

## **Updated Guidelines for the Use of Rifamycins for the Treatment of Tuberculosis Among HIV-Infected Patients Taking Protease Inhibitors or Nonnucleoside Reverse Transcriptase Inhibitors**

Two previously published reports provided guidelines for managing the pharmacologic interactions that can result when patients are treated with protease inhibitors or nonnucleoside reverse transcriptase inhibitors (NNRTIs) for human immunodeficiency virus (HIV) infection together with rifamycins for tuberculosis (TB) (1, 2). This notice presents current data pertaining to interactions between these agents, with recommendations for their use from a group of CDC scientists and outside expert consultants; these include initial recommendations for the protease inhibitors lopinavir/ritonavir, atazanavir, and fos-amprenavir (a phosphate ester prodrug of amprenavir).

### **Mechanisms of rifamycin-antiretroviral drug interactions**

The principal locus of these drug-drug interactions is the cytochrome P450 (CYP) system in the intestinal wall and liver, specifically the isoenzyme CYP3A4 (3). Rifamycins are antituberculosis agents that induce the activity of CYP3A4 and may thereby substantially decrease serum concentrations of protease inhibitors and NNRTIs. The available rifamycins differ in potency as CYP3A4 inducers, with rifampin being the most potent, rifapentine being intermediate, and rifabutin being the least potent inducer (4). As such, rifabutin can be safely used with most protease inhibitors and NNRTIs, except saquinavir and delavirdine (Table 2). Unlike rifampin and rifapentine, however, rifabutin is also a substrate for CYP3A4; thus, its serum concentration is affected by the degree to which CYP3A4 is inhibited or induced by protease inhibitors and NNRTIs. Rifapentine, a long-acting rifamycin, is not recommended for the treatment of TB in HIV-infected persons because of its association with acquired rifamycin resistance in such patients (5).

Among the available antiretroviral agents, ritonavir has the highest potency in inhibiting CYP3A4, a quality that increases the serum concentrations of other coadministered protease inhibitors (6), though it can also increase concentrations of rifabutin and a rifabutin metabolite to toxic levels (7).

### **Rifampin and antiretroviral therapy (Table 1)**

Initial guidance from CDC stated that use of rifampin was contraindicated for persons taking NNRTIs and protease inhibitors (1). Subsequent data, however, have supported the use of rifampin with certain combinations of antiretroviral agents. These include-

- ritonavir with nucleoside/tide reverse transcriptase inhibitors (NRTIs) (8)

- efavirenz with NRTIs (9-11)

Alternative, less supported, antiretroviral combinations for use with rifampin include:

- ritonavir (400 mg twice daily) and saquinavir (400 mg twice daily) with NRTIs (12)
- ritonavir (400 mg twice daily) and lopinavir (400 mg twice daily) with NRTIs (when the current coformulated lopinavir/ritonavir combination is supplemented with additional ritonavir, see Table 1) (13)
- nevirapine with NRTIs (14-18)
- triple NRTIs (1,2)

It is noteworthy that the ritonavir dose typically used for pharmacoenhancement of coadministered protease inhibitors (i.e., 100 mg or 200 mg twice daily) (20), though less likely to produce adverse events than higher doses, still results in net CYP3A4 induction when used with rifampin (13, 21). Data are lacking for other protease inhibitors coadministered with rifampin and with ritonavir 400 mg twice daily. The use of nevirapine and NRTIs with rifampin is of particular importance in limited-resource countries in which rifabutin may not be available and for pregnant patients for whom efavirenz cannot be used. Despite pharmacokinetic data showing a significant reduction in nevirapine concentrations when coadministered with rifampin (14-17), two small studies demonstrated a favorable clinical and virologic response (16,18). Nonetheless, until additional data are available, rifampin- and nevirapine-containing antiretroviral regimens should only be used when no other options are available and close clinical and virologic monitoring can be performed.

### **Rifabutin and antiretroviral therapy (Table 2)**

Rifabutin could be used with most protease inhibitors, including atazanavir and fosamprenavir, provided the dose of rifabutin is reduced (22). Use of rifabutin with saquinavir alone is not advised given the significant decrease in saquinavir concentration; however, rifabutin may be used with saquinavir if coadministered with ritonavir. Other protease inhibitor/ritonavir combinations, including lopinavir/ritonavir, can be safely coadministered with rifabutin as long as the dose of rifabutin is decreased (23). Conversely, as a CYP3A4 inducer, efavirenz can reduce concentrations of rifabutin, necessitating an increase in the dose of rifabutin (24).

### **Other drug-interaction issues**

Further study is needed regarding the coadministration of other complex antiretroviral combinations (e.g., the concurrent use of a CYP3A4 inducer and inhibitor, such as efavirenz and a protease inhibitor) with rifabutin and rifampin. One observational study

found that the use of rifabutin with such complex antiretroviral regimens was associated with low serum concentrations of rifabutin, particularly when the rifabutin dose was reduced to 150 mg twice weekly for use with ritonavir-containing regimens (24).

The nucleoside reverse transcriptase inhibitors, which include zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, and emtricitabine, are not metabolized by CYP3A4; therefore, NRTIs and rifamycins may be coadministered without dose adjustments. However, antiretroviral therapy consisting exclusively of NRTIs appears to have reduced potency compared with regimens that contain either a protease inhibitor or NNRTI, and current guidelines recommend NRTI-based regimens only if protease inhibitor-based or NNRTI-based regimens cannot be used (25). As with NRTIs, *in vitro* and pharmacokinetic data suggest that CYP3A4 is not involved in the metabolism of either the NRTI tenofovir or the fusion inhibitor enfuvirtide, and thus each is considered safe to use with any of the rifamycins (26,27).

### **Acquired rifamycin resistance**

Rifamycin resistance has developed during the treatment of TB in HIV-infected persons, and has been associated with all rifamycins, particularly with highly-intermittent administration (once- or twice-weekly). Rifapentine, which can be administered once per week, is not recommended for HIV-infected patients because of their risk of developing rifamycin resistance (5). In addition, rifamycin resistance has developed in patients who have advanced HIV disease (i.e., CD4 < 100 cells/ $\mu$ l) and are receiving rifampin or rifabutin twice weekly (28-30). To prevent acquired rifamycin resistance in persons with advanced HIV infection and TB, more frequent therapy (thrice-weekly or daily) with either rifampin or rifabutin-based TB regimens is recommended.

As new antiretroviral agents and additional pharmacokinetic data become available, recommendations for the use of these agents during the treatment of TB are likely to be revised and updated. The purpose of this Web site is to provide a platform for periodic updates with the latest information. More general information on antiretroviral drug interactions can be obtained at <http://www.aidsinfo.nih.gov/guidelines> and <http://www.hiv-druginteractions.org>.

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**Table 1. Recommendations for Coadministering Protease Inhibitors and Nonnucleoside Reverse Transcriptase Inhibitors with RIFAMPIN – United States, 2004 (references provided for combinations with either inconclusive or limited data)**

<i>Single protease inhibitors</i>			
	<b>Antiretroviral Dose Change</b>	<b>Rifampin Dose Change</b>	<b>Comments</b>
<b>Ritonavir</b>	None	None (600 mg/day)	Ritonavir AUC ↓ by 35%; no change in rifampin concentration.
<b>Amprenavir</b>	Rifampin and amprenavir should not be used together.		Amprenavir AUC ↓ by 82%, Cmin ↓ by 92%.
<b>fos-Amprenavir</b>	Rifampin and fos-amprenavir should not be used together.		See amprenavir.
<b>Atazanavir</b>	Rifampin and atazanavir should not be used together.		Interaction studies not performed, but marked decrease in atazanavir concentrations predicted.
<b>Indinavir</b>	Rifampin and indinavir should not be used together.		Indinavir AUC ↓ by 89%.
<b>Nelfinavir</b>	Rifampin and nelfinavir should not be used together.		Nelfinavir AUC ↓ 82%.

<b>Saquinavir</b>	Rifampin and saquinavir should not be used together.	Saquinavir AUC ↓ by 84%.	
<b>Dual protease-inhibitor combinations</b>			
	<b>Recommended Change in Dose of Antiretroviral Drug</b>	<b>Recommended Change in Dose of Rifampin</b>	<b>Comments</b>
<b>Saquinavir / ritonavir</b>	Saquinavir 400 mg + ritonavir 400 mg twice-daily	None (600 mg/day)	Limited clinical experience ( <b>12</b> ).
<b>Pharmacoaugmented lopinavir / ritonavir (Kaletra®)</b> <i>Note: Additional ritonavir required.</i>	Lopinavir / ritonavir (Kaletra®) - 3 capsules + 300 mg of ritonavir twice-daily	None (600 mg/day)	Limited clinical experience. Increased hepatotoxicity from ritonavir is likely ( <b>13</b> ).
<b>Lopinavir / ritonavir (Kaletra®)</b>	Rifampin and lopinavir/ritonavir (Kaletra®) should not be used together. If Kaletra® is used with rifampin, additional ritonavir is required (see above).	Lopinavir AUC ↓ by 75% & Cmin ↓ by 99%.	
<b>Nonnucleoside reverse transcriptase inhibitors</b>			
	<b>Recommended Change in Dose of Antiretroviral Drug</b>	<b>Recommended Change in Dose of Rifampin</b>	<b>Comments</b>

<b>Efavirenz</b>	↑ to 800 mg/day*	None (600 mg/day)	Efavirenz AUC ↓ by 22%; no change in rifampin concentration. *May ↓ to 600 mg/day if 800 mg dose not easily tolerated.
<b>Nevirapine</b>	200 mg twice daily	None (600 mg/day)	Nevirapine AUC ↓ 37%-58% and C <sub>min</sub> ↓ 68% with 200 mg 2x/day dose ( <b>14-17</b> ). Limited, though favorable, data for efficacy of 200 mg BID dose, although should only be used if no other options exist and clinical and virologic monitoring possible ( <b>16, 18</b> ). May consider 300 mg BID only if close biochemical monitoring feasible; however, no clinical, pharmacokinetic, or safety data available for 300 mg BID dose.
<b>Delavirdine</b>	Rifampin and delavirdine should not be used together.		Delavirdine AUC ↓ by 95%.

**Table 2. Recommendations for Coadministering Protease Inhibitors and Nonnucleoside Reverse Transcriptase Inhibitors with RIFABUTIN – United States, 2004**

<i>Single protease inhibitors</i>			
	<b>Antiretroviral Dose Change</b>	<b>Rifabutin Dose Change<sup>¥</sup></b>	<b>Comments</b>
<b>Amprenavir</b>	None	↓ to 150 mg/day or 300 mg 3x/week	Rifabutin AUC ↑ by 193%; no change in amprenavir concentration.
<b>fos-Amprenavir</b>	None	↓ to 150 mg/day or 300 mg 3x/week	Comparable to amprenavir.
<b>Atazanavir</b>	None	↓ to 150 mg every other day or 150 mg 3x/week *	*Recommendation as per package insert. Rifabutin AUC ↑ by 250%.
<b>Indinavir</b>	↑ to 1000 mg q8h	↓ to 150 mg/day or 300 mg 3x/week	Rifabutin AUC ↑ by 204%; indinavir AUC ↓ by 32%.
<b>Nelfinavir</b>	↑ to 1000 mg q8h	↓ to 150 mg/day or 300 mg 3x/week	Rifabutin AUC ↑ by 207%; nelfinavir AUC ↓ by 32%.
<b>Ritonavir</b>	None	↓ to 150 mg every other day or 150 mg 3x/week	Rifabutin AUC ↑ by 430%; no change in ritonavir concentration.

<b>Saquinavir</b>	Rifabutin and saquinavir should not be used together.	Saquinavir AUC ↓ by 43%.	
<b><i>Dual protease inhibitor combinations</i></b>			
	<b>Antiretroviral Dose Change</b>	<b>Rifabutin Dose Change</b>	<b>Comments</b>
<b>Lopinavir / ritonavir (Kaletra™)</b>	None	↓ to 150 mg every other day or 150 mg 3x/week	Rifabutin AUC ↑ by 303%; 25-O-des-acetyl rifabutin AUC ↑ by 47.5-fold.
<b>Ritonavir (any dose) with saquinavir, indinavir, amprenavir, fos-amprenavir, or atazanavir</b>	None	↓ to 150 mg every other day or 150 mg 3x/week	
<b><i>Nonnucleoside reverse-transcriptase inhibitors</i></b>			
	<b>Antiretroviral Dose Change</b>	<b>Rifabutin Dose Change</b> †	<b>Comments</b>
<b>Efavirenz</b>	None	↑ to 450 mg/day or 600 mg 3x/week	Rifabutin AUC ↓ by 38%. Effect of efavirenz + protease inhibitor(s) on rifabutin concentration has not been studied.
<b>Nevirapine</b>	None	300 mg/day or 300 mg 3x/week	Rifabutin and nevirapine AUC not significantly changed.

<b>Delavirdine</b>	Rifabutin and delavirdine should not be used together.	Delavirdine AUC ↓ by 80%; rifabutin AUC ↑ by 100%.
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¥ If CD4 count is greater than 100 cells/mm<sup>3</sup>, may consider twice-weekly administration of rifabutin with amprenavir, fos-amprenavir, indinavir, nelfinavir, efavirenz, and nevirapine.