Rifamycin-Resistant Mycobacterium tuberculosis in the Highly Active Antiretroviral Therapy Era: A Report of 3 Relapses with Acquired Rifampin Resistance following Alternate-Day Rifabutin and Boosted Protease Inhibitor Therapy

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Rifamycin-resistant Mycobacterium tuberculosis infection (i.e., by a strain of M. tuberculosis that is only resistant to rifamycins) occurs disproportionately among patients infected with the human immunodeficiency virus (HIV) who have a low CD4 cell count. We observed 3 genetically confirmed cases of relapse with rifamycin-resistant M. tuberculosis infection following concurrent treatment with rifabutin (dosage, 150 mg every other day) and a ritonavir-boosted HIV protease inhibitor during a prior episode of drug-susceptible tuberculosis. Higher doses of rifabutin and a ritonavir-boosted HIV protease inhibitor as treatment for tuberculosis should be studied further.

Among individuals treated for drug-susceptible Mycobacterium tuberculosis infection, rifamycin-resistant M. tuberculosis infection (i.e., by a strain of M. tuberculosis that is only resistant to rifamycins) occurs disproportionately among patients infected with the human immunodeficiency virus (HIV) [1–4]. Rifamycin-resistant M. tuberculosis infection among HIV-infected patients has consistently been associated with a low CD4 cell count [1–9] as well as nonadherence to antituberculosis therapy [2, 3], disseminated or extrapolmonary tuberculosis [4–6], intermittent dosing during the initial intensive treatment phase [7, 8], gastrointestinal symptoms [2, 9], use of azole antifungal drugs [6, 9], and prior rifabutin therapy [9]. Most descriptions of rifamycin-resistant M. tuberculosis infection either predated the highly active antiretroviral therapy (HAART) era or did not include information on the use of HAART. Because rifampin increases the metabolic degradation of the protease inhibitor class of antiretroviral drugs via the induction of the cytochrome P450 system, rifabutin, a less potent inducer, is the rifamycin derivative of choice for treating tuberculosis in HIV-infected patients receiving protease inhibitors [10]. Ritonavir-boosted protease inhibitors are considered to be the preferred agents [11] for the treatment of HIV infection. Dosing guidelines for the use of rifabutin with a ritonavir-boosted protease inhibitor are based on pharmacokinetic studies involving healthy subjects. Few data are available that substantiate successful treatment outcomes for patients with tuberculosis who received rifabutin 150 mg every other day (which is the dosage recommended in current guidelines) along with a ritonavir-boosted protease inhibitor.

The number of cases of rifamycin-resistant M. tuberculosis infection associated with HIV-infected patients in New York City has been decreasing. From the New York City tuberculosis registry for 1993–1994, Munsiff et al. [3] identified 32 cases of rifamycin-resistant M. tuberculosis infection (29 in HIV-infected individuals). Only 10 cases of rifamycin-resistant M. tuberculosis infection (7 in HIV-infected individuals) were identified from the same registry for 1997–2000 [6]. During the period 2002–2006, there were 0–2 cases per year of rifamycin-resistant M. tuberculosis infection according to the New York City annual summaries for tuberculosis [12]. It was therefore remarkable to encounter 2 patients with rifamycin-resistant M. tuberculosis infection in 1 year at the North Bronx Healthcare Network. Both patients had a prior case of tuberculosis infection that was treated with rifabutin (dosage, 150 mg every other day) along with a ritonavir-boosted protease inhibitor. Soon after the identification of these 2 cases, the Bronx County Health Department identified a third case that was very similar. The 3 cases are detailed in this article and in figure 1.

Case 1. A 42-year-old man tested positive for HIV infection in 1999; his CD4 cell count was 223 cells/mm³. He remained healthy until March 2005, when drug-susceptible pulmonary tuberculosis was diagnosed (on the basis of a positive result of acid-fast bacilli smear microscopy) at another health care facility. He received directly observed therapy at the Bronx County tuberculosis clinic. He was treated with 300 mg of isoniazid once daily, 600 mg of rifampin once daily, 1500 mg...
Figure 1. Treatment history of 3 patients with human immunodeficiency virus infection and tuberculosis (TB). CD4, CD4 cell count; DOT, directly observed therapy; HAART, highly active antiretroviral therapy; NA, not available; PI, protease inhibitor; PI/r, ritonavir-boosted protease inhibitor; QOD, every other day; RBT, rifabutin; RIF, rifampin; RR-MTb, rifamycin-resistant Mycobacterium tuberculosis; Rx, prescription; S-MTb, drug-susceptible M. tuberculosis.

of pyrazinamide once daily, and 800 mg of ethambutol once daily for 2 months followed by intermittent doses of 900 mg of isoniazid and 600 mg of rifampin, mostly thrice weekly, for 4 months. Smear and culture test results were negative after the first month of therapy. He remained off of HAART. In January 2006, he presented to the North Bronx Hospital Network HIV clinic with fever, cough, and a CD4 cell count of 3 cells/mm³. Sputum samples were positive for acid-fast bacilli on the basis of smear microscopy. Drug-susceptible M. tuberculosis grew from sputum and blood samples. He resumed directly observed therapy with 600 mg of rifampin once daily, 300 mg of isoniazid once daily, and 2000 mg of pyrazinamide once daily for 2 months followed by 300 mg of isoniazid once daily and 600 mg of rifampin once daily; culture and smear test results were negative after 3 weeks of therapy. In May 2006, HAART was initiated with 300 mg of atazanavir plus 100 mg of ritonavir once daily, 300 mg of zidovudine twice daily, and 150 mg of lamivudine twice daily. Simultaneously, rifabutin 150 mg every other day replaced rifampin 600 mg once daily. Because of an inadequate HIV virologic response, lopinavir 400 mg plus ritonavir 100 mg twice daily replaced atazanavir 300 mg plus ritonavir 100 mg once daily. Tuberculosis therapy was stopped in July 2006 after nearly 7 months. While receiving the new HAART, the patient’s CD4 cell count increased to 111 cells/mm³, and he began to feel better. However, in November 2006, he had fevers and experienced weight loss. Despite having repeatedly normal chest radiograph findings, the patient’s blood and sputum samples from December 2006 yielded rifampin-resistant M. tuberculosis on culture. Molecular characterization by restriction fragment length polymorphism [13], which is routinely done on all New York City isolates (at the Public Health Research Institute in Newark, New Jersey), confirmed the identity of the isolates from all 3 episodes. Therapeutic drug monitoring was done to optimize therapy for the unexpected second tuberculosis relapse. Drug concentrations, obtained 2 h after receipt of drug dosage, were measured by use of high-performance liquid chromatography at National Jewish Health in Denver, Colorado. The serum concentration after 300 mg of isoniazid was 1.09 µg/mL (range, 3–6 µg/mL), and the serum concentration after 1200 mg of ethambutol was 1.18 µg/mL (range, 2–6 µg/mL); the serum concentrations of the other concurrent drugs (ie, pyrazinamide, streptomycin, and moxifloxacin) were within their therapeutic ranges.

Case 2. A 47-year-old man tested positive for HIV infection in 1992; his CD4 cell count was >700 cells/mm³. He remained healthy without HAART. In July 2006, with a CD4 cell count of 30 cells/mm³, his blood, urine, and sputum samples yielded drug-susceptible M. tuberculosis on culture. His acid-fast bacilli smear and culture test results were positive for drug-susceptible M. tuberculosis through November 2006 because of poor com-
Pliance. He was served a New York City Commissioner of Health’s order of detention. Once detained for directly observed therapy in December 2006, his acid-fast bacilli smear and culture test results were negative within 1 month. After 7 weeks of receiving a supervised dose of isoniazid 300 mg once daily, rifabutin 300 mg once daily, ethambutol 1200 mg once daily, and pyrazinamide 2000 mg once daily, supervised HAART was begun with 400 mg of lopinavir plus 100 mg of ritonavir twice daily, 300 mg of tenofovir once daily, and 200 mg of emtricitabine once daily. Rifabutin, reduced to 150 mg thrice weekly, was given with 300 mg of isoniazid once daily to complete 9 months of treatment. A daily dose of pyrazinamide was stopped after 3 months. The patient’s CD4 cell count increased to 134 cells/mm$^3$. He took no medications after he was released from detention. Four months later, he presented to the North Bronx Hospital Network with cough, weight loss, and a normal chest radiograph. Because of his history, sputum samples were requested for acid-fast bacilli smear and culture, which yielded rifampin-resistant \textit{M. tuberculosis}. Molecular characterization confirmed that the original and relapse isolates were identical. No therapeutic drug monitoring data were available.

\textbf{Case 3.} A third HIV-infected patient with rifampin-resistant \textit{M. tuberculosis} infection and a treatment history similar to those of the other 2 patients was reported to the Bronx County Health Department in April 2008. The patient, a 43-year-old man, previously received a diagnosis of disseminated infection and a treatment history similar to those of the other 2 patients was reported to the Bronx County Health Department in April 2008. The patient, a 43-year-old man, previously received a diagnosis of disseminated \textit{M. tuberculosis} in April 2007 (with a CD4 cell count of 51 cells/mm$^3$) as a result of a sputum sample and a biopsy sample from the mediastinal lymph node that yielded \textit{M. tuberculosis} on culture, even though both samples were negative for acid-fast bacilli on microscopy. Sputum samples tested negative for \textit{M. tuberculosis} on culture after treatment with isoniazid 300 mg once daily, rifampin 600 mg once daily, pyrazinamide 1500 mg once daily, and ethambutol 800 mg once daily. The patient was transferred to a nursing facility. Daily doses of isoniazid, rifampin, and pyrazinamide were given until August 2007. Then doses of atazanavir 300 mg plus ritonavir 100 mg once daily, tenofovir 300 mg once daily, and emtricitabine 200 mg once daily were begun, and rifabutin 150 mg thrice weekly was substituted for rifampin 600 mg once daily. He took rifabutin 150 mg thrice weekly and daily isoniazid 300 mg once daily until November 2007 and then left the nursing facility. In April 2008, with a CD4 cell count of 26 cells/mm$^3$, he presented with a psoas muscle abscess. A sputum sample and a biopsy sample from the psoas muscle yielded rifampin-resistant \textit{M. tuberculosis} on culture. Molecular characterization confirmed that the original and relapse isolates were identical. No follow-up therapeutic drug monitoring data were available.

\textbf{Discussion.} All 3 patients had disseminated drug-susceptible tuberculosis concurrent with very low CD4 cell counts (i.e., <50 cells/mm$^3$) prior to their rifamycin-resistant \textit{M. tuberculosis} infection relapse. Rifamycin-resistant \textit{M. tuberculosis} infection developed despite fully supervised directly observed therapy, which included at least a 2-month daily intensive phase followed by daily therapy during the continuation phase, in accordance with current guidelines. Rifamycin-resistant \textit{M. tuberculosis} infection relapse occurred not only after adequate treatment for tuberculosis but after HAART, which was known to be successful in cases 1 and 2.

The dosage of rifabutin is not a recognized risk factor for rifamycin-resistant \textit{M. tuberculosis} infection, although intermittent dosing of rifamycin during the induction phase of tuberculosis treatment [7, 8], highly intermittent dosing of rifamycin during the continuation phase, and weekly dosing of rifapentine [6] have been associated with rifamycin-resistant \textit{M. tuberculosis} infection. A pharmacokinetic substudy by the Tuberculosis Trials Consortium Study 23, which used a twice-weekly dose of rifabutin during the continuation phase of tuberculosis treatment, showed that the median rifabutin area under the concentration-time curve (AUC$_{0-24}$) was lower for patients who developed rifamycin-resistant \textit{M. tuberculosis} infection than for those who did not (AUC$_{0-24}$ 3.3 vs. 5.2 $\mu g$ $\times$ h/mL) and that a dose of <300 mg of rifabutin was associated with a lower rifabutin AUC$_{0-24}$, compared with a dose $\geq$300 mg of rifabutin [14].

Therapeutic levels of protease inhibitors and rifabutin were demonstrated in pharmacokinetic studies involving healthy subjects who received rifabutin 150 mg/day or 150 mg every other day with conventional [15] or boosted protease inhibitors [16, 17]. The levels of rifabutin and its 25-O-desacetyl metabolite in healthy subjects actually increased as a result of the lower dose of rifabutin coadministered with protease inhibitors, compared with the levels in healthy subjects that resulted from a full dose of rifabutin (300 mg/day) without a protease inhibitor. Unlike pharmacokinetic data derived from healthy adults, pharmacokinetic data derived from patients coinfected with tuberculosis and HIV demonstrated that the AUC$_{0-24}$, for a dose of rifabutin 300 mg thrice weekly (2.23 $\mu g$ $\times$ h/mL) or rifabutin 150 mg thrice weekly coadministered with lopinavir-ritonavir (3.06 $\mu g$ $\times$ h/mL) resulted in rifabutin levels that were similar to those associated with rifamycin-resistant \textit{M. tuberculosis} infection relapse and treatment failure in the Tuberculosis Trials Consortium Study 23 (<3.3 $\mu g$ $\times$ h/mL). By contrast, the AUC$_{0-24}$ for rifabutin 300 mg thrice weekly coadministered with lopinavir-ritonavir was 4.12 $\mu g$ $\times$ h/mL [18]. Past studies that have shown lower levels of isoniazid, rifampin, and ethambutol in HIV-infected patients with tuberculosis, compared with the levels in HIV-uninfected patients with tuberculosis, argue against extrapolating dosing recommendations for rifabutin and protease inhibitors from healthy control subjects [19, 20]. It is plausible that the currently recommended
dose of rifabutin may be inadequate for some HIV-infected patients.

The phenomenon of rifamycin resistance in HIV-infected patients with tuberculosis may hold important clues. Rifampin is believed to eliminate the persistent tubercle bacilli responsible for relapse [21]. The association between rifamycin-resistant M. tuberculosis infection relapse and HIV infection suggests that these persister bacilli may be relatively more important in patients with AIDS. Until more studies substantiate the favorable outcomes for both tuberculosis and HIV infection when a reduced dose of rifabutin is used with a ritonavir-boosted protease inhibitor, it might be prudent to document adequate drug concentrations, particularly in patients with very low CD4 cell counts who are at greatest risk for rifamycin-resistant M. tuberculosis infection relapse.

Acknowledgments


References