



Florida/Caribbean AIDS Education and Training Center

HIV CareLink

A Newsletter for HIV/AIDS Primary Care Providers

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ABOUT US

The Florida/Caribbean AIDS Education and Training Center provides state-of-the-art HIV education, consultation, and resource materials to health care providers in Florida, Puerto Rico and the US Virgin Islands.

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Journal Watch: Rifabutin and Lopinavir-ritonavir Interaction

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Tuberculosis (TB) and Human Immunodeficiency Virus (HIV) infection are ongoing public health threats worldwide. HIV infection predisposes an individual to becoming infected with TB or reactivation from a latent state. When both infections are present in an individual, it becomes difficult to treat due to the interaction between antiretrovirals (ARVs) and rifamycins. Underdosing of ARVs or rifabutin can result in a selection of HIV drug-resistant mutants or acquired rifamycin resistance, respectively. Overdosing of rifamycin may also lead to toxicities. Several different approaches have been suggested, including the avoidance of protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) when treating tuberculosis in HIV infection.

HIV-Associated Tuberculosis

- Patients with HIV infection are most likely to develop reactivation of latent tuberculosis or become infected with *Mycobacterium Tuberculosis*
- When treated for tuberculosis, HIV-infected patients are more likely to relapse than non-infected patients
- Rifabutin is often used for the treatment of HIV-associated TB due to its lower hepatic microsomal enzyme-induction potential compared to rifampin
- Lopinavir-ritonavir is widely used as part of ARV therapy in patients with HIV-associated TB based on data from healthy volunteers suggesting a reduced dose of rifabutin may be used without compromising efficacy

Pharmacokinetics of Rifabutin and Lopinavir-Ritonavir

- Rifabutin plasma concentration may be increased by HIV protease inhibitors and lower doses have been used in combination with lopinavir-ritonavir to avoid rifabutin toxicity
- Rifabutin may induce low lopinavir levels which could compromise virologic and clinical response
- A recent clinical study examined the bidirectional drug interaction between rifabutin and lopinavir-ritonavir in 10 patients with HIV-associated tuberculosis

Methods

Ten HIV-infected patients diagnosed with pulmonary TB received rifabutin 300 mg thrice weekly as part of a TB regimen, including isoniazid, pyrazinamide, and ethambutol. Concentrations of rifabutin, its desacetyl metabolite, and lopinavir were determined using validated high-performance liquid chromatography assay. At 2 to 4 weeks, steady-state levels of rifabutin were measured at 4 hours (represents maximum concentration, C_{max}) and 8 hours (assesses delayed absorption) after dosing. At that time, patients were started on lopinavir-ritonavir (400 and 100 mg, respectively) twice daily, plus tenofovir and emtricitabine, and the doses of rifabutin were decreased to 150 mg thrice weekly, as it is currently recommended. New samples were taken 2 weeks after the addition of ART. If both rifabutin plasma concentrations were below the normal range ($\leq 0.30 \mu\text{g/mL}$, normal C range 0.30-0.9 0 mcg/mL), the rifabutin dose was increased to 300 mg thrice weekly and samples were again obtained 2 weeks later.

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Results

Half of the patients on treatment for HIV-associated TB had low rifabutin C_{max} even before the initiation of combination ART. After the addition of lopinavir-ritonavir and lowering the doses of rifabutin to 150 mg thrice weekly, 9 out of 10 patients had lower C_{max} of rifabutin requiring adjustment of rifabutin doses to reach therapeutic levels. When the dose of rifabutin was increased to 300 mg thrice weekly, with lopinavir-ritonavir, only 3 patients had total rifabutin values of 0.45 $\mu\text{g/mL}$ or greater (associated with favorable outcomes in the US Public Health Service-Tuberculosis Trials Consortium (USPHS-TBTC) Study 23). The authors suggest that a rifabutin dose of 450 mg 5 times weekly, when used in combination with lopinavir-ritonavir, would be necessary to achieve the C_{max} and AUC values associated with good clinical and microbiological success in the USPHS-TBTC Study 23.

Summary

- Standard starting doses of rifabutin, at 300 mg thrice weekly, may be inadequate for HIV-infected individuals
- The standard adjusted rifabutin dose of 150 mg thrice weekly (with lopinavir-ritonavir) is potentially inadequate for HIV-infected patients
- It is advisable to either monitor rifabutin plasma concentrations or consider alternative dosing to prevent acquired rifabutin resistance tuberculosis in patients receiving treatment for HIV-associated TB. Rifabutin levels should be obtained at steady -state between 4 to 8 hours after dosing
- Dose adjustment should be made to achieve the recommended C_{max} ($\geq 30 \mu\text{g/mL}$). In the USPHS-TBTC Study 23, lower plasma concentrations of rifabutin, and perhaps, isoniazid, were associated with acquired rifamycin resistance failure or relapse in patients with tuberculosis and HIV infection treated with twice-weekly therapy
- Patients may also benefit from the measurement of lopinavir concentrations, since almost half of the patients had values below the target level for treatment-experienced patients

LabCorp Drug Level Ordering and Specimen Requirements⁷

Test #	Test Name	Specimen Requirement	Special Handling	Client Price
808376	Isoniazid (INH)	2ml Serum or plasma	Serum/plasma should be separated from cells within 2 hours of venipuncture. Send serum/plasma in a plastic transport tube. Note: Recommended no gel-barrier tubes	\$96.25
857336	Rifabutin Level	2ml Frozen Serum	Serum should be separated from cells within 2 hours of venipuncture. Send serum in a plastic transport tube before freezing.	\$109.00
892986	Lopinavir, HPLC	2ml Frozen Serum	The exact time of dose and the time of blood draws should be recorded. The samples should be promptly centrifuged, and the serum (2 mL) harvested into labeled polypropylene tubes and frozen at -70 degrees C until shipment. The tubes should be labeled with the patient's name, date and time of collection and the drug(s) to be assayed. Transfer specimen to plastic transport tube before freezing.	\$109.00

References

1. Boulanger C, et al. Pharmacokinetic Evaluation of Rifabutin in Combination with Lopinavir-ritonavir in Patients with HIV Infection and Active Tuberculosis. *Clin Infect Dis*. November 1, 2009;(49):1305-11
2. Kaletra [product monograph]. Abbott Pharmaceuticals. Available at <http://abbott.ca/static/content/document/Kaletra-PM13JUL09.pdf>
3. El-Sadr WM. HIV-associated Tuberculosis: diagnostic and treatment challenges. *Semin Respir Crit Care Med*. 2008 Oct29;(5):525-31
4. Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-infected Adults and Adolescents: Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep*. 2009 Apr 10;58(RR-4):1-207
5. Armstrong-James D. The utility of nucleos(t)ide-only regimens in the treatment of Mycobacterium tuberculosis-HIV-1 coinfection. *AIDS*. April 2009;27(7):865-867
6. Weiner M, et al. Association between acquired rifamycin resistance and the pharmacokinetics of rifabutin and isoniazid among patients with HIV and tuberculosis. Tuberculosis Trials Consortium. *Clin Infect Dis* 2005;40:1481-91
7. E-mail from LabCorp; December 17, 2009



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