Ribavirin-Antiretroviral/Antiviral Interactions

Antiretroviral	Interaction Information
Abacavir	Ribavirin is a guanosine analogue. Theoretically, ribavirin and abacavir may compete for intracellular phosphorylation, possibly reducing anti-HCV activity of ribavirin. Some controversy exists whether concomitant abacavir therapy may be associated with a reduced response to pegylated interferon and ribavirin,[1-3] but a recent in vitro study showed that the anti-HCV activity of ribavirin was not modified by abacavir[4]. In a pharmacokinetic substudy in patients from the ANRS CO-13 HEPAVIH cohort, ribavirin Cmin was similar in abacavir users and non-users, and there was no evidence that abacavir use affected HCV treatment outcomes including rapid (RVR), early (EVR) and sustained (SVR) virological response.[5] Similarly, in a prospective study, 28 HCV^+ patients without HIV infection who had been cured or failed prior HCV treatment were randomized to 8 weeks of weight-adjusted ribavirin alone or with abacavir 300 mg q12h. In the 26 subjects who completed the study (n=23 with 100% adherence), mean plasma RBV trough and RBV-TP intracellular concentrations were not significantly different after co-administration of ABC, compared to RBV alone at any visit.[6] Achieving adequate ribavirin trough levels via weight-based dosing should overcome any potential negligible effect of abacavir,[7, 8] and there is insufficient evidence to recommend avoiding this combination.[9]
Atazanavir, Atazanavir/ritonavir	Hemolysis secondary to ribavirin use may lead to increased production of bilirubin. Atazanavir inhibits UGT1A1, which is responsible for normal clearance of bilirubin. In a cohort of HIV/hepatitis C coinfected patients who started hepatitis C treatment with pegylated interferon and ribavirin 1000-1200 mg daily, grade 3-4 hyperbilirubinemia increased from 9% to 45% in patients who were on concomitant atazanavir (boosted or unboosted, n=22). In comparison, there were no cases of grade 3-4 hyperbilirubinemia in patients who initiated hepatitis C treatment and were not on concomitant atazanavir (n=30).[10]
Didanosine	*In vitro,* ribavirin ↑ levels of active didanosine metabolite, dideoxyadenosine 5'-triphosphate (ddATP). Potential for ↑ mitochondrial toxicity (i.e. pancreatitis, hyperlactatemia, fatal lactic acidosis, peripheral neuropathy).[11-15] Given availability of other NRTIs and the concern for potential didanosine-induced hepatotoxicity in patients with underlying liver disease (those receiving ribavirin as part of Hepatitis C treatment), the **coadministration of ribavirin and didanosine is now contraindicated**.[15]
Etravirine	A significant drug interaction is not expected between ribavirin and etravirine; combination may be given without dose adjustment.[16]
Lamivudine	In a prospective kinetic study, ribavirin 800 mg/daily did not affect the intracellular phosphorylation or plasma kinetics of zidovudine, lamivudine, or stavudine in HCV/HIV-co-infected patients when assessed after 8-12 weeks of co-administration.[17] Combination may be given without dose adjustment.
Maraviroc	An interaction trial in healthy volunteers between maraviroc and pegylated interferon and ribavirin has not been conducted. No interaction is expected, and maraviroc and ribavirin may be coadministered without dose adjustment.[18]
Rilpivirine	No clinically relevant drug-drug interaction is expected when rilpivirine is co-administered with ribavirin.[19]
Stavudine	In vivo, a case series failed to demonstrate increased viral loads with patients on

Antiretroviral	Interaction Information
	HAART, suggesting that stavudine may be used with ribavirin.[20] In a prospective kinetic study, ribavirin 800 mg/daily did not affect the intracellular phosphorylation or plasma kinetics of zidovudine, lamivudine, or stavudine in HCV/HIV-co-infected patients when assessed after 8-12 weeks of co-administration.[17] **Avoid combination if possible. Potential for ↑ mitochondrial toxicity (i.e. pancreatitis, lactic acidosis).[11-13]**
Telaprevir	Ribavirin pharmacokinetics were determined in 21 HCV-infected subjects, 16 on pegylated interferon/ribavirin (PR) alone, and 5 on telaprevir/PR. Dose-adjusted ribavirin plasma AUC was 1.54-fold higher in those receiving telaprevir/PR vs PR alone (p=0.002). Ribavirin mono-, di- and tri-phosphate in red blood cells were 3.3, 2.3, and 2.4-fold higher in those on telaprevir/PR compared to those on PR alone; similarly, ribavirin mono-, di- and tri-phosphate in PBMC were 2.5, 3, and 2-fold higher in those on telaprevir/PR compared to those on PR alone (all statistically significant). In patients on telaprevir/PR, intracellular ribavirin concentrations declined after stopping telaprevir. Besides telaprevir use, no other variables including Clcr, age, gender or race were associated with plasma or intracellular ribavirin pharmacokinetics. Increased ribavirin concentrations due to telaprevir coadministration may possibly be a factor in the increased rates of anemia observed with triple therapy.[21]
Tenofovir	Kinetic study in 22 healthy subjects of single 600 mg dose ribavirin and multi-dose tenofovir showed no significant changes in ribavirin pharmacokinetics.[22] Dose adjustment is likely not necessary.
Zidovudine	In vitro, ribavirin may antagonize zidovudine via competition for phosphorylation.[23] In vivo, a case series failed to show increased viral loads with patients on combined antiretroviral therapy, suggesting that zidovudine may be used with ribavirin.[20] In a prospective kinetic study, ribavirin 800 mg/daily did not affect the intracellular phosphorylation or plasma kinetics of zidovudine, lamivudine, or stavudine in HCV/HIV-co-infected patients when assessed after 8-12 weeks of co-administration.[17] **However, potential for ↑ mitochondrial toxicity (e.g., lactic acidosis) & hematotoxicity.** In a cohort of 50 HIV/HCV subjects on HAART who started pegylated interferon and weight-adjusted ribavirin, 8/20 (40%) on concomitant zidovudine developed grade 1 or higher anemia, versus 4/30 (13.3%) of those not on zidovudine, p=0.04.[24] **Therefore, avoid combination whenever possible;[25] otherwise, close monitoring for toxicity is recommended.**

Please note: This chart summarizes some of the major drug interactions identified to date, based on current available data; other drug interactions may exist. Please use caution whenever adding/modifying therapy. The information in this table is intended for use by experienced physicians and pharmacists. It is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Due to the rapidly changing nature of information about HIV treatment and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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