Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Abacavir (ABC, Ziagen)  

**Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection**

**Selected Adverse Events**
- Hypersensitivity reactions (HSR) can be fatal. HSRs usually occur during the first few weeks of starting therapy. Symptoms may include fever, rash, nausea, vomiting, malaise or fatigue, loss of appetite, and respiratory symptoms (e.g., cough and shortness of breath).

**Special Instructions**
- Test patients for the HLA-B*5701 allele before starting therapy to predict risk of HSR. Patients positive for the HLA-B*5701 allele should not be given abacavir. Patients with no prior HLA-B*5701 testing who are tolerating abacavir do not need to be tested.
- Warn patients and parents about risk of serious, potentially fatal HSRs. Occurrence of HSRs requires immediate and permanent discontinuation of abacavir. Do not rechallenge.
- Abacavir can be given without regard to food. Oral solution does not require refrigeration.
- When using fixed-dose combination (FDC) tablets, see other sections of the Drug Appendix for special instructions and additional information about the individual components of the FDC.

**Formulations**
- Tablets: 300 mg (scored)
- Pediatric Oral Solution: 20 mg/mL
- Fixed-Dose Combination Tablets:
  - [Epzicom] Abacavir 600 mg plus lamivudine 300 mg
  - [Trizivir] Abacavir 300 mg plus lamivudine 150 mg plus zidovudine 300 mg
  - [Triumeq] Abacavir 600 mg plus dolutegravir 50 mg plus lamivudine 300 mg
- Generic Formulations:
  - Abacavir sulfate 300 mg tablets
  - Fixed-dose combination tablets of abacavir 300 mg plus lamivudine 150 mg
  - Fixed-dose combination tablets of abacavir 300 mg plus lamivudine 150 mg plus zidovudine 300 mg

**Dosing Recommendations**
- **Neonate/Infant Dose:**
  - Not approved for infants aged <3 months.

- **Pediatric Dose**
  **Oral Solution (Aged ≥3 Months):**
  - 8 mg/kg (maximum 300 mg per dose) twice daily or 16 mg/kg once daily (maximum 600 mg per dose) (see text below).
  - In infants and young children being treated with liquid formulations of abacavir, initiation with once-daily abacavir is not generally recommended. In clinically stable patients with undetectable viral load and stable CD4 T lymphocyte (CD4) cell count/percentage for more than 6 months (24 weeks) on liquid formulation of abacavir twice daily, dose can be changed from twice daily to once daily with liquid or tablet formulations (see text below).

- **Weight Band Dosing (Weighing ≥14 kg)**

<table>
<thead>
<tr>
<th>Weight</th>
<th>Scored 300-mg Tablet</th>
<th>Twice Daily AM Dose</th>
<th>Twice Daily PM Dose</th>
<th>Once Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 kg to &lt;20 kg</td>
<td>½ tablet (150 mg)</td>
<td>½ tablet (150 mg)</td>
<td>1 tablet (300 mg)</td>
<td></td>
</tr>
<tr>
<td>≥20 kg to &lt;25 kg</td>
<td>½ tablet (150 mg)</td>
<td>1 tablet (300 mg)</td>
<td>1 ½ tablets (450 mg)</td>
<td></td>
</tr>
<tr>
<td>≥25 kg</td>
<td>1 tablet (300 mg)</td>
<td>1 tablet (300 mg)</td>
<td>2 tablets (600 mg)</td>
<td></td>
</tr>
</tbody>
</table>

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf/
Abacavir does not inhibit, nor is it metabolized by, hepatic cytochrome P (CYP) 450 enzymes. Therefore, it does not cause significant changes in clearance of agents metabolized through these pathways, such as protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors. Abacavir plasma area under the drug-concentration-by-time curve (AUC) has been reported to be decreased by 17% and 32% with concurrent use of the PIs atazanavir/ritonavir and lopinavir/ritonavir (LPV/r), respectively.\(^1\) Another study reported decrease in plasma abacavir AUC by 40% with concurrent use of LPV/r; however, the intracellular metabolite carbovir triphosphate concentrations appeared to be increased with LPV/r exposure.\(^2\) Co-administration with darunavir/ritonavir has produced a decrease in abacavir plasma AUC and trough concentrations by 27% and 38%, respectively; the carbovir triphosphate AUC and trough concentrations were also decreased by 12% and 32%, respectively.\(^3\) The mechanism and the clinical significance of these drug interactions with the PIs are unknown. No dose adjustments for abacavir or PIs are currently recommended.

Through interference with alcohol dehydrogenase and glucuronyltransferase, alcohol exposure (0.7 g per kg ethanol, which is equivalent to five alcoholic drinks) has been shown to increase abacavir AUC plasma exposure by 41% in adult men with HIV receiving 600 mg of abacavir daily.\(^4\)

Abacavir oral solution contains sorbitol, which decreased exposure of concurrently administered lamivudine solution in adults.\(^4\)

### Major Toxicities

- **More common:** Nausea, vomiting, fever, headache, diarrhea, rash, and anorexia.
- **Less common (more severe):** Serious and sometimes fatal hypersensitivity reactions (HSRs) observed in approximately 5% of adults and children (rate varies by race/ethnicity) receiving abacavir. HSR to abacavir is a multi-organ clinical syndrome usually characterized by rash or signs or symptoms in two or more of the following groups:

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**Drug Interactions** (see also the Adult and Adolescent Guidelines and the HIV Drug Interaction Checker)

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• Fever
• Constitutional, including malaise, fatigue, or achiness
• Gastrointestinal, including nausea, vomiting, diarrhea, or abdominal pain
• Respiratory, including dyspnea, cough, or pharyngitis
• Laboratory and radiologic abnormalities, including elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, lymphopenia, and pulmonary infiltrates. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have also been reported. Pancreatitis can occur. This reaction generally occurs in the first 6 weeks of therapy, but has also been reported after a single dose. If a HSR is suspected, abacavir should be stopped immediately and not restarted—hypotension and death may occur upon re-challenge. The risk of abacavir HSR is associated with the presence of HLA-B*5701 allele; it is greatly reduced by not using abacavir in those who test positive for the HLA-B*5701 allele.

• Rare: Increased liver enzymes, elevated blood glucose, elevated triglycerides, and possible increased risk of myocardial infarction (in observational studies in adults). Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Pancreatitis can occur.
• Rare: Drug reaction (or rash) with eosinophilia and systemic symptoms (DRESS) syndrome
• Rare: Several observational cohort studies suggest increased risk of myocardial infarction in adults with recent or current use of abacavir; however, other studies have not substantiated this finding, and there are no data in children.

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
Abacavir is Food and Drug Administration (FDA)-approved for use in children aged 3 months and older with HIV infection as part of the nucleoside reverse transcriptase inhibitor (NRTI) component of antiretroviral therapy.

Efficacy
Abacavir used either twice daily or once daily has demonstrated durable antiviral efficacy in pediatric clinical trials and is of comparable efficacy to other NRTIs in children. Abacavir in combination with lamivudine has been compared to tenofovir disoproxil fumarate (TDF) with emtricitabine in several adult studies and meta-analyses with variable results.

Pharmacokinetics
Pharmacokinetics in Children
Pharmacokinetic (PK) studies of abacavir in children aged <12 years have demonstrated that children have more rapid clearance of abacavir than adults. Metabolic clearance of abacavir in adolescents and young adults (aged 13–25 years) is slower than that observed in younger children and approximates clearance seen in older adults.

The PK of abacavir dosed once daily in pediatric subjects (aged 3 months through 12 years) with HIV-1 infection was evaluated in three crossover, open-label PK trials of twice- versus once-daily dosing of abacavir and lamivudine (PENTA 13 [n = 14], PENTA 15 [n = 18], and ARROW [n = 36]). PK abacavir modeling based on the data from these three pediatric trials predicted overall equivalent systemic plasma abacavir exposure after once- or twice-daily dosing regimens in infants and children up to age 12 years.
These trials, in combination with PK modeling, demonstrated that once-daily abacavir dosing with either the tablet or liquid formulation provides comparable plasma PK exposures to twice-daily dosing of abacavir at the same total daily dose.21

**Dosing**

**Dosing and Formulations**

The initially recommended abacavir dose for pediatric use was 8 mg/kg/dose twice daily, or 16 mg/kg total daily dose. A 2015 FDA review suggested that a total daily dose of 600 mg of abacavir could be safely used in a 25-kg person (i.e., 24 mg/kg/day, a 50% increase from the previously recommended dose). The weight band dosing table recommends total daily doses as high as 21.5 to 22.5 mg/kg/day when treating with the tablet formulation.4 There is no difference in the abacavir plasma C\text{\textsubscript{\text{max}}} and AUC for abacavir liquid formulation compared to tablet formulation.22 Doses of liquid abacavir formulation are similar to those used for weight band dosing with tablet formulations and might be considered in some situations, especially in rapidly growing younger children.

In all three abacavir dosing pediatric trials described above,16-19 only children who had low viral loads and who were clinically stable on twice-daily formulation of abacavir were eligible to change to once-daily abacavir dosing. Efficacy data from a 48-week follow-up in the ARROW trial demonstrated clinical non-inferiority of once-daily abacavir (336 children) versus twice-daily abacavir (333 children) in tablet formulation combined with a once- or twice-daily lamivudine-based antiretroviral regimen.8 To date, no clinical trials have been conducted involving children who initiated therapy with once-daily dosing of abacavir liquid formulation. In children who can be treated with pill formulations, initiation of therapy with once-daily dosing of abacavir (at a dose of 16 mg/kg/dose [maximum of 600 mg] once daily) is recommended. However, in infants and young children initiating therapy with liquid formulations of abacavir, twice-daily dosing is recommended, and switching to once-daily dosing after 6 months (24 weeks) should be considered if viral load is undetectable and CD4 cell count/percentage is stable (without decline).

**Toxicity**

Abacavir has less of an effect on mitochondrial function than the NRTIs zidovudine, stavudine, or didanosine,6,7 and less bone and renal toxicity when compared to TDF.13,23

**References**


21. Food and Drug Administration. FDA approved revisions to the Epivir (lamivudine) and Ziagen (abacavir sulfate) labels. 2015. Available at http://content.govdelivery.com/accounts/USFDA/bulletins/fa3e70.
