Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Dosing Recommendations

Neonate/Infant Dose:
• Not approved for use in neonates/infants.

Pediatric Dose:
• Not approved for use in children aged <6 years. Studies in infants and children aged 2 months to 6 years are under way.

Antiretroviral-Experienced Children and Adolescents Aged 6–18 Years and Weighing ≥16 kg

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Dose</th>
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<tbody>
<tr>
<td>16 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 (Antiretroviral-Experienced Patients):
• 200 mg twice daily following a meal

Selected Adverse Events

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

Special Instructions

• Always administer etravirine following a meal. Area under the curve of etravirine is decreased by about 50% when the drug is taken on an empty stomach. The type of food does not affect the exposure to etravirine.
• Etravirine tablets are sensitive to moisture; store at room temperature in original container with desiccant.

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 enough liquid to cover the medication, and stir well until the water looks milky. If desired, add more water or, alternatively, orange juice or milk. Note: Patients should not place the tablets in orange juice or milk without first adding water. The use of grapefruit juice, warm (>40° C) drinks, 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.

Metabolism/Elimination

• Etravirine is an inducer of cytochrome P450 3A4 (CYP3A4) and an inhibitor of CYP2C9, CYP2C19, and P-glycoprotein. It is a substrate
Drug Interactions (see also the Adult and Adolescent Guidelines and HIV Drug Interaction Checker)

- Etravirine is associated with multiple drug interactions. Before administration, the patient’s medication profile should be carefully reviewed for potential drug interactions with etravirine.

- Etravirine should not be co-administered with the following antiretroviral (ARV) drugs: tipranavir/ritonavir, fosamprenavir/ritonavir, and unboosted protease inhibitors (PIs). It should not be administered with other non-nucleoside reverse transcriptase inhibitors (NNRTIs) (i.e., nevirapine, efavirenz, rilpivirine). 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 and elvitegravir/cobicistat (EVG/c). Dolutegravir should only be used with etravirine when co-administered with atazanavir/ritonavir, darunavir/ritonavir (DRV/r), or lopinavir/ritonavir. Etravirine should not be co-administered with EVG/c.

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 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). Clinical status including liver transaminases should be monitored and appropriate therapy initiated. Delay in stopping etravirine treatment after the onset of severe rash may result in a life-threatening reaction. It is recommended that patients who have a prior history of severe rash with nevirapine or efavirenz not receive etravirine.

Resistance

The International AIDS 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 Food and Drug Administration-approved for use in ARV-experienced children and adolescents aged 6 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 <50 copies/mL. At Week 48, 56% of the participants had <50 copies/mL and a mean increase in their CD4 T lymphocyte cell counts of 156 cells/mm³ from baseline. A greater fraction of children aged 6 years to <12 years had plasma HIV-1 RNA <50 copies/mL than adolescents aged 12 years to <18 years (68% vs. 48%).

In a retrospective study of 23 adolescents and young adults, 78% of participants achieved an HIV-1 RNA <50 copies/mL at a median of 48.4 weeks of follow-up.

Pharmacokinetics

In a Phase 1 dose-finding study involving children aged 6 years to 17 years, 17 children were given etravirine 4 mg/kg twice daily. Two pharmacokinetic (PK) parameters—area under the curve for 12 hours post-dose (AUC\text{0-12h}) and minimum plasma concentration (C\text{min})—were below preset statistical targets based on prior studies involving adults. On the basis of acceptable PK parameters, the higher dose (etravirine 5.2 mg/kg twice daily; maximum 200 mg per dose) was chosen for evaluation in the Phase 2 PIANO study. Exposures (mean AUC\text{0-12h}) 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 C\text{0h} <145 ng/mL) were less likely to achieve sustained virologic responses (plasma viral load <50 copies/mL) after 48 weeks of treatment than those with etravirine concentrations in the upper three quartiles.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Mean AUC\text{0-12h} (ng*h/mL)</th>
<th>Mean C\text{0h} (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children Aged 6–11 Years (N = 41)</td>
<td>5,684</td>
<td>377</td>
</tr>
<tr>
<td>Adolescents Aged 12–17 Years (N = 60)</td>
<td>4,895</td>
<td>325</td>
</tr>
<tr>
<td>Adults</td>
<td>5,506</td>
<td>393</td>
</tr>
</tbody>
</table>

Key to Acronyms: AUC\text{0-12h} = Area under the curve for 12 hours post-dose; C\text{0h} = pre-dose concentration during chronic administration

Etravirine is often combined with DRV/r for treatment of adults with HIV with prior 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 with high interindividual variability. The PKs of both drugs 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 co-administered with etravirine, particularly when the latter was given in doses of 200 mg twice daily. Etravirine exposures were lower when given with DRV/r, particularly when etravirine was given twice daily, although the authors commented on the limited sample size involved in these studies. While the combination of etravirine and DRV/r has been 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 study of PK interactions involving etravirine and other ARV agents in pediatric patients, including 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.
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 females (17 of 64; 26.6%) than in males (6 of 37; 16.2%). Etravirine was discontinued due to rash in four individuals (4% of all participants), all of whom were female. Diarrhea occurred in three individuals (3% of participants) and was only reported in adolescents.

References


