



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Abacavir (ABC, Ziagen) (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf/>

Formulations

Tablet: 300 mg (scored)

Pediatric Oral Solution: 20 mg/mL

Generic Formulations:

Tablet: 300 mg

Fixed-Dose Combination Tablets:

- [Epzicom **and Generic**] Abacavir 600 mg/lamivudine 300 mg
- [Triumeq] Abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg
- [Trizivir] Abacavir 300 mg/lamivudine 150 mg/zidovudine 300 mg

Dosing Recommendations

Neonate and Infant Dose:

- Abacavir is not approved for use in infants aged <3 months.

Infant and Child (Aged ≥3 Months) Dose

Oral Solution:

- Abacavir 8 mg/kg twice daily (maximum 300 mg per dose) or abacavir 16 mg/kg once daily (maximum 600 mg per dose)
- In infants and young children who are being treated with liquid formulations of abacavir, initiation with once-daily abacavir is not generally recommended. **In older children who can be treated with pill formulations, therapy can be initiated with once-daily administration.** In clinically stable patients who have undetectable viral loads and stable CD4 T lymphocyte cell counts while receiving the liquid formulation of abacavir twice daily, the abacavir dose can be changed from twice-daily dosing to once-daily dosing with the liquid or tablet formulations (see text below).

Weight-Band Dosing for Children and Adolescents Weighing ≥14 kg

Weight	Scored 300-mg Tablet		
	Twice-Daily AM Dose	Twice-Daily PM Dose	Once-Daily Dose
14 kg to <20 kg	½ tablet (150 mg)	½ tablet (150 mg)	1 tablet (300 mg)
≥20 kg to <25 kg	½ tablet (150 mg)	1 tablet (300 mg)	1½ tablets (450 mg)
≥25 kg	1 tablet (300 mg)	1 tablet (300 mg)	2 tablets (600 mg)

Selected Adverse Events

- Hypersensitivity reactions (HSRs) 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, shortness of breath).

Special Instructions

- Test patients for the HLA-B*5701 allele before starting therapy to predict the risk of HSRs. Patients who test 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 the risk of serious, potentially fatal HSRs. Occurrence of an HSR requires **immediate and permanent discontinuation of abacavir. Do not re-challenge.**
- Abacavir can be given without regard to food. The oral solution does not require refrigeration.
- When using FDC tablets that contain abacavir, see other sections of the [Drug Appendix](#) for special instructions and additional information about the individual components of the FDC.

Metabolism/Elimination

- Systemically metabolized by alcohol dehydrogenase and glucuronyl transferase.

Child and Adolescent (Weighing ≥ 25 kg) and Adult Dose:

- Abacavir 300 mg twice daily or 600 mg once daily

[Epzicom] Abacavir/Lamivudine

Child and Adolescent (Weighing ≥ 25 kg) and Adult Dose:

- One tablet once daily

[Triumeq] Abacavir/Dolutegravir/Lamivudine

Child and Adolescent (Weighing ≥ 25 kg) and Adult Dose:

- One tablet once daily
- This fixed-dose combination (FDC) tablet can be used in patients who are antiretroviral (ARV)-naive or ARV-experienced (but integrase strand transfer inhibitor-naive) and who are not being treated with uridine diphosphate glucuronosyltransferase 1A1 or cytochrome P450 3A inducers.

- The FDA-approved dose for pediatric patients is one tablet once daily for patients weighing ≥ 40 kg.

[Trizivir] Abacavir/Lamivudine/Zidovudine

Child and Adolescent (Weighing ≥ 30 kg) and Adult Dose:

- One tablet twice daily

- Eighty-two percent of abacavir metabolites are excreted in urine.
- Abacavir requires a dose adjustment in patients with hepatic insufficiency.
- **Do not use** FDCs such as Trizivir, Epzicom, and Triumeq (or the generic equivalents of these FDCs) in patients with impaired hepatic function, because the dose of abacavir cannot be adjusted.
- **Do not use** Trizivir, Epzicom, and Triumeq (or the generic equivalents of these FDCs) in patients with creatinine clearance < 50 mL/min and patients on dialysis, because the dose of lamivudine cannot be adjusted.

Drug Interactions (see also the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#))

- Abacavir does not inhibit, nor is it metabolized by, hepatic cytochrome P450 enzymes. Therefore, it does not cause significant changes in the clearance of agents that are metabolized through these pathways, such as protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors. Abacavir plasma concentrations can decrease when abacavir is used concurrently with the boosted PIs atazanavir/ritonavir, lopinavir/ritonavir, and darunavir/ritonavir.¹⁻³ The mechanism and the clinical significance of the drug interactions with these PIs are unknown. There are currently no recommendations for dose adjustments when coadministering abacavir and one of these boosted PIs.
- Alcohol exposure (0.7 g per kg ethanol, which is equivalent to five alcoholic drinks) has been shown to interfere with abacavir metabolism by affecting activity of alcohol dehydrogenase and glucuronyl transferase. This interference led to a 41% increase in abacavir area under the curve plasma exposure in adult men with HIV who received abacavir 600 mg daily.⁴
- Abacavir oral solution contains sorbitol, which decreased the exposure of lamivudine solution in adults when the drugs were administered concurrently.⁵

Major Toxicities

- *More common:* Nausea, vomiting, fever, headache, diarrhea, rash, anorexia.

- *Less common (more severe)*: Serious and sometimes fatal hypersensitivity reactions (HSRs) that have been observed in approximately 5% of adults and children (the rate varies by race/ethnicity) receiving abacavir. HSR to abacavir is a multi-organ clinical syndrome that is usually characterized by rash or signs or symptoms in two or more of the following groups:
 - Fever
 - Constitutional symptoms, including malaise, fatigue, or achiness
 - Gastrointestinal signs and symptoms, including nausea, vomiting, diarrhea, or abdominal pain
 - Respiratory signs and symptoms, 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. HSRs generally occur during the first 6 weeks of therapy, but they have also been reported after a single dose of abacavir. If an HSR is suspected, abacavir **should be stopped immediately and not restarted—hypotension and death may occur upon re-challenge**. The risk of an abacavir HSR is associated with the presence of HLA-B*5701 allele; the risk is greatly reduced by not using abacavir in those who test positive for the HLA-B*5701 allele.
- *Rare*: Increased levels of liver enzymes, elevated blood glucose levels, elevated triglycerides (see cardiac risk below). Pancreatitis, lactic acidosis, and severe hepatomegaly with steatosis, including fatal cases, have been reported.
- *Rare*: Drug reaction (or rash) with eosinophilia and systemic symptoms (DRESS) syndrome.
- *Rare*: Several observational cohort studies suggest an increased risk of myocardial infarction in adults who are currently using abacavir or who have recently used abacavir; however, other studies have not substantiated this finding, and there are no data on cardiovascular risks associated with abacavir use 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 approved by the Food and Drug Administration (FDA) for use in children with HIV aged ≥ 3 months as part of the nucleoside reverse transcriptase inhibitor (NRTI) component of antiretroviral therapy (ART). The World Health Organization (WHO), however, recommends using abacavir as a component of the NRTI backbone for children weighing ≥ 3 kg, starting at 4 weeks of age (see [WHO Dosages of Antiretroviral Drugs](#)). This recommendation is based on the general principle of using non-thymidine analogues in first-line regimens and thymidine analogues in second-line regimens. This recommendation also takes into account the availability of President's Emergency Plan for AIDS Relief-approved pediatric generic abacavir formulations, including coformulations that include lamivudine, and the cost of ART in resource-limited settings. No systematic safety assessment has been conducted for using abacavir in children weighing < 14 kg.

Efficacy

Both the once-daily and twice-daily doses of abacavir have demonstrated durable antiviral efficacy in pediatric clinical trials, and this drug is of comparable efficacy to other NRTIs in children.⁶⁻¹⁰

Pharmacokinetics

Pharmacokinetics in Children

Pharmacokinetic (PK) studies of abacavir in children aged <12 years have demonstrated that metabolic clearance of abacavir in adolescents and young adults (aged 13 years–25 years) is slower than that observed in younger children and approximates clearance seen in older adults.¹¹

The PKs of abacavir administered once daily in children with HIV aged 3 months through 12 years were evaluated in three crossover, open-label PK trials of twice-daily versus once-daily dosing of abacavir and lamivudine (PENTA 13 [N = 14], PENTA 15 [N = 18], and ARROW [N = 36]).^{4,12-15} The data from these three pediatric trials was used to develop a model for abacavir PKs; this model predicted that systemic plasma abacavir exposure after once-daily dosing would be equivalent to the exposure seen after twice-daily dosing in infants and children aged ≤12 years.¹²⁻¹⁶ These trials, in combination with PK modeling, demonstrated that once-daily abacavir dosing with either the tablet or the liquid formulation provides plasma PK exposures that are comparable to those seen with twice-daily dosing of abacavir at the same total daily dose.¹⁷

Dosing

Dosing and Formulations

Initially, the recommended dose for pediatric use was abacavir 8 mg/kg twice daily, for a total of 16 mg/kg per day. A 2015 FDA review suggested that a total daily dose of abacavir 600 mg could be safely used in a person weighing 25 kg (i.e., abacavir 24 mg/kg per day, a 50% increase from the previously recommended dose). The weight-band dosing table recommends total daily doses as high as abacavir 21.5 mg/kg per day to abacavir 22.5 mg/kg per day when treating patients with the tablet formulation.⁴ There is no difference in the abacavir plasma C_{max} and AUC for the abacavir liquid formulation compared to the tablet formulation.¹⁸ Doses of liquid abacavir formulation are similar to those used for weight-band dosing with tablet formulations and should be considered for use **in younger children who are unable to swallow a pill.**

In all three abacavir dosing pediatric trials described above,¹²⁻¹⁵ only children who had low viral loads and who were clinically stable on the twice-daily dose 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 noninferiority of once-daily abacavir (N = 336) versus twice-daily abacavir (N = 333) in tablet form combined with a once-daily 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, initiating therapy with once-daily dosing of abacavir at a dose of 16 mg/kg (with a maximum dose of abacavir 600 mg) is recommended. However, in infants and young children who initiate therapy with the liquid formulation of abacavir, twice-daily dosing is recommended. Switching to once-daily dosing **with the liquid or pill formulation could be considered in clinically stable children with suppressed viral loads and stable CD4 T lymphocyte cell counts.**

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 than TDF.^{19,20}

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