Use of Rifabutin with Protease Inhibitors for Human Immunodeficiency Virus–Infected Patients with Tuberculosis

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Drug interactions between rifamycins and highly active antiretroviral therapy (HAART) have raised concerns in the treatment of human immunodeficiency virus (HIV)–infected patients with tuberculosis. We conducted a study of this interaction by measuring serum drug levels of all HIV-infected patients with tuberculosis who were admitted to A. G. Holley State Tuberculosis Hospital (Florida) from October 1997 through December 1998, who were concomitantly treated with rifabutin and HAART. All 25 patients studied became culture-negative within 2 months of initiation of therapy for tuberculosis and remained negative for a median of 13 months follow-up after completion of therapy. HIV viral loads (mean ± SEM) decreased significantly from 4.95 ± 0.21 log10 copies/mL before initiation of HAART to 2.77 ± 0.07 log10 copies/mL before discharge (P < .001); 20 of 25 patients achieved viral loads of <500 copies/mL. In summary, the concomitant use of rifabutin and HAART can lead to successful treatment of HIV-infected patients with tuberculosis without increased side effects.

The copathogenicity of tuberculosis (TB) and HIV infection is well recognized [1]. HIV infection accelerates the progression of TB, and the host immune response to Mycobacterium tuberculosis enhances HIV replication and may accelerate the natural progression of HIV disease [1, 2]. Therefore, it may be critical to treat both HIV infection and active TB in coinfected patients. As highly active antiretroviral therapy (HAART) for HIV infection has emerged, less morbidity and mortality has been seen in association with HIV infection [3, 4]. HAART generally employs a combination of nucleoside reverse-transcriptase inhibitors (NRTIs) plus a protease inhibitor (PI) and/or non–nucleoside reverse-transcriptase inhibitors (NNRTIs). Because of the incidence of significant drug interactions between the rifamycins and either PIs or NNRTIs, concurrent treatment has raised serious concerns [1, 5, 6].

Rifampin markedly lowers the serum levels of PIs and NNRTIs by inducing the activity of cytochrome P450 CYP3A [7]. It may result in suboptimal antiretroviral activity and, therefore, subsequent acquired drug resistance [8]. Thus, the use of rifampin to treat tuberculosis disease in a patient who is receiving a PI or an NNRTI is not recommended [1]. Rifabutin has been shown to be as effective against tuberculosis as rifampin [9–11] and has the advantage of being a less potent inducer of the hepatic cytochrome CYP 450 enzyme system [12, 13]. Therefore, rifabutin may play a potential role in the treatment of TB in HIV-infected patients who are receiving HAART. The concurrent use of rifabutin and either indinavir or nelfinavir has been reported to cause a 30%–40% decrease in PI serum levels and an approximately twofold increase in rifabutin levels [14, 15].

Currently the guidelines from the Centers for Disease Control and Prevention (CDC) [1] recommend that rifabutin be substituted for rifampin when treating patients with TB who are receiving HAART. Although rifabutin treatment of pulmonary TB has been examined in 3 studies [9–11], including a trial [11] that studied HIV-coinfected patients not treated with antiretroviral therapy, the use of rifabutin in patients who are concurrently receiving PIs or NNRTIs has not been studied extensively, and there are only a few reports in abstract form [16]. We report successful treatment of coinfected patients with both rifabutin and a PI-containing HAART.

Patients and Methods

Clinical study. We retrospectively reviewed the medical records of all patients with culture-proven TB who were admitted to A. G. Holley State Tuberculosis Hospital (Lantana, Florida) from 1 October 1997 through 31 December 1998. For patients who were HIV positive, the CD4+ percentage (percentage of total peripheral blood lymphocyte count), total CD4+ absolute cell count, and CD4+/CD8+ ratio were measured by use of flow cytometry (SmithKlein Beecham Clinical Laboratories, Miami, Florida), and an HIV RNA viral load was quantified by use of PCR amplification (HIV viral load) at SmithKlein Beecham Clinical Laboratories.
These analyses were done on admission, on the day before antiretroviral therapy was initiated, 2 weeks after antiretroviral therapy was started, and periodically thereafter when clinically indicated. Before starting HAART, anti-TB therapy was begun with a daily dose (including rifabutin, 300 mg/d) and then switched to a dose once every 2 weeks (including rifabutin, 300 mg every 2 weeks). For most patients, antiretroviral therapy was started at least 2 weeks after the initiation of anti-TB therapy. Sputum specimens for acid-fast bacilli smear and culture were collected on days 1, 2, and 3 of the hospitalization, and then at least weekly until discharge. Sputum culture conversion was defined as at least 3 consecutive negative M. tuberculosis cultures without the development of a subsequent positive culture until completion of treatment.

Drug susceptibility testing of M. tuberculosis was performed at the Florida State Laboratory (Jacksonville, Florida) by use of the BACTEC-TB460 system (Becton-Dickinson, NJ).

Pharmacokinetic studies. All consenting HIV-infected patients underwent therapeutic drug monitoring for TB medications and PIs. For the pharmacokinetic portion of this study, the study period was extended through 30 April 1999. Serum drug levels were determined when a steady state level was established for each medication, usually 2 weeks after their introduction. Blood was drawn at 2 and 6 h after the oral dose of medications. (Peak levels of isoniazid and indinavir typically occur ~1 hour after oral administration of a dose, whereas both rifabutin and nelfinavir levels peak ~3 h after. In order to reduce the number of times blood was drawn, 2-hour levels were obtained and compared with expected 2-hour levels from healthy individuals [17].) Blood samples were promptly centrifuged and the serum was transferred into labeled polypropylene tubes on dry ice and sent to the National Jewish Center for Immunology and Respiratory Medicine, where drug levels were measured by use of high-performance liquid chromatography. Dosages of medications were subsequently adjusted on the basis of these results. Specifically, the dose of rifabutin was adjusted after the initiation of HAART if (1) the drug level at 2 h was <0.26 µg/mL and if (2) the drug level at 6 h was considerably lower than at 2 h, which suggests no delayed drug absorption.

Reference levels of isoniazid, rifabutin, and PIs were derived from data from normal healthy volunteers [17]. Isoniazid serum levels appear to be linear in dose response (C. Peloquin, National Jewish Medical and Research Center, personal communication). At a dosage of 900 mg once every 2 weeks, serum levels were expected to be 9-18 µg/mL.

Results

Clinical study. Forty-seven HIV-infected patients with TB were admitted to A. G. Holley State Tuberculosis Hospital from 1 October 1997 through 31 December 1998. Of these 47, 33 were treated with HAART that contained a PI (indinavir and/or nelfinavir) and standard TB regimens that replaced rifampin with rifabutin. Six of 33 patients did not tolerate HAART and required it to be discontinued (5 because of gastrointestinal intolerance and 1 because of hepatitis). Two of the remaining 27 patients were found to have M. tuberculosis resistant to rifamipin and rifabutin, and therefore rifabutin was discontinued. The median age of the 25 patients was 36 years (range, 27–65 years); 16 (64%) of the patients were men and 9 (36%) were women, 2 (8%) were white, 19 (76%) were black, and 4 (16%) were Hispanic. Twenty-four of these 25 patients were placed on TB therapy a median of 4 weeks before admission to A. G. Holley State Tuberculosis Hospital. All 24 patients were, however, nonadherent to TB therapy, so it was difficult to determine the exact number of doses they had taken as outpatients. Upon admission to our hospital, 19 of the 25 patients had negative smears and 17 of the 25 patients had negative cultures for M. tuberculosis. Before admission, 18 of 25 patients had experience with 1 NRTI and 9 of these 18 patients had experience with a PI-containing HAART; 7 patients were antiretroviral-therapy naive. In addition, all of the patients had a history of nonadherence to their antiretroviral regimen. Susceptibility testing of M. tuberculosis from 2 patients revealed low-level isoniazid resistance at 0.1 µg/mL only, with susceptibility at a critical concentration of 0.4 µg/mL, and another 2 patients were resistant to isoniazid at a critical concentration of 2 µg/mL. No isolates were found to be resistant to ethambutol or pyrazinamide.

Culture conversion occurred within 2 months of admission in all 8 patients with initial positive cultures, and all 25 patients remained culture-negative throughout the remainder of their hospitalization (median, 6 months; range, 4–12 months). After completion of TB therapy, there has been no reported case of TB relapse after a median of 13 months follow-up (range, 2–28 months). None of the patients developed rifabutin-related uveitis or leukopenia.

Mean CD4+ counts ± SEM before HAART were 124 ± 28.4 cells/mm³ (n = 24). Two weeks after initiation of HAART, mean follow-up CD4+ counts ± SEM were 176.9 ± 28 cells/mm³ (n = 21). Before discharge on HAART, after a mean duration of antiretroviral therapy ± SEM of 17.5 ± 3 weeks, mean final CD4+ counts ± SEM were 218.4 ± 40.4 cells/mm³ (n = 20). There was a statistically significant increase in CD4+ counts (P = .038) when initial CD4 counts were compared to the final CD4+ counts (CD4+ counts increased in 18 [90%] of 20 patients with data available). Before HAART, mean HIV viral loads ± SEM were 4.95 ± 0.21 log₁₀ copies/mL (n = 25). At follow-up 2 weeks after initiation of HAART, viral loads were 3.38 ± 0.16 log₁₀ copies/mL (n = 25). Final viral loads before discharge on HAART were 2.77 ± 0.07 log₁₀ copies/mL (n = 24). None of 25 patients experienced a viral load increase, and, moreover, 20 (80%) of 25 patients achieved a viral load of <500 copies/mL before discharge. When initial viral load was compared with final viral load, there was a statistically significant decrease (P < .001). When we categorized patients into antiretroviral-therapy-naive, NRTI-experienced, and PI-experienced groups, we found the same trends (table 1).

Pharmacokinetic studies. Thirteen patients had serum rifabutin levels measured while receiving an dosage of 300 mg orally twice a week. The expected range 2 h after ingestion is 0.3–0.9 µg/mL. Before HAART, mean rifabutin levels ±
SEM were 0.10 ± 0.02 μg/mL (n = 13) at 2 h, and 2 weeks after initiation of HAART, levels were 0.23 ± 0.03 μg/mL (n = 13) at 2 h. This was a significant increase in rifabutin levels (P < .001) and approached the expected range (table 2).

Five patients who received isoniazid, 900 mg orally twice weekly, had serum isoniazid levels measured. The expected range at 2 h after ingestion is 9–18 μg/mL. Before the initiation of HAART, mean isoniazid levels ± SEM were 9.56 ± 2.84 μg/mL (n = 5) at 2 h. Two weeks after initiation of HAART, levels were 12.11 ± 3.39 μg/mL (n = 5) at 2 h. There was no statistically significant difference between the 2 levels (P = .48; table 2).

All consenting patients had serum PI levels measured while they received therapy for TB. There were 37 serum indinavir levels measured. Nine samples were obtained from patients receiving 800 mg every 8 h; mean serum indinavir level ± SEM at 2 h was 1.7 ± 0.74 μg/mL. Six samples were obtained from patients receiving 1000 mg every 8 h; mean serum indinavir level ± SEM at 2 h was 3.22 ± 1.08 μg/mL. Nine samples were obtained from patients receiving 1200 mg every 8 h; mean serum indinavir level ± SEM at 2 h was 5.92 ± 1.60 μg/mL. Two samples were obtained from patients receiving 1600 mg every 8 h; mean serum indinavir level ± SEM at 2 h was 2.7 ± 1.78 μg/mL. Eleven samples were obtained from patients receiving 1200 mg every 12 h; mean serum indinavir level ± SEM at 2 h was 5.86 ± 1.24 μg/mL. (The difference in dosage regimen reflects both differences in clinical guidelines and dosage adjustment after drug levels. For patients receiving 800 mg every 8 h, the expected range at 2 h is 5–11 μg/mL; table 3.)

There were 31 serum nelfinavir levels measured. A patient was placed on both indinavir and nelfinavir plus at least 2 NRTIs if they had a history of previous exposure to antiretroviral therapy and/or if drug resistance was suspected. Fifteen samples were obtained from patients receiving 1000 mg every 12 h; mean nelfinavir levels ± SEM at 2 h were 2.66 ± 0.51 μg/mL. Another 14 samples were obtained from patients receiving 1250 mg every 12 h; for these, mean nelfinavir levels ± SEM at 2 h were 2.6 ± 0.34 μg/mL. (For a patient receiving 750 mg every 8 h, the expected range at 2 h is 2–5 μg/mL.) We compared the nelfinavir levels at 2 h (dosage, 1250 mg every 12 h) of the patients receiving concomitant indinavir therapy with the levels of those not receiving indinavir and found an apparent increase in the level of nelfinavir with the concomitant use of indinavir, but it lacks statistical difference (2.73 ± 0.41 [n = 11] vs. 2.11 ± 0.64 [n = 3]; P = 0.181).

**Discussion**

There are improved outcomes in the management of HIV-infected patients with the use of HAART [4, 5]. However, drug interactions during therapy with HAART may affect the treatment and prophylaxis of opportunistic infections [2, 6]. One dilemma has been the interactions between components of HAART (namely, PIs and NNTRIs) and the rifamycins that are used to treat TB in HIV-infected patients [18]. Our analysis indicates that rifabutin and PIs may be given concomitantly with successful clinical responses in both HIV and tuberculous diseases. The current duration of follow-up is <2 years (median, 13 months; range, 2–28 months) after completion of TB medications, and therefore the relapse rate cannot yet be determined. However, it is noteworthy that all patients receiving concomitant HAART experienced culture conversion within 2 months of starting TB regimens containing rifabutin; this is a marker of successful TB therapy. Further, they remained cul-

<table>
<thead>
<tr>
<th>Table 1. CD4⁺ counts and HIV RNA viral loads of 25 HIV-infected patients with tuberculosis.</th>
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<tbody>
<tr>
<td>Values</td>
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<tr>
<td>CD4⁺ count, cells/mm³</td>
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<tr>
<td>Final</td>
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<td>HIV RNA viral loads, log₁₀ copies/mL</td>
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<td>Initial</td>
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<tr>
<td>Final</td>
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<tr>
<td>No. of patients with viral load &lt;500 copies/mL</td>
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NOTE: Data are mean ± SEM unless otherwise indicated. ART, antiretroviral therapy; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

a n = 8.

<table>
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<tr>
<th>Table 2. Tuberculosis drug serum levels (2 h after ingesting the drug) of HIV-infected patients with tuberculosis before and 2 weeks after the initiation of highly active antiretroviral therapy (HAART).</th>
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<tbody>
<tr>
<td>Drug</td>
</tr>
<tr>
<td>Rifabutin</td>
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<td>Isoniazid</td>
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NOTE: Data are mean ± SEM unless otherwise indicated.

a Every 2 weeks.
Nelnavir loads of percent of concomitantly treated patients attained HIV viral suppression by the treatment of active TB disease on viral loads [19]. Seventy-seven percent of this improvement may be due to the effect of the concomitant therapy for HIV and tuberculous diseases, although viral loads decreased significantly during the course of concomitant treatment (e.g., uveitis or leukopenia).

There was no observed increase in rifabutin-related side effects in the majority of patients (range, 4–12 months), and to date no relapse has been reported. There was no observed increase in rifabutin-related side effects (e.g., uveitis or leukopenia).

The HIV response in our patients was also marked. HIV viral loads decreased significantly during the course of concomitant therapy for HIV and tuberculous diseases, although part of this improvement may be due to the effect of the treatment of active TB disease on viral loads [19]. Seventy-seven percent of concomitantly treated patients attained HIV viral loads of <500 copies/mL before discharge; this level was achieved at a mean time ± SEM of 15.6 ± 2.4 weeks after the initiation of HAART. In previous reports on HIV-infected patients, HAART (i.e., zidovudine, lamivudine, and indinavir) resulted in 45%–85% of zidovudine-experienced subjects attaining viral loads of <500 copies/mL at 24 weeks [20, 21]. Even when we categorized patients in the present study into antiretroviral-therapy-naïve, NRTI-experienced, and PI-experienced groups, we found that all groups achieved a similar response rate. It is important to note that with the concomitant use of rifabutin, the dosage of indinavir had to be increased from a standard dosage of 800 mg every 8 h to 1200 mg every 8 h in order to approach the expected range for serum indinavir levels. However, it may be possible to achieve therapeutic nelnavir levels with a dosage of 1000 or 1250 mg every 12 h. Although this study examined the pharmacokinetic measurements of twice-daily indinavir administration, it is important to note that this regimen has been subsequently proven inferior to thrice-daily administration and is now not recommended when indinavir is used as the single PI. Drug levels may be a useful measurement for adjusting medication dosages to achieve maximal drug effect, especially improved viral suppression.

In summary, this study demonstrates that concomitant use of rifabutin and PIs is successful in the treatment of HIV-infected patients with TB. Bactericidal activity of rifabutin and viral suppression by PIs appear to persist throughout therapy without increasing side effects. Further studies examining the clinical use of rifabutin and PIs (as well as NNRTIs) need to be conducted.

### Table 3. Antiretroviral drug serum levels (2 h after ingestion) for HIV-infected patients with tuberculosis while they received therapy for tuberculosis.

<table>
<thead>
<tr>
<th>Drug and Dosage</th>
<th>n</th>
<th>Mean serum level ± SEM, µg/mL</th>
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<tr>
<td>Indinavir&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>800 mg q8h</td>
<td>9</td>
<td>1.7 ± 2.21</td>
</tr>
<tr>
<td>1000 mg q8h</td>
<td>6</td>
<td>3.22 ± 2.64</td>
</tr>
<tr>
<td>1200 mg q8h</td>
<td>9</td>
<td>5.92 ± 4.8</td>
</tr>
<tr>
<td>1200 mg q12h</td>
<td>11</td>
<td>5.86 ± 4.12</td>
</tr>
<tr>
<td>Nelnavir&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1000 mg q12h</td>
<td>15</td>
<td>2.66 ± 1.98</td>
</tr>
<tr>
<td>1250 mg q12h</td>
<td>14</td>
<td>2.60 ± 1.29</td>
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<sup>a</sup> Expected range of serum level for a dosage of 800 mg q8h is 5–11 µg/mL.

<sup>b</sup> Expected range of serum level for a dosage of 750 q8h is 2–5 µg/mL.

### Acknowledgments

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### References


