



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Abacavir (ABC, Ziagen) (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

Pediatric Oral Solution: 20 mg/mL

Tablets: 300 mg (scored)

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 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 counts for more than 6 months (24 weeks) on abacavir twice daily, dose can be changed from twice daily to once daily (see text below).

Weight Band Dosing (Weighing ≥14 kg)

| Weight (kg) | Scored 300-mg Tablet | | |
|---------------|----------------------|---------------------|----------------------|
| | Twice Daily AM Dose | Twice Daily PM Dose | Once Daily Dose |
| 14 to <20 kg | ½ tablet (150 mg) | ½ tablet (150 mg) | 1 tablet (300 mg) |
| ≥20 to <25 kg | ½ tablet (150 mg) | 1 tablet (300 mg) | 1 ½ tablets (450 mg) |
| ≥25 kg | 1 tablet (300 mg) | 1 tablet (300 mg) | 2 tablets (600 mg) |

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).
- 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.

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 re-challenge.
- Abacavir can be given without regard to food. Oral solution does not require refrigeration.

- In patients who can be treated with pill formulations, therapy can be initiated with once-daily administration. If therapy was initiated with twice-daily liquid abacavir, then it can be changed from twice daily to once daily in clinically stable patients with undetectable viral load and stable CD4 cell counts (without decline) for more than 6 months (24 weeks) (see text below).

Adolescent (Weighing ≥ 25 kg) and Adult Dose:

- 300 mg twice daily or 600 mg once daily.

[Trizivir] Abacavir plus Lamivudine plus Zidovudine

Adolescent (Weight ≥ 40 kg)/Adult Dose:

- One tablet twice daily.

[Epzicom] Abacavir plus Lamivudine

Adolescent (Weight ≥ 25 kg) and Adult Dose:

- One tablet once daily.

[Triumeq] Abacavir plus Dolutegravir plus Lamivudine

Adolescent (Weight ≥ 40 kg) and Adult Dose:

- One tablet once daily.

Metabolism/Elimination

- Systemically metabolized by alcohol dehydrogenase and glucuronyltransferase.
- Intracellularly metabolized to carbovir triphosphate (CBV-TP).
- Active metabolite is 82% renally excreted.
- Abacavir requires dosage adjustment in hepatic insufficiency.
- Do not use fixed-dose combinations such as Trizivir, Epzicom, and Triumeq (or the fixed-dose combination's generic equivalents), in patients with impaired hepatic function because the dose of abacavir cannot be adjusted.
- Do not use Trizivir, Epzicom, and Triumeq (or the fixed-dose combination's generic equivalents) in patients with creatinine clearance (CrCl) < 50 mL/min and patients on dialysis (because of the fixed dose of lamivudine).

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/>)

- Abacavir does not inhibit, nor is it metabolized by, hepatic cytochrome P (CYP) 450 enzymes. Therefore, it does not cause changes in clearance of agents metabolized through these pathways, such as protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (see more information in Drug Interaction section under [Pediatric Use](#)).
- Through interference with alcohol dehydrogenase and glucuronyltransferase, alcohol increases abacavir levels by 41%.

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:
 - 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 include 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 an 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

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

Abacavir is Food and Drug Administration (FDA)-approved for use in children 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.¹⁻⁵ Abacavir in combination with lamivudine has been compared to tenofovir disoproxil fumarate with emtricitabine in several adult studies and meta-analyses with variable results.⁶⁻⁹

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.¹⁰

Exposure-Response Relationship

Plasma area under the drug-concentration-by-time curve (AUC) correlates with virologic efficacy of abacavir, although the association is weak.^{11,12} The active form of abacavir is the intracellular metabolite carbovir triphosphate (CBV-TP). Measurement of intracellular CBV-TP is more difficult than measurement of plasma AUC, and changes in plasma AUC may not reflect true changes in intracellular active drug.¹³

Drug Interactions

Abacavir plasma 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.¹⁴ In a study comparing PK parameters of abacavir in combination with either LPV/r or nevirapine, abacavir plasma AUC was decreased 40% by concurrent use of LPV/r; however, the CBV-TP concentrations appeared to be increased in the LPV/r cohort.¹⁵ When combined with darunavir/ritonavir, abacavir plasma AUC and trough concentrations were decreased by 27% and 38%, respectively; the CBV-TP AUC and trough concentrations were decreased by 12% and 32%, respectively.¹⁶ The mechanism and the clinical significance of these drug interactions with the PIs are unknown and need to be evaluated. No dose adjustments for abacavir or PIs are currently recommended.

Dosing

Appropriate Total Daily Dose

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 abacavir of 600 mg 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 pill formulation.¹⁷ There is no difference in the abacavir plasma C_{max} and AUC for abacavir oral solution compared to tablet formulations.¹⁸ Doses of liquid abacavir similar to those used for weight band dosing with tablets might be considered in some situations, especially in rapidly growing younger children.

Frequency of Administration

New PK data suggest that once-daily dosing of abacavir in children is feasible. 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, but in infants and young children initiating therapy with liquid formulations of abacavir, twice-daily dosing is recommended with consideration of a switch to once-daily dosing after 6 months (24 weeks) when viral load is undetectable and CD4 cell count is stable (without decline). This recommendation is based on the data presented below.

The PK of abacavir dosed once daily in pediatric subjects with HIV-1 infection aged 3 months through 12 years was evaluated in three trials (PENTA 13 [n = 14], PENTA 15 [n = 18], and ARROW [n = 36]).^{17,19-22} All three trials were two-period, crossover, open-label PK trials of twice- versus once-daily dosing of abacavir and lamivudine. For the oral solution as well as the tablet formulation, these three trials demonstrated that once-daily dosing provides comparable AUC₀₋₂₄ to twice-daily dosing of abacavir at the same total daily dose. The mean C_{max} was approximately 1.6- to 2.3-fold higher with abacavir once-daily dosing compared with twice-daily dosing.²³

A pediatric PK model developed based on data from 69 children in the PENTA-13 and PENTA-15 trials and the ARROW study predicted that steady state peak (C_{max}) and AUC₀₋₁₂ abacavir concentrations on standard twice-daily dosing were lower in toddlers, and infants aged 0.4 to 2.8 years when compared with children aged 3.6 to 12.8 years. Model-based predictions also showed that equivalent systemic plasma abacavir exposure was achieved after once- or twice-daily dosing regimens in infants, toddlers and children up to age 12 years.²⁴ The pediatric studies referenced above enrolled only patients who had low viral loads and were clinically stable on twice-daily abacavir before changing to once-daily dosing. Efficacy data from 48-week follow-up in the ARROW trial demonstrated clinical non-inferiority of once-daily (336 children) versus twice-daily abacavir (333 children) in combination with a once- or twice-daily lamivudine-based regimen.³ No clinical trials have been conducted involving children who initiated therapy with once-daily dosing of abacavir solution.

Toxicity

Abacavir has less of an effect on mitochondrial function than the NRTIs zidovudine, stavudine, or didanosine,^{1,2,25} and fewer bone and renal toxicities than tenofovir disoproxil fumarate.^{8,26}

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