Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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**Dosing Recommendations**

**Ritonavir as a Pharmacokinetic Enhancer:**
- Ritonavir is used as a pharmacokinetic enhancer of other protease inhibitors (PIs). The recommended dose of ritonavir varies and is specific to the drug combination selected. See other sections of the Drug Appendix for information about ritonavir dosing with specific PIs.

**Formulation Considerations:**
- The oral solution contains propylene glycol and ethanol.
- The oral powder is preferred over the oral solution for children who cannot swallow the tablets and who need a dose of at least 100 mg, because the oral powder does not contain propylene glycol or ethanol.
- Ritonavir oral powder should be used only for dosing increments of 100 mg and cannot be used for doses <100 mg.

**Selected Adverse Events**
- Gastrointestinal intolerance, nausea, vomiting, diarrhea
- Paresthesia (circumoral and extremities)
- Hyperlipidemia, especially hypertriglyceridemia
- Hepatitis
- Asthenia
- Taste perversion
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia
- Toxic epidermal necrolysis and Stevens-Johnson syndrome

**Special Instructions**
- Administer ritonavir with food to increase absorption and reduce gastrointestinal adverse effects.
- **Do not administer** ritonavir with cobicistat or drugs that contain cobicistat (e.g., Stribild, Genvoya, Prezobix, Evotaz).
- If ritonavir is prescribed with didanosine, administer the drugs 2 hours apart.
- **Do not refrigerate** ritonavir oral solution; store at 68° F to 77° F (20° C to 25° C). Shake the solution well before use.
- Ritonavir oral powder should be mixed with a soft food (e.g., apple sauce, vanilla pudding) or a liquid (e.g., water, chocolate milk, infant formula) to help mitigate the bitter taste. Administer or discard within 2 hours of mixing.
Drug Interactions (see also the Adult and Adolescent Guidelines and HIV Drug Interaction Checker)

- **Metabolism:** Ritonavir is extensively metabolized by (and is one of the most potent inhibitors of) hepatic cytochrome P (CYP) 450 3A. There is potential for multiple drug interactions with ritonavir.

- Before ritonavir is administered, a patient’s medication profile should be carefully reviewed for potential interactions with ritonavir and overlapping toxicities with other drugs.

- Ritonavir and cobicistat are not interchangeable and may result in different drug interactions.¹

- Avoid concomitant use of intranasal or inhaled fluticasone, because adrenal insufficiency has been reported.² Use caution when prescribing ritonavir with other inhaled steroids. Limited data suggest that beclomethasone may be a suitable alternative to fluticasone when a patient who is taking ritonavir requires an inhaled or intranasal corticosteroid.³⁴ See Drug Interactions between Protease Inhibitors and Other Drugs in the Adult and Adolescent Guidelines for additional information.

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¹ Ritonavir has antiviral activity, but it is not used as an antiviral agent (see text).

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To Increase Tolerability of Ritonavir Oral Solution in Children:

- Mix solution with milk, chocolate milk, ice cream, or vanilla or chocolate pudding.

- Before administering ritonavir, give a child ice chips, a Popsicle, or spoonfuls of partially frozen orange or grape juice concentrate to dull the taste buds. Another option is to give a child peanut butter to coat the mouth.

- After administration, give strong-tasting foods (e.g., maple syrup, cheese).

- Check food allergy history before making these recommendations.

- Counsel parents or patients that the bad taste will not be completely masked.

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Metabolism/Elimination

- Cytochrome P (CYP) 3A and CYP2D6 inhibitor; CYP1A2, CYP2B6, CYP2C9, CYP2C19, and glucuronidation inducer.

Ritonavir Dosing in Patients with Hepatic Impairment:

- Ritonavir is primarily metabolized by the liver. No dose adjustment is necessary in patients with mild or moderate hepatic impairment. Data are unavailable on ritonavir dosing for adult or pediatric patients with severe hepatic impairment. Use caution when administering ritonavir to patients with moderate-to-severe hepatic impairment.
Major Toxicities

- **More common**: Nausea, vomiting, diarrhea, headache, abdominal pain, anorexia, circumoral paresthesia, lipid abnormalities.
- **Less common (more severe)**: Exacerbation of chronic liver disease, fat maldistribution.
- **Rare**: New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, spontaneous bleeding in hemophiliacs, pancreatitis, and hepatitis (life-threatening in rare cases). Allergic reactions, including bronchospasm, urticaria, and angioedema. Toxic epidermal necrolysis and Stevens-Johnson syndrome have occurred.  

Resistance

Resistance to ritonavir is not clinically relevant when the drug is used as a pharmacokinetic (PK) enhancer of other antiretroviral (ARV) medications.

Pediatric Use

Approval

Ritonavir has been approved by the Food and Drug Administration for use in the pediatric population.

Efficacy: Effectiveness in Practice

Use of ritonavir as the sole protease inhibitor (PI) in ARV therapy in children is not recommended. Although ritonavir has been well studied in children as an ARV agent, it is no longer used as a sole PI for therapy because ritonavir is associated with a higher incidence of gastrointestinal toxicity and has a greater potential for drug-drug interactions than other PIs. In addition, poor palatability of the liquid preparation and a large pill burden with the tablets (the adult dose is six tablets, twice daily) limit its use as a sole PI. However, in both children and adults, ritonavir is recommended as a PK enhancer for use with other PIs. Ritonavir is a CYP3A inhibitor and functions as a PK enhancer by slowing the metabolism of the PIs.

Dosing

Pediatric dosing regimens, including boosted fosamprenavir, tipranavir, darunavir, atazanavir, and the PI co-formulation lopinavir/ritonavir (LPV/r), are available. For more information about individual PIs, see other sections of the Drug Appendix.

Toxicity

Full-dose ritonavir has been shown to prolong the PR interval in a study of healthy adults who were given ritonavir 400 mg twice daily. Potentially life-threatening arrhythmias have been reported in premature newborn infants treated with LPV/r; the use of LPV/r is not recommended until the gestational age of 42 weeks. Co-administration of ritonavir with other drugs that prolong the PR interval (e.g., macrolides, quinolones, methadone) should be undertaken with caution because it is unknown how co-administering any of these drugs with ritonavir will affect the PR interval. In addition, ritonavir should be used with caution in patients who may be at increased risk of developing cardiac conduction abnormalities, such as patients who have underlying structural heart disease, conduction system abnormalities, ischemic heart disease, or cardiomyopathy.

References


