



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Didanosine (ddl, Videx) (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

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 Didanosine Delayed-Release Capsules: 125 mg, 200 mg, 250 mg, and 400 mg

Tablets for Oral Suspension: 100 mg, 150 mg, and 200 mg

Dosing Recommendations

Neonatal/Infant Dose (Aged 2 Weeks to <3 Months):

- 50 mg/m² of body surface area every 12 hours
- See dosing section below for justification of this dose.

Infant Dose (Aged ≥3 Months to 8 Months):

- 100 mg/m² body surface area every 12 hours

Pediatric Dose of Oral Solution (Age >8 Months):

- 120 mg/m² body surface area every 12 hours
- Dose range: 90–150 mg/m² body surface area every 12 hours. Do not exceed maximum adult dose; see table below.
- In treatment-naïve children ages 3–21 years, 240 mg/m² body surface area once daily (oral solution or capsules) has effectively resulted in viral suppression.

Pediatric Dose of Videx EC or Generic Capsules (Aged 6–18 Years and Weighing ≥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

Adolescent and Adult Dose

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

Selected Adverse Events

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

Special Instructions

- Administer didanosine on an empty stomach (30 minutes before or 2 hours after a meal). To improve adherence, some practitioners administer didanosine without regard to timing of meals (see text below).
- Didanosine powder for oral solution and tablets for oral suspension contain antacids that may interfere with the absorption of other medications, including protease inhibitors (PIs). See individual PI for instructions on timing of administration.
- Shake didanosine oral solution well before use. Keep refrigerated; solution is stable for 30 days.
- If using tablets for oral suspension: Tablets are not to be swallowed whole. For full

Pediatric/Adolescent Dose of Didanosine when Combined with Tenofovir Disoproxil Fumarate (TDF):

- This combination should be avoided because of enhanced didanosine toxicity, reports of immunologic non-response, high rates of early virologic failure and rapid selection of resistance mutations ([Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents](#)).

therapeutic effect, 2 tablets may be chewed or dispersed in water before administration. To disperse tablets: add 2 tablets to at least 1 ounce (30 mL) of water. Drink entire dispersion immediately. For children 1 or 2 tablets may be chewed or dispersed in water before administration.

Metabolism/Elimination

- Renal excretion 50%
- Decrease dosage 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](#) and <http://www.hiv-druginteractions.org/>)

- *Absorption:* Antacids in didanosine oral solution and tablets for oral can decrease the absorption of a number of medications if given at the same time. Avoid giving other medications concurrently with didanosine oral solution.
- *Mechanism unknown:* Didanosine serum concentrations are increased when didanosine is co-administered with tenofovir disoproxil fumarate (TDF) and this combination should be avoided.
- *Renal elimination:* Drugs that decrease renal function can decrease didanosine clearance.
- *Overlapping toxicities:* The combination of stavudine with didanosine may result in enhanced toxicity. That combination should be avoided (see below).

Major Toxicities

- *More common:* Diarrhea, abdominal pain, nausea, and vomiting.
- *Less common (more severe):* Peripheral neuropathy, electrolyte abnormalities, and hyperuricemia. Lactic acidosis and hepatomegaly with steatosis, including fatal cases, have been reported, and are more common with didanosine in combination with stavudine. Pancreatitis (less common in children than in adults, more common when didanosine is used in combination with TDF or stavudine) can occur. Increased liver enzymes and retinal depigmentation and optic neuritis have been reported. Fall in CD4 T lymphocyte count is reported with use of didanosine with TDF.
- *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.¹
- *Possible risk of cancer after in-utero exposure:* In a study of 15,163 children without HIV infection who were exposed to at least 1 NRTI *in utero*, 21 cancers were identified. Didanosine accounted for only 10% of prescriptions but was associated with one-third of cancers, and, in multivariate analysis, was associated with a 5.5-fold (95% C, 2.1–14.4) increased risk with first-trimester exposure. Pregnant adolescents or sexually active female adolescents on didanosine should be cautioned about this risk.

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 didanosine is a Food and Drug Administration (FDA)-approved NRTI for use in children as part of antiretroviral therapy, **it is not recommended for use due to its significant toxicity and the availability of safer agents.**

Dosing

Standard Dose in Children Aged >8 months

The standard dose of didanosine oral solution in children aged >8 months is 120 mg/m² body surface area twice daily.^{2,3} Doses higher than 180 mg/m² body surface area twice daily are associated with increased toxicity.⁴

Special Considerations in Ages 2 Weeks to <8 Months

For infants aged 2 weeks to 8 months, the FDA recommends 100 mg/m² body surface area per dose twice daily. However, because pharmacokinetic (PK) differences in younger infants (aged 2 weeks–3 months) compared with older children raise concern for increased toxicity in this younger age group, the Panel recommends a dose of 50 mg/m² of body surface area twice daily for infants aged 2 weeks to 3 months, with an increase to 100 mg/m²/dose twice daily at 3 months, and finally increasing to 120 mg/m² body surface area per dose twice daily at age 8 months (as above).

Frequency of Administration (Once-Daily or Twice-Daily)

In those older than 3 years of age, a once-daily dosing regimen may be preferable to promote adherence, and multiple studies support the favorable PKs and efficacy of once-daily dosing of 240 mg/m² body surface area.⁵

Food Restrictions

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 systemic exposure measured by area under the curve was similar whether didanosine oral solution was given to children with or without food; absorption of didanosine administered with food was slower and elimination more prolonged.⁶ 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.^{7,8} A European study dosed didanosine oral solution as part of a 4-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.⁹

References

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