients at a dose of 120 mg/m^2 body surface area twice daily,[7] which is the currently recommended dose for children aged 8 months to 3 years.

For infants aged 2 weeks to 8 months, the FDA recommends 100 mg/m^2 body surface area per dose twice daily, increasing to 120 mg/m^2 body surface area per dose twice daily at age 8 months. However, 2 small studies suggest that a higher AUC is seen in infants aged <6 weeks and that a dose of 100 mg/m^2 body surface area per day (either as 50 mg/m^2 body surface area per dose twice daily or 100 mg/m^2 body surface area once daily) in infants aged <6 weeks achieves AUCs consistent with those for higher doses in older children.[8, 9] Therefore, because these PK differences in younger infants (aged 2 weeks–3 months) compared with older children raise concern for increased toxicity in that age group, the Panel recommends a dose of 50 mg/m^2 of body surface area twice daily for infants younger than 3 months.

A once-daily dosing regimen may be preferable to promote adherence, and multiple studies support the favorable PKs and efficacy of once-daily dosing. In a study of 10 children aged 4 to 10 years, EC didanosine (Videx EC) administered as a single dose of 240 mg/m^2 body surface area once daily was shown to have similar plasma AUC (although lower peak plasma concentrations) compared with the equivalent dose of buffered didanosine.[8] The resultant intracellular (active) drug concentrations are unknown. In 24 HIV-infected children, didanosine oral solution at a dose of 180 mg/m^2 body surface area once daily was compared with 90 mg/m^2 body surface area twice daily, and the AUC was actually higher in the once-daily group than in the twice-daily group.[10] Long-term virologic suppression with a once-daily regimen of efavirenz, emtricitabine, and didanosine (oral solution or EC beadlet capsules) was reported in 37 treatment-naive children aged 3 to 21 years.[11] The didanosine dose used in that study was 240 mg/m^2/dose once daily, and PK analysis showed no dose changes were needed to reach PK targets.[11] A European trial of once-daily combination therapy in 36 children aged 3 to 11 years that included didanosine at a dose of 200 to 240 mg/m^2 body surface area demonstrated safety and efficacy with up to 96 weeks of follow up.[12] In 53

children with advanced symptomatic HIV infection, once- versus twice-daily didanosine at a dose of 270 mg/m^2 body surface area per day showed no difference in surrogate marker or clinical endpoints, except that weight gain was less in the children given once-daily therapy.[13] In 51 children (median age 6.0 years, range 2.5 to 15.0 years) in Burkina Faso, the once-daily combination of didanosine-lamivudine-efavirenz resulted in week-48 viral load <300 copies/mL in 81% of treated participants. That study used didanosine at a dose of 240 mg/m^2/day, administered in the fasting state as tablets with a separate antacid (not enteric-coated capsules).[6]

Although the prescribing information recommends taking didanosine on an empty stomach, this is impractical for infants who must be fed frequently and it may decrease medication adherence by increasing regimen complexity. A comparison showed that regardless of whether didanosine oral solution was given to children with or without food systemic exposure measured by AUC was similar; absorption of didanosine administered with food was slower and elimination more prolonged.[14] To improve adherence, some practitioners administer didanosine without regard to timing of meals. Studies in adults suggest that didanosine can be given without regard to food.[15, 16] A European study dosed didanosine oral solution as part of a four-drug regimen either 1 hour before or 1 hour after meals, but allowed the extended-release formulation to be given without food restriction, and showed good virologic outcome with up to 96 weeks of follow-up.[17]

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