Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Etravirine (ETR, Intelencc) *(Last updated April 16, 2019; last reviewed April 16, 2019)*

For additional information, see Drugs@FDA: [http://www.accessdata.fda.gov/scripts/cder/daf/](http://www.accessdata.fda.gov/scripts/cder/daf/)

**Formulations**

**Tablets:** 25 mg, 100 mg, 200 mg

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**Dosing Recommendations**

**Neonate/Infant Dose:**
- Etravirine is not approved for use in neonates/infants.

**Child Dose:**
- Etravirine is not approved for use in children aged <2 years. Studies in infants and children aged 2 months to 2 years are under way.

**Etravirine Dosing Table for Antiretroviral-Experienced Children and Adolescents Aged 2 Years to 18 Years and Weighing ≥10 kg**

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 kg to &lt;20 kg</td>
<td>100 mg twice daily</td>
</tr>
<tr>
<td>20 kg to &lt;25 kg</td>
<td>125 mg twice daily</td>
</tr>
<tr>
<td>25 kg to &lt;30 kg</td>
<td>150 mg twice daily</td>
</tr>
<tr>
<td>≥30 kg</td>
<td>200 mg twice daily</td>
</tr>
</tbody>
</table>

**Adult Dose for Antiretroviral-Experienced Patients:**
- 200 mg twice daily with food

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**Selected Adverse Events**

- Nausea
- Diarrhea
- Rash, including Stevens-Johnson syndrome
- Hypersensitivity with rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure.

**Special Instructions**

- Area under the curve of etravirine is decreased by about 50% when the drug is taken on an empty stomach. Always administer etravirine with food. The type of food does not affect the exposure to etravirine.

**Instructions for Dispersing Etravirine Tablets in Liquid:**

- Patients who are unable to swallow etravirine tablets may disperse the tablets in liquid.
- Place the tablet(s) in 5 mL (1 teaspoon) of water, or at least enough liquid to cover the medication, and stir well until the water looks milky. **Add approximately 15 mL (1 tablespoon) of additional liquid. Water may be used, but other liquids, such as orange juice or milk, may improve the taste of the medication.** Patients should not place the tablets in orange juice or milk without first adding water. **Warm beverages (with temperatures >104°F or >40°C) or carbonated beverages should be avoided.**
- Drink immediately, then rinse the glass several times with water, orange juice, or milk and completely swallow the rinse each time to make sure the entire dose is consumed.
- Etravirine tablets are sensitive to moisture; store the tablets at room temperature in the original container with desiccant.
**Drug Interactions** (see also the Adult and Adolescent Antiretroviral Guidelines and HIV Drug Interaction Checker)

- Etravirine is associated with multiple drug interactions. A patient’s medication profile should be carefully reviewed for potential drug interactions before etravirine is administered.

- Etravirine **should not be administered** with tipranavir/ritonavir, fosamprenavir/ritonavir, and unboosted protease inhibitors (PIs).

- Etravirine **should not be administered** with other non-nucleoside reverse transcriptase inhibitors (NNRTIs) (i.e., nevirapine, efavirenz, rilpivirine, doravirine).

- Limited data in adults suggest that etravirine may reduce the trough concentration of raltegravir, but no dose adjustment is currently recommended when etravirine and raltegravir are used together. Etravirine significantly reduces plasma concentrations of dolutegravir, elvitegravir/cobicistat (EVG/COBI), and darunavir/cobicistat. Dolutegravir should only be used with etravirine when these drugs are coadministered with atazanavir/ritonavir, darunavir/ritonavir (DRV/r), or lopinavir/ritonavir. Etravirine **should not be coadministered** with EVG/COBI.

**Major Toxicities**

- *More common:* Nausea, diarrhea, and mild rash. Rash occurs most commonly during the first 6 weeks of therapy. Rash generally resolves after 1 week to 2 weeks on continued therapy. A history of NNRTI-related rash does not appear to increase the risk of developing rash with etravirine. However, patients who have a history of severe rash with prior NNRTI use **should not receive etravirine.**

- *Less common (more severe):* Peripheral neuropathy, severe rash, hypersensitivity reactions (HSRs), and erythema multiforme have all been reported. Instances of severe rash have included Stevens-Johnson syndrome, and HSRs have included constitutional findings and organ dysfunction, including hepatic failure. Discontinue etravirine immediately if signs or symptoms of severe skin reactions or HSRs develop (including severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, and eosinophilia). Clinicians should
monitor a patient’s clinical status, including levels of liver transaminases, and initiate appropriate therapy when necessary. Continuing to use etravirine after the onset of severe rash may result in a life-threatening reaction. People who have a history of severe rash while using nevirapine or efavirenz should not receive etravirine.

**Resistance**

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

**Pediatric Use**

**Approval**

Etravirine is approved by the Food and Drug Administration for use in antiretroviral (ARV)-experienced children and adolescents aged 2 years to 18 years.

**Efficacy in Clinical Trials**

In the PIANO study, ARV-experienced children aged 6 years to <18 years received etravirine with a ritonavir-boosted PI as part of an optimized background regimen. At Week 24, 67% of these participants had plasma HIV RNA concentrations <400 copies/mL and 52% had HIV RNA <50 copies/mL. At Week 48, 56% of the participants had HIV RNA <50 copies/mL and a mean increase in their CD4 T lymphocyte (CD4) cell counts of 156 cells/mm³ from baseline. At Week 48, 68% of children aged 6 years to <12 years had plasma HIV RNA <50 copies/mL, while only 48% of adolescents aged 12 years to <18 years achieved a plasma viral load of <50 copies/mL.

In a retrospective study of 23 adolescents and young adults in Spain receiving etravirine-based therapy, 78% of participants achieved HIV RNA <50 copies/mL at a median of 48.4 weeks of follow-up.

**Pharmacokinetics**

In a Phase 1 dose-finding study that involved children aged 6 years to 17 years, 17 children were given etravirine 4 mg/kg twice daily. The study reported that two pharmacokinetic (PK) parameters—area under the curve for 12 hours post-dose (AUC₀₋₁₂ₕ) and minimum plasma concentration (Cₘᵢₙ)—were lower than the corresponding parameters observed in adults during previous studies. However, a higher dose (etravirine 5.2 mg/kg twice daily; maximum 200 mg per dose) yielded acceptable parameters and was chosen for evaluation in the Phase 2 PIANO study. Exposures (mean AUC₀₋₁₂ₕ) remained lower in older adolescents than in adults and younger children, and exposures were lower in Asian participants than in either white or black participants. In the PIANO study, children and adolescents with etravirine concentrations in the lowest quartile (~2,704 ng*h/mL or C₀h <145 ng/mL) were less likely to achieve sustained virologic responses (defined as plasma viral loads <50 copies/mL) after 48 weeks of treatment than those with etravirine concentrations in the upper three quartiles.

### Table A. Pharmacokinetic Parameters in Children, Adolescents, and Adults Receiving Etravirine Twice Daily

<table>
<thead>
<tr>
<th></th>
<th>Mean Etravirine AUC₀₋₁₂ₕ (ng*h/mL)</th>
<th>Mean Etravirine C₀h (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children Aged 6 Years–11 Years (N = 41)</td>
<td>5,684</td>
<td>377</td>
</tr>
<tr>
<td>Adolescents Aged 12 Years–17 Years (N = 60)</td>
<td>4,895</td>
<td>325</td>
</tr>
<tr>
<td>Adults (N = 575)</td>
<td>5,506</td>
<td>393</td>
</tr>
</tbody>
</table>

**Key to Acronyms:** AUC₀₋₁₂ₕ = area under the curve for 12 hours post-dose; C₀h = pre-dose concentration during chronic administration
IMPAACT P1090 examined the PKs and safety of etravirine in treatment-experienced children with HIV aged ≥2 years to <6 years. Etravirine was initially given at a dose of 5.2 mg/kg twice daily to a cohort of six children; however, at this dose the geometric mean etravirine AUC0-12h values fell below the target range of 60% of the values seen in adults. Subsequent participants were given doses of twice-daily etravirine that were determined by weight band: children weighing 10 kg to <20 kg were given 100 mg per dose and children weighing 20 kg to <25 kg were given 125 mg per dose.

The tablets were swallowed whole or dispersed in liquid. The protocol-specified PK targets for etravirine were achieved at these doses; the geometric mean AUC0-12h was 3,504 ng*hr/mL, which was within the target range of 2,713 to 6,783 ng*hr/mL (60% to 150% of the AUC0-12h value seen in adults). However, considerable intersubject variability was observed, with five of 14 participants (36%) having AUC0-12h values that were below the tenth percentile for the adult AUC0-12h range (<2,350 ng*hr/mL). The etravirine AUC0-12h values were significantly lower in children who received dispersed tablets than in children who swallowed intact etravirine tablets: 2,841 ng*hr/mL versus 10,721 ng*hr/mL, respectively (P < 0.0001).

Five children with HIV aged 1 year to <2 years were also enrolled in P1090. The etravirine exposure in these children was lower than the etravirine exposure reported in adults; the AUC0-12h geometric mean ratio was 0.59 (90% confidence interval, 0.34–1.01). Virologic failure, which was defined as a confirmed viral load ≥400 copies/mL, occurred in three of four evaluable children by Week 24.

Etravirine is often combined with DRV/r for treatment of adults with HIV who have previously experienced virologic failure. Cressey et al. examined PK data from 36 adolescents and young adults receiving etravirine 200 mg twice daily in combination with DRV/r 600 mg/100 mg twice daily. The PK exposures of both agents were similar to those seen in adults, although interindividual variability was high. The PKs of etravirine and darunavir were also studied in adolescents and young adults receiving DRV/r 800 mg/100 mg once daily with either etravirine 200 mg twice daily or etravirine 400 mg once daily. Darunavir concentrations were higher when darunavir was coadministered with etravirine, particularly when the latter was given in doses of 200 mg twice daily. Etravirine exposures were lower when etravirine was given with DRV/r, particularly when etravirine was given twice daily; however, the authors noted that these studies had limited sample sizes. While the combination of etravirine and DRV/r was effective in a small cohort of adolescents with HIV and in 51% of participants in the PIANO study, these data suggest a need for additional data on the PK interactions for etravirine and other ARV agents in pediatric patients. Most notably, data is needed on regimens that do not include ritonavir-boosted PIs. Until such data become available, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends using etravirine as part of a regimen that includes a ritonavir-boosted PI.

P1090 evaluated the antiviral activity of etravirine in treatment-experienced pediatric patients with HIV aged ≥2 years to <6 years. At baseline, the mean plasma HIV RNA viral load was approximately 247,000 copies/mL, the median CD4 cell count was 818 cells/mm³, and the mean CD4 percentage was 26%. At Week 24, etravirine administered in combination with other ARV drugs produced a virologic response (defined as HIV RNA <400 copies/mL) in 15 of 16 evaluable participants (94%). The median CD4 cell count increase from baseline to Week 24 was 298 cells/mm³, and the median CD4 percentage increase was 5%.

Toxicity

In the PIANO study, rash and diarrhea were the most common adverse drug reactions deemed possibly related to etravirine. Rash (Grade 2 or higher) occurred in 13% of pediatric subjects and emerged at a median of 10 days, lasting a median of 7 days. Rash was observed more frequently in female patients (13 of 64 patients; 20.3%) than in male patients (2 of 37 patients; 5.4%). In P1090, adverse drug reactions that were reported for children aged ≥2 years to <6 years were comparable in frequency, type, and severity to those reported for adults. Ten participants (50%) developed rashes within 4 weeks of beginning the study, but these rashes were not attributed to the use of etravirine. In this study, rash occurred in 6% of female patients and 7% of male patients, and no subjects discontinued the study prematurely due to rash. Diarrhea occurred in five of 20 patients (25%).
References


