Protease Inhibitors and Rifabutin: Isn’t the Jury Still Out?

Sir—The attempt by Narita et al. [1] to delineate the pharmacokinetic interactions between HIV type 1 protease inhibitors (PIs) and rifabutin administered intermittently addresses the practical question of juggling intermittent directly observed therapy (DOT) for tuberculosis (TB) with PI-based highly active antiretroviral therapy (HAART). Although the authors provide data that reassure that toxicity was not problematic and that virologic outcomes were reasonably successful in a supervised inpatient facility, their data do not provide unequivocal support for the use of PIs with rifabutin.

The authors measured 2-h levels of PI, rather than trough levels. Since rifabutin speeds up the hepatic metabolism of PIs more than their intestinal metabolism [2], PI trough levels are preferentially decreased. Virologic failure with the use of PIs is thought to be related to the extent to which PI trough levels fall short of the inhibitory concentration of the drug for the virus [3]. Without demonstration of adequate PI trough levels, the adequacy of PI levels with rifabutin is still in doubt. Furthermore, the authors’ data showed equivalence in the 2-h levels of indinavir, 1200 mg q8h, which is the dosage they recommend with rifabutin, and indinavir, 1200 mg q12h, which is a dosage that has been discouraged by indinavir’s manufacturer since that dosage was associated with an unacceptable rate of virologic failure (Merck, data on file).

The authors showed virologic suppression to the level of 500 copies/mL. Since durability of viral suppression by antiretroviral therapy relates to a nadir virus load [4], the assay that uses 500 copies/mL cannot be considered the gold standard by which to validate a regimen. Of concern was that only 4 of 8 antiretroviral therapy (ART)—naïve patients achieved an undetectable virus load while receiving a PI and rifabutin. The patients who were not ART-naïve fared better, but, as a group, they had a lower virus load in comparison with the naïve patients.

Our experience at Jacobi Medical Center (Bronx, NY) illustrates practical obstacles to delivering HAART to patients with TB and loss of virologic suppression in a small number of patients concurrently treated with rifabutin and a PI. We have cared for 32 patients with HIV/TB infection since 1996 [5]. Fifteen patients had known HIV infection prior to TB; only 5 of these patients were receiving HAART. Seventeen had newly diagnosed HIV infection, consequent to TB. Seven patients died during their hospitalization for TB. Three other patients, including 2 who have regularly declined care for HIV infection since the 1980s, continued receiving care elsewhere. Two eventually died of multidrug-resistant CNS TB after refusing HAART because of its pill burden. Two patients refused HIV testing until ultimately fatal conditions supervened. Nine patients, all of whom eventually were cured of TB, chose not to take HAART. They had no opportunistic conditions occur within 6 months after the start of TB therapy. Two patients, who had high virus loads despite receiving HAART before TB therapy, were treated without a rifamycin; 1 died without evidence of TB, and 1 completed 18 months of TB treatment. Three of 4 regular clinic patients lost virologic suppression (<400 copies/mL in 2 patients and 837 copies/mL in 1 patient [before therapy with rifabutin]) after rifabutin, 150 mg given twice weekly, was added to a PI. Four patients treated with HAART without concurrent rifamycin maintain undetectable virus loads, including 1 patient who deferred HAART until after TB therapy.

In our experience, like that of Narita et al., most patients dually infected with HIV/TB require the establishment of regular medical care. This obstacle cannot be minimized in any implicit recommendation to use HAART and rifamycins in outpatients. The outcomes described by Narita et al. occurred in patients for whom supervised therapy was mandated. It would be imprudent to generalize those results to the usual outpatient setting.

In recognition of the importance of rifampin, deferring HAART should be considered, since this can be done safely in many cases. For patients in urgent need of HAART, for whom rifabutin is prescribed concurrently with a PI, adequate PI trough levels should be demonstrated. Successful treatment of TB may ultimately be the greatest inducement for patients to participate in health care. By contrast, judicious use of rifabutin with unsupervised PIs may jeopardize patients’ future antiretroviral therapy.

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References
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Reply

Sir—We appreciate Dr. Jenny-Avital’s thoughtful comments on and shared experience with the use of rifabutin (RBT) in HIV-infected patients with tuberculosis (TB) receiving highly active antiretroviral therapy (HAART) including protease inhibitors (PIs) [1], and we also appreciate Dr. Slain’s interest in and comments on [2] our article [3].

As Dr. Jenny-Avital points out, one of the reasons for virologic failure associated with the use of PIs is that PI trough levels fall short of the inhibitory concentration. Although it has now become our practice to measure peak and trough levels of PIs, at the time our study was designed, it was decided to measure the drug levels of PIs at the time of “standard” monitoring of TB drug levels (i.e., at 2 and 6 h after dosing). Nonetheless, 20 (80%) of 25 patients achieved a virus load of <500 copies/mL prior to discharge, which was comparable to the results of previous studies, in which 45%–85% of zidovudine-experienced subjects attained virus loads of <500 copies/mL at 24 weeks [4, 5]. Once again, 500 copies/mL was used as the lower limit of detection because of the sensitivity of the tests available at the time.

We share Dr. Jenny-Avital’s concerns regarding why, in subanalysis, only 4 of 8 antiretroviral therapy (ART)–naïve patients achieved a virus load of <500 copies/mL while receiving a PI and rifabutin, and why the patients who were not ART-naïve fared better (7 of 9 achieved a virus load of <500 copies/mL). However, this may be due to the small number of patients in subanalysis. Findings of a comparison of 3 groups (ART-naïve patients, nuclease reverse transcriptase–experienced patients, and PI-experienced patients) were not statistically significant (P > .3).

We reiterate that the purpose of our original study was to evaluate the utilization of PIs and rifabutin, with regard to a patient’s clinical response, drug side effects, and pharmacokinetics. Although deferring HAART may be a consideration, there has been no study to compare aggressive HAART with deferred HAART with regard to the clinical outcome of patients dually infected with HIV and TB. Because TB may accelerate the natural progression of HIV disease, further studies are necessary to delineate the best approach for treatment of individuals with this increasingly more prevalent combination of deadly diseases.

With regard to Dr. Slain’s comment, we received the same questions by e-mail soon after the electronic publication of our article. We asked Clinical Infectious Diseases to print an erratum, which appeared on page 992 of the June 2000 issue (volume 30, number 6).

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References


Good’s Syndrome: The Association of Thymoma and Hypogammaglobulinemia

Sir—Among the many causes of recurrent airway infections is the rare Good’s syndrome, a classic example of which is reported in the following patient. In 1992, a 59-year-old woman presented with a 6-month history of productive cough. She had never smoked and mentioned having a “spot” on a chest radiograph that was obtained in 1943, for which she had to take bed rest for several months, at the time her mother had tuberculosis diagnosed. A chest radiograph obtained in 1992 revealed a homogenous oval consolidation in the region of the left upper lobe; comparison of this radiograph with earlier routine preoperative radiographs indicated that the consolidation had not changed. Cultures of sputum samples yielded Haemophilus species. Results of a cytological examination of the mass were inconclusive and the mass was presumed to have resulted from an old case of tuberculosis with residual atelectasis. Antibiotic treatment resulted in gradual resolution of her symptoms. However, from 1992 through 1997, she required antibiotic treatment of bronchitis at least 3 times per year. In 1998, she was admitted to the hospital with increased dyspnea and cough which produced green sputum. She complained of fatigue, had a temperature up to 39°C, and had experienced night sweats during the past months; she also had gradually lost 12 kg of weight since 1992. On physical examination, she appeared ill and bi-