Ritonavir (Norvir)

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Drug Summary

Ritonavir was the second FDA-approved HIV protease inhibitor and initially held promise as a potent antiviral agent. Soon after approval, however, use of full-dose ritonavir as an HIV protease inhibitor was largely abandoned due to severe gastrointestinal side effects. Subsequently, based on ritonavir's potent inhibition of the cytochrome P450 3A4 (CYP 3A4) enzyme, investigators explored low-dose ritonavir as a pharmacologic booster for other HIV protease inhibitors. Multiple studies found that pharmacologic boosting by ritonavir increased the levels of HIV protease inhibitors and reduced the risk of virologic failure and HIV drug resistance. Currently, almost all ritonavir use occurs as a low-dose booster for HIV protease inhibitors. Although ritonavir can also boost levels of the integrase strand transfer inhibitor elvitegravir, this combination is rarely used in clinical practice. Because ritonavir is a nonselective enzymatic blocker, it can raise the level of any medication that is metabolized by CYP 3A4, thereby potentially causing many drug interactions. Ritonavir commonly causes gastrointestinal side effects, which is more problematic at higher daily doses. Ritonavir is available as tablets, soft gel capsules, and liquid; the tablet is most commonly used because the capsule requires refrigeration and may cause more gastrointestinal adverse effects.

Key Clinical Trials

Full-dose ritonavir was studied as the anchor drug combined with 2 NRTIs for initial treatment of HIV infection and had high efficacy in suppressing HIV RNA but also frequent intolerable side effects [CPCRA 042]. Subsequently, low-dose ritonavir was studied as a pharmacokinetic booster of a number of other protease inhibitors, including atazanavir [CASTLE] and [ARDENT (ACTG 5257)], darunavir [FLAMINGO], fosamprenavir [SOLO (APV30002)] and [KLEAN], indinavir [ACTG 5055], saquinavir [GEMINI], and tipranavir [BI-1182.33]. In addition, low-dose ritonavir has been studied in combination with lopinavir and is approved as fixed-dose lopinavir-ritonavir [M97-720].

Adverse Effects

Common adverse effects with ritonavir are nausea, diarrhea, and other gastrointestinal upset. It can
also cause elevations in hepatic aminotransferase levels and hyperlipidemia; similar to effects observed with some other protease inhibitors, ritonavir has been associated with abnormalities of glucose metabolism and body fat distribution, as well as prolongation of the cardiac PR interval. All of these side effects are less common and less severe when ritonavir is used at low dose. The liquid formulation of ritonavir has a foul taste and the ritonavir capsules and liquid formulation contain alcohol and therefore may cause vomiting if combined with disulfiram.

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**Key Drug Interactions**

For complete information on ritonavir-related drug interactions, see the [Drug Interactions section in the Ritonavir (Norvir) Prescribing Information](https://www.hiv.uw.edu/page/treatment/drugs/ritonavir).