Serum Concentrations of Antimycobacterial Drugs in Patients with Pulmonary Tuberculosis in Botswana

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Background. We conducted a pharmacokinetic study of antimycobacterial drugs involving a cohort of patients with pulmonary tuberculosis (TB) in Gaborone, Botswana, to assess the prevalence of and risk factors for low drug concentrations in serum.

Methods. Adults participated if they had a history of cough ⩾2 weeks, had abnormal chest radiograph findings, consented to testing for human immunodeficiency virus (HIV), had sputum cultures positive for *Mycobacterium tuberculosis,* and were receiving antituberculous therapy for >7 days. Observed maximum serum concentrations were compared with published normal ranges.

Results. Of 91 patients enrolled, 89 (98%) were outpatients, and 59 (68%) of 87 patients tested had HIV infection. The following numbers of patients had low serum concentrations of the following drugs: isoniazid, 27 (30%) of 90; rifampin, 71 (78%) of 91; ethambutol, 37 (41%) of 91; and pyrazinamide, 1 (1%) of 91. Low serum concentrations of both isoniazid and rifampin occurred in 23 (26%) of 90 patients. Low serum concentrations of rifampin were found in both HIV-infected and non–HIV-infected patients, and such patients were less likely to have >4 weeks of symptoms, more likely to have lymphadenopathy, and more likely to have low serum albumin levels ($P < .05$ for all). The associations with noncavitary pulmonary disease ($P = .12$) and HIV infection ($P = .07$) did not reach statistical significance. Delayed absorption was most common with ethambutol, followed by rifampin.

Conclusions. These data, predominantly from HIV-infected patients with TB, suggest that low isoniazid, rifampin, and ethambutol concentrations are common in Botswana. In contrast, pyrazinamide usually is well absorbed.

Although most patients with tuberculosis (TB) respond well to treatment, failures of therapy and relapses remain an ongoing challenge [1, 2]. Nonadherence to therapy is a contributing factor, but even with directly observed therapy, treatment failures and relapses still occur [2, 3]. In some reports, patients with TB who were coinfected with HIV experienced higher rates of treatment failure, relapse, and acquired drug-resistance, but the precise causes were not known [4–8]. In con-

trast, treatment failures or relapses caused by rifampin-monoresistant organisms clearly have been associated with HIV infection [4].

Malabsorption of orally administered drugs is one explanation for adverse outcomes in treatment-compliant patients. Furthermore, selective malabsorption of ⩾1 of the drugs could promote drug resistance. Malabsorption has been defined as drug concentrations in serum that are lower than the expected normal range. Some (but not all) reports have suggested that coinfection with HIV is an important risk factor for malabsorption and may lead to adverse clinical outcomes [9–17]. Recent reports from the Centers for Disease Control and Prevention (CDC) show that, in HIV-seronegative patients receiving once weekly isoniazid and rifapentine therapy or in HIV-seropositive patients receiving twice weekly isoniazid and rifabutin, low

isoniazid and rifabutin serum concentrations are associated with adverse outcomes, including relapses, treatment failures, and the development of rifamycin resistance [18, 19].

To determine the prevalence of low serum concentrations of TB drugs and the associated patient characteristics, we studied a group of predominately ambulatory patients with pulmonary TB in Gaborone, Botswana. These patients reflect the typical experience of patients with TB in an urban center in sub-Saharan Africa, where comorbid conditions, including HIV infection and gastrointestinal disease, are prevalent.

METHODS

From July 1997 through November 1999, outpatients in Gaborone, Botswana, who were >17 years old were asked to participate in the study if they had a history of cough ⩾2 weeks, had abnormal chest radiograph findings, and consented to HIV testing. Patients who were determined to have sputum cultures positive for *Mycobacterium tuberculosis* and who were receiving daily, directly observed antituberculous therapy for at least 7 days could participate. The internal review boards of the Botswana Ministry of Health (MOH), CDC, University of California at Berkeley, and University of California at San Francisco approved the protocol, and all patients gave written consent.

Baseline evaluations included a questionnaire, physical examination, chest radiography, complete blood cell count, circulating CD4 lymphocyte count, HIV type 1 and HIV type 2 antibody measurements, and serum concentrations of albumin, creatinine, and alanine aminotransferase (ALT). Low serum albumin level was defined as <36 g/L, high creatinine level was defined as >97 μmol/L for male patients and >80 μmol/L for female patients, and high ALT level was defined as >41 U/L. Low hemoglobin level was defined as <13.5 g/dL. Three sputum specimens were collected for acid-fast staining and were cultured on LJ media. Stool samples were examined microscopically for ova and parasites and were cultured for bacteria.

Single-component antituberculous drugs were supplied by and administered in accordance with MOH guidelines (table 1). Samples of drugs were assayed by thin-layer chromatography for active drug content [20]. Patients fasted ⩾8 h prior to witnessed simultaneous ingestion of all drugs, and blood samples were drawn 1, 2, and 6 h after ingestion. Serum was separated and frozen at −70°C within 1 h after samples were obtained. Drug concentrations were assayed at National Jewish Medical and Research Center (NJMRC) in Denver, Colorado, using validated high-performance liquid chromatography (for isoniazid and rifampin) or gas chromatography (for pyrazinamide and ethambutol) with mass spectrometry [21–24].

Analyses of pharmacokinetic parameters were performed using noncompartmental techniques (WinNonlin PK software, version 4; Pharsight), consistent with previous reports [18, 19]. Maximum serum concentrations (C_{max}) and the times when

they occurred (T_{max}) were determined directly from the concentration-versus-time data, and the area under the serum concentration-time curve (AUC) was determined using the trapezoidal rule for $AUC_{0-6\ h}$. $AUC_{0-12\ h}$ was determined by extrapolating from 6 h to 12 h using standard formulas. Low C_{max} values were defined as follows, using published reference ranges that were determined worldwide beginning in the 1950s and were subsequently validated at NJMRC in the 1990's [21–28]: isoniazid, <3 μg/mL (300-mg dose) or <4 μg/mL (400-mg dose); rifampin, <8 μg/mL (weight-adjusted dose, 450 or 600 mg); pyrazinamide, <35 μg/mL (median dose, 35 mg/kg); and ethambutol, <2 μg/mL (median dose, 21 mg/kg). Very low C_{max} values were defined as follows: isoniazid, <2 μg/mL (300-mg dose) or <3 μg/mL (400-mg dose); rifampin, <4 μg/mL; pyrazinamide, <20 μg/mL; and ethambutol, <1 μg/mL. Delayed absorption was defined as a T_{max} >3 h. The elimination rate constant and the elimination half-life were calculated using the 2 h and 6 h concentrations, provided that the concentration at 2 h was greater than the concentration at 6 h. Isoniazid acetylator status was defined as fast if the half-life was <2 h and as slow if the half-life was ⩾2 h. A second acetylator status determination included only patients for whom the isoniazid concentration at 1 h was greater than the concentration at 2 h, to exclude patients with ongoing absorption.

For comparison, US pharmacokinetic data for intensively sampled healthy volunteers, HIV-negative patients with TB (i.e., the National Institutes of Health [NIH] A group), and sparsely sampled HIV-negative patients with TB (i.e., the NIH B group) were included [21–24, 29–31]. NIH B patients had samples collected at 2 h and 6 h after dosing only. Volunteers were studied after administration of single doses, and NIH A and NIH B patients were studied when drug concentrations has reached a steady state. Median values at each time point were calculated for each of these data sets. Concentrations for each drug were standardized to a common dose, to facilitate direct comparisons (isoniazid, 5 mg/kg; rifampin, 600 mg; pyrazinamide, 30 mg/kg; and ethambutol, 20 mg/kg).

Data were analyzed with Epi Info software, version 6.04d (CDC), and SPSS software (SPSS). The primary analyses compared C_{max} and $AUC_{0-6\ h}$ of HIV-infected versus non–HIV-infected patients for each drug separately (8 comparisons). Secondary analysis compared demographic data for HIV-infected and non–HIV-infected patients and patient characteristics associated with low serum drug concentrations. Statistically significant findings from these secondary analyses can only be considered suggestive of an association, given the problem of multiple comparisons. Categorical variables were analyzed using a χ^2 or Fisher's exact test, and continuous variables were analyzed using a Student's *t* test or analysis of variance procedure. Because of small sample sizes within subgroups and numerous variables associated with low concentration, multi-

Table 1. Botswana Ministry of Health daily dose guidelines for antimycobacterial drugs.

Drug	Dose in μg, by body weight	
	30–50 kg	>50 kg
Isoniazid	300	400[a]
Rifampin	450	600
Ethambutol	1000	1200
Pyrazinamide	1500	2000

[a] Not the standard dose.

variate analyses were not sufficiently powered for their data to be reported.

RESULTS

Through November 1999, a total of 293 eligible patients presented for care; 91 (31%) met all study criteria and were evaluated. HIV test results were available for 87 (96%) of 91 patients, and 59 (68%) of 87 test results were positive (table 2). HIV-infected patients had more oral thrush and lower CD4 cell counts than others (both $P < .01$). HIV-infected patients

were somewhat younger than others, were more likely to have had a prior episode of TB, were less likely to have had cavitary pulmonary disease, and were less likely to have had either diarrhea or unformed stools (P = not statistically significant [NS]). Only 8 (9%) of 91 patients reported diarrhea (defined as ⩾3 loose stools within a 24-h period) in the 2 weeks prior to the study, and none had evidence of bacterial or parasitic pathogens. All study drugs were identical (in terms of manufacturers and batches) to those drugs used concurrently in the clinics; all contained the correct drug, and all doses were within 85%–115% of the stated amount.

Pharmacokinetic results were available from all 91 patients for rifampin, ethambutol, and pyrazinamide, and from 90 patients for isoniazid (insufficient sample volume). The frequencies of low serum drug concentrations are displayed in table 3. Of the 91 patients studied, 81 (89%) had low concentrations of at least 1 drug (isoniazid in 30% [$n = 90$], rifampin in 78%, ethambutol in 41%, and pyrazinamide in 1%). Furthermore, 29 patients (32%) had very low concentrations of at least 1 drug (isoniazid in 12%, rifampin in 23%, ethambutol in 3%, and pyrazinamide in 0%). Of 90 patients evaluable, 23 (26%) had low isoniazid and rifampin concentrations, with 13 (57%)

Table 2. Demographic and clinical characteristics, by HIV infection status.

Characteristic	HIV infection ($n = 59$)	No HIV infection ($n = 28$)	P[a]
Median age, years	30	34.5	.10
Male sex, % of patients	59	71	.27
History of tuberculosis, % of patients	17	4	.10
Recent hospitalization, % of patients	15	11	.74
Inpatient at diagnosis, % of patients	3	0	1.00
Symptomatic for >4 weeks, % of patients	59	71	.27
Diarrhea within past 2 weeks, % of patients	5	18	.11
Nausea within past 2 weeks, % of patients	36	32	.75
Emesis within past 2 weeks, % of patients	27	18	.35
Weight loss reported, % of patients, % of patients	92	93	.83
Wasting at the time of physical examination, % of patients	69	71	.85
Thrush at the time of physical examination, % of patients	32	4	<.01
Unformed stool at the time of physical examination, % of patients	4[b]	19[c]	.07
Smear-positive sputum samples, % of patients	85	89	.74
Cavity on chest radiograph, % of patients	29	46	.11
Low serum hemoglobin level,[d] % of patients	90[e]	74[f]	.06
Mean CD4 cell count, cells/mm^3	236	565	<.01
Low serum albumin level,[g] % of patients	72[e]	64	.77
High creatinine level,[h] % of patients	34[e]	21	.22
High ALT level,[i] % of patients	10[e]	21	.17

NOTE. ALT, alanine aminotransferase.
[a] Secondary statistical analyses.
[b] $n = 46$.
[c] $n = 21$.
[d] Defined as <13.5 g/dL.
[e] $n = 58$.
[f] $n = 27$.
[g] Defined as <36 g/L.
[h] Defined as >97 μmol/L for men and >80 μmol/L for women.
[i] Defined as >41 U/L.

Table 3. Distribution of concurrent low serum drug-concentration values.

Drug	Isoniazid	Rifampin	Ethambutol	Isoniazid and rifampin
	Ratio (%) of patients with low serum drug-concentration values, by drug			
Overall	27/90 (30)	71/91 (78)	37/91 (41)	23/90 (26)
Isoniazid	…	23/70 (33)	15/37 (41)	…
Rifampin	23/27 (85)	…	29/37 (78)	…
Ethambutol	15/27 (56)	29/71 (41)	…	13/23 (57)
Pyrazinamide	0/27 (0)	1/71 (1)	1/27 (4)	0/23 (0)

of 23 also showing low ethambutol concentrations. Five patients (6%) had very low isoniazid and rifampin concentrations, and no patient had very low concentrations of 3 drugs.

Pharmacokinetic parameters are shown in tables 4–9. Pyrazinamide concentrations were statistically significantly lower in HIV-infected patients, although nearly all values were normal. Median isoniazid and rifampin concentrations were only modestly lower in HIV-infected patients (P = NS). Importantly, the concentrations of isoniazid, rifampin, and ethambutol were highly variable, and the median rifampin concentrations were well below the expected 8 μg/mL, regardless of HIV infection status. Given the limited number of samples per patient, the apparent T_{max} was similar for all drugs and patient groups. Delayed absorption (T_{max}, >3 h) was most common with ethambutol, followed by rifampin.

The $AUC_{0-6 h}$ values were similar regardless of HIV infection status, with the exception of pyrazinamide (which had lower $AUC_{0-6 h}$ values in HIV-infected patients). $AUC_{0-12 h}$ values, which required extrapolation using the calculated half-life, facilitate comparisons with other published studies. Note that the number of patients is variable for $AUC_{0-12 h}$, because it was not possible to calculate the half-life in patients with delayed absorption. Thirty-four (40%) of 86 patients for whom half-life could be calculated were fast acetylators of isoniazid, whereas the restricted data set (including only patients with a concentration at 1 h greater than the concentration at 2 h) showed that 26 (47%) of 55 patients were fast acetylators. HIV-infected patients had longer calculated pyrazinamide half-lives.

Table 4. Maximum serum concentration (C_{max}) of tuberculosis drugs, by HIV infection status.

Drug	Median C_{max} (range), μg/mL		P
	HIV infection (n = 59)	No HIV infection (n = 28)	
Isoniazid	3.99 (0–9.23)	4.35 (0.72–11.84)	.54
Rifampin	5.60 (0–13.71)	5.96 (2.16–14.63)	.89
Ethambutol	2.20 (0–6.91)	2.22 (1.01–7.00)	.73
Pyrazinamide	48.7 (35.6–118.8)	55.5 (36.7–78.9)	.01

Figures 1–4 compare serum concentrations across different studies. The study of healthy volunteers from the United States (who were dosed after an overnight fast) had the least variable data, and these data serve as the reference standards for these figures. Patients with TB from the United States who were sampled intensively (NIH A) or sparsely (NIH B) received their medications either fasted or fed, according to each patient's routine, to match real-world conditions at TB clinics in the United States. Finally, the data from the current study are divided into data from HIV-infected and non–HIV-infected patients. For isoniazid (figure 1), the median values for the Botswana patients, who also fasted prior to dosing, are comparable to the data from healthy volunteers in the United States. However, because of the variability in the absorption characteristics of isoniazid, 30% of these patients had low isoniazid concentrations, and the median values do not reflect these low outliers. US patients with TB had lower isoniazid concentrations, reflecting, in part, the negative impact of food on isoniazid absorption.

Figure 2 shows that rifampin absorption in the Botswana patients (fasted) was significantly lower than in the US patients with TB (fasted or fed) and lower still than in the US healthy volunteers (fasted). This is consistent with table 3, which shows that 78% of the Botswana patients had low rifampin values. Figure 3 shows that pyrazinamide is well absorbed under nearly all conditions, although the HIV-infected patients from Botswana showed lower absorption than did non–HIV-infected patients.

Finally, figure 4 shows that ethambutol absorption in the Botswana patients (fasted), as seen with rifampin, was significantly lower than in the US patients with TB (fasted or fed) and lower still than in the US healthy volunteers (fasted). This is consistent with table 3, which shows that 41% of the Botswana patients had low ethambutol values.

The following clinical characteristics were associated with low serum concentrations in the secondary data analyses. Among patients with low isoniazid serum concentrations, fewer were men (37% vs. 62%; P = .29), fewer had a prior history of TB (4% vs. 17%; P = .01), fewer reported laxative use (37% vs. 100%; P = .12), and more had low serum hemoglobin levels

Table 5. Median time to maximum serum concentration (T_{max}) of tuberculosis drugs, by HIV infection status.

Drug	Median T_{max} (range), h		P[a]
	HIV infection (n = 59)	No HIV infection (n = 28)	
Isoniazid	2 (2–6.0)	2 (1.8–6.1)	.47
Rifampin	2 (2–6.3)	2 (1.8–6.3)	.90
Ethambutol	2 (2–6.3)	2 (1.8–6.3)	.75
Pyrazinamide	2 (2–6.3)	2 (1.8–6.3)	.32

[a] Secondary statistical analyses.

Table 6. Delayed absorption of tuberculosis drugs, by HIV infection status.

	No. (%) of patients		
Drug	HIV infection (n = 59)	No HIV infection (n = 28)	P^a
Isoniazid	2 (3)	1 (4)	.95
Rifampin	17 (29)	8 (29)	.94
Ethambutol	20 (34)	12 (43)	.41
Pyrazinamide	8 (14)	1 (4)	.15

NOTE. Delayed absorption was defined as time to maximum serum concentration of >3 h.

[a] Secondary statistical analyses.

(96% vs. 80%; $P = .06$). For patients with low rifampin serum concentrations, the data were more suggestive of an association with HIV infection than was seen with the median pharmacokinetic parameter analysis. For patients with low rifampin serum concentrations, fewer had symptoms for >4 weeks (58% vs. 90%; $P = .01$), more had lymphadenopathy (37% vs. 5%; $P = .01$), fewer had cavities visible on chest radiographs (31% vs. 50%; $P = .12$), more had low serum albumin values (74% vs. 50%; $P = .04$), and more were HIV positive (72% vs. 50%; $P = .07$). For patients with low ethambutol serum concentrations, more were men (73% vs. 56%; $P = .09$), more had recent weight loss (100% vs. 87%; $P = .04$), more had low serum albumin levels (86% vs. 57%; $P = .01$), and more had low hemoglobin values (95% vs. 74%; $P = .04$). Given the problem of multiple comparisons, these associations should be viewed with caution.

DISCUSSION

Eighty-nine percent of these ambulatory patients with TB in Gaborone, Botswana, had low serum concentrations of at least 1 TB drug. Three-quarters of the patients had low rifampin concentrations, and approximately one-quarter had low rifampin plus low isoniazid concentrations. Furthermore, >40% of the patients had low ethambutol concentrations. Given the recent experience with US public health service TB trials 22 [18] and 23 [19], in which low concentrations of isoniazid and rifabutin during intermittent therapy were associated with poorer treatment outcomes, these results in Botswana are of concern. The lone bright spot in this report was pyrazinamide, which, consistent with the findings of previous reports [29, 32], is well absorbed in nearly all patients.

In the primary analyses, serum drug concentrations were not strongly associated with HIV infection or CD4 cell counts. HIV-infected patients did have lower pyrazinamide values than other patients, but nearly all of their values were in the normal range. In the secondary analyses, low rifampin concentrations were associated with a number of factors linked to HIV infection. Nonetheless, the median rifampin C_{max} and

$AUC_{0-6\,h}$ values were similar between HIV-infected and non–HIV-infected patients. Once again, we see a difference between North American patients, in whom HIV infection seems to be a factor associated with TB drug malabsorption, and patients from other continents, where such associations are not as apparent [9–17]. Importantly, we only tested Botswana patients with pulmonary TB, which differs from the common presentation of extrapulmonary TB in North American patients, and this may indicate differences in the degree of immunosuppression across patient groups.

Delayed absorption (T_{max}, >3 h) was common with ethambutol and rifampin, suggesting the need for samples obtained 2 h and 6 h after administration when therapeutic drug monitoring is considered for these drugs [26–28]. Although such testing is readily available within the United States, many countries lack such facilities. After controlling for the rate of drug absorption, the proportion of fast isoniazid acetylators (47%) was consistent with the expected value in African populations [23, 25, 28]. Because of the sparse sampling scheme and given the prolonged or delayed absorption in some patients, the half-life values should be considered only as rough estimates, but they are generally consistent with the published literature [21–30].

The reference ranges were based on extensive published experience in Europe, the United States, and the various British Medical Research Council studies that were conducted globally [28]. These ranges were confirmed at NJMRC with studies involving healthy volunteers that controlled for nutrition, concurrent medications, and adherence [21–24]. These ranges represent the expected drug concentrations in the serum and not the minimally effective concentration [26, 27]. The additional data for US patients with TB show real-world conditions, including the fact that some patients tolerate the TB drugs better with food in their stomachs. However, given the known deleterious effects of high-fat food on the absorption of isoniazid and rifampin, it would be advisable to restrict intake of such foods to a light snack [23, 24]. In the current study, all patients fasted before dosing; therefore, food was not a factor in the results. Our patients did not absorb rifampin and ethambutol

Table 7. Median area under the serum concentration-time curve (AUC) 0–6 h after the administration of tuberculosis drugs, by HIV infection status.

	Median $AUC_{0-6\,h}$ (range), $\mu g \times h/mL$		
Drug	HIV infection (n = 58)	No HIV infection (n = 28)	P
Isoniazid	15.1 (4.1– 35.0)	15.2 (2.6– 42.8)	.86
Rifampin	24.0 (7.0– 52.4)	21.7 (7.1– 52.9)	.74
Ethambutol	9.1 (3.7– 28.4)	9.4 (4.4– 24.9)	.66
Pyrazinamide	219 (156– 519)	241 (156– 372)	.06

Table 8. Median area under the serum concentration-time curve (AUC) 0–12 h after the administration of tuberculosis drugs, by HIV infection status.

Drug	HIV infection		No HIV infection		
	No. of patients	Median AUC$_{0-12\,h}$ (range)[a], μg/mL per h	No. of patients	Median AUC$_{0-12\,h}$ (range)[a], μg/mL per h	P[b]
Isoniazid	56	18.1 (5.4–51.1)	26	17.9 (3.2–53.0)	.97
Rifampin	41	36.3 (10.8–95.0)	20	34.7 (15.5–77.4)	.88
Ethambutol	51	16.9 (9.1–43.8)	27	17.5 (7.4–30.1)	.27
Pyrazinamide	36	385(247–705)	14	424 (259–737)	.29

[a] Extrapolated from 6 h to 12 h using the calculated half-life.
[b] Secondary statistical analyses.

(and, to a lesser degree, isoniazid) as well as historical control subjects.

Rifampin-monoresistant TB occurs almost exclusively in HIV-infected patients, suggesting that HIV infection or an associated condition is the cause [4, 18, 19]. HIV-infected patients may have a greater total body burden of *M. tuberculosis* and a lesser ability to contain their spread systemically. Low drug concentrations would be expected to exacerbate this problem. Clearly, HIV-infected patients who are treated with highly intermittent regimens containing isoniazid and a rifamycin are at particular risk for acquired rifamycin resistance [33, 34]. In our study of daily isoniazid and rifampin therapy, there was a modest association between low rifampin concentrations and HIV infection (76% of 69 HIV-positive patients vs. 50% of 18 HIV-negative patients; $P = .07$). We may not have had sufficient power to fully assess this relationship. HIV-infected patients do represent a large and diverse group of patients, and identifying HIV infection alone may not differentiate between those more likely and those less likely to malabsorb their TB drugs.

Additional factors, such as infectious gastroenteritis, hypoalbuminemia, and gastric achlorhydria, all could impair drug absorption. The lack of demonstrable enteric pathogens revealed by stool examination discounts but does not eliminate an infectious cause for the malabsorption. The relatively low frequency of diarrhea in this patient population suggests that

diarrhea was not the major factor causing low drug concentrations in serum. Hypoalbuminemia was prevalent among our patients and was associated with low rifampin and ethambutol concentrations. Low serum albumin levels reduce intravascular oncotic pressure and could lead to edema, thickening of the intestinal wall, and impaired drug absorption. Hypoalbuminemia could also make more rifampin available for hepatic clearance.

This study had several limitations. The sample size was relatively small, and most patients were HIV infected, limiting our ability to assess the impact of HIV status on serum drug concentrations. Strict protocols were in place to ensure specimen integrity, and we found no evidence that sample mishandling led to falsely low concentrations, but that is a theoretical concern in any such study. Finally, the problem of multiple comparisons limited our ability to characterize the associations between low serum concentrations and the clinical characteristics of the patients.

Early clinical trials demonstrated that, in combination with isoniazid, a daily rifampin dose of 450 mg, compared with 600 mg, resulted in a higher incidence of treatment failure, supporting the notion that moderate malabsorption of rifampin could lead to adverse outcomes [35]. Those results are consistent with the accumulated data showing a clear dose-response relationship for rifampin [26, 27]. Low and variable rifampin

Table 9. Median half-life of tuberculosis drugs, by HIV infection status.

Drug	HIV infection		No HIV infection		
	No. of patients	Median half-life (range),[a] h	No. of patients	Median half-life (range),[a] h	P[b]
Isoniazid	56	2.26 (1.30–5.65)	26	2.15 (1.30–>10)	.16
Rifampin	41	3.02 (1.81–>10)	20	2.88 (1.56–>10)	.29
Ethambutol	51	4.12 (1.81–>10)	27	4.36 (2.17–>10)	.58
Pyrazinamide	36	9.19 (2.56–>20)	14	7.41 (4.30–>20)	.02

[a] Half-life values >10 h (or >20 h with pyrazinamide) represent falsely high values because of prolonged or delayed absorption.
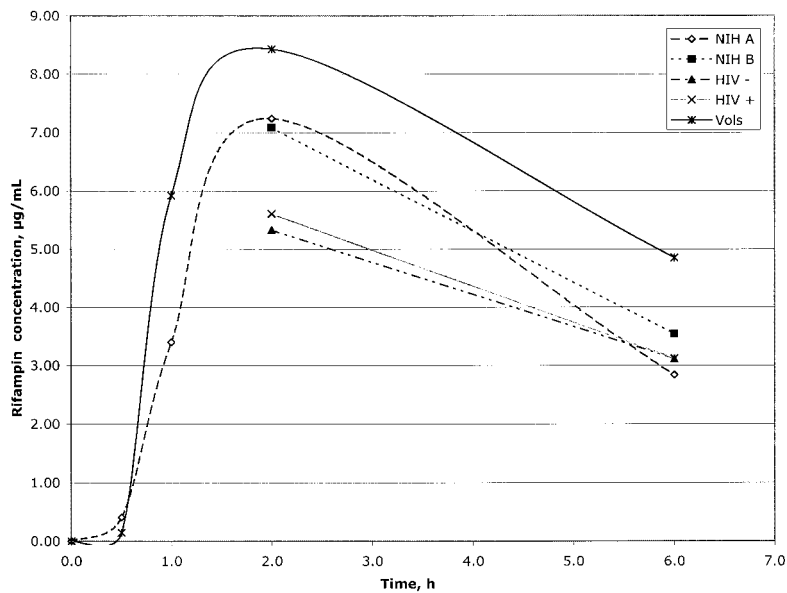[b] Secondary statistical analyses.
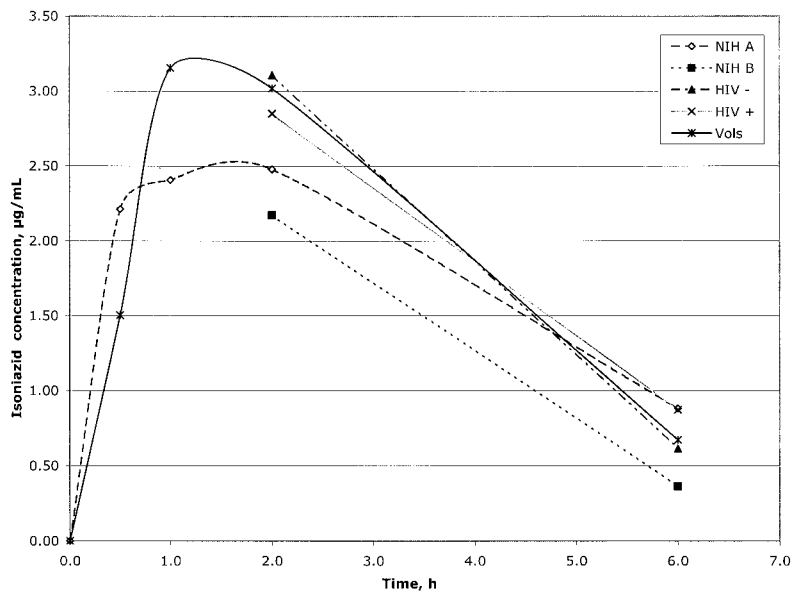
Figure 1. Isoniazid serum concentrations for healthy volunteers from the United States (Vols), intensively sampled HIV-negative US patients with tuberculosis (TB) (NIH A), sparsely sampled HIV-negative US patients with TB (NIH B), and patients with TB from Botswana who were HIV infected (HIV+) or non–HIV infected (HIV−).

absorption was common in our study (found in 78% of patients) and in a recent AIDS Clinical Trials Group study of US patients with pulmonary TB who were coinfected with HIV and treated with daily rifampin (600 mg) (found in 26 [76%] of 34 patients) (D. Perlman, personal communication). Rifampin is the cornerstone of short-course antituberculous chemotherapy, and it clearly exhibits concentration-dependent kill-

ing of mycobacteria [26, 27, 36]. It would be advisable to restudy the use of higher doses of rifampin within the context of controlled clinical trials [36].

For isoniazid, it appears that the pharmacodynamically linked variable is exposure over time [18, 19, 27]. Pyrazinamide shows a dose-response relationship for both efficacy and hepatotoxicity [37, 38]. Although the pharmacodynamically linked
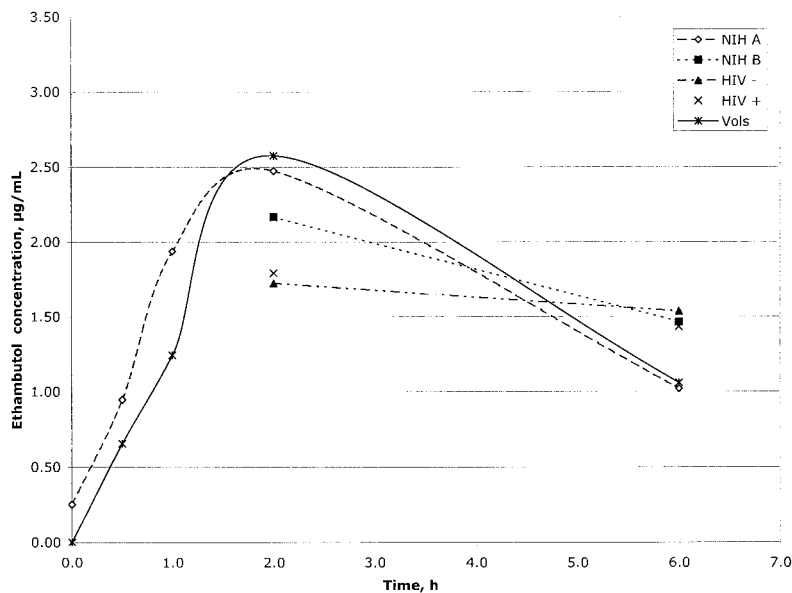

Figure 2. Rifampin serum concentrations for healthy volunteers from the United States (Vols), intensively sampled HIV-negative US patients with tuberculosis (TB) (NIH A), sparsely sampled HIV-negative US patients with TB (NIH B), and patients with TB from Botswana who were HIV infected (HIV+) or non–HIV infected (HIV−).
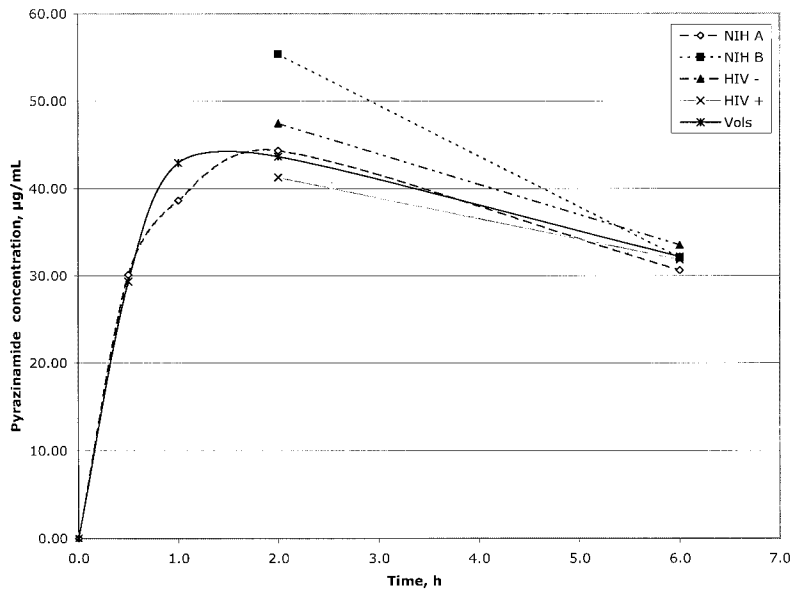
Figure 3. Pyrazinamide serum concentrations for healthy volunteers from the United States (Vols), intensively sampled HIV-negative US patients with tuberculosis (TB) (NIH A), sparsely sampled HIV-negative US patients with TB (NIH B), and patients with TB from Botswana who were HIV infected (HIV+) or non–HIV infected (HIV−).

variable for ethambutol has yet to be defined, doses of <12 mg/kg per day appear to be no more effective than placebo [27, 30, 39]. Also, it is clear that some minimum serum concentration is required for antituberculosis activity for any of these drugs. Our growing knowledge of TB drug pharmacodynamics should allow us to better understand the implications of low serum drug concentrations. Other variables, such as the extent

of disease, tissue destruction, total body burden of organisms, effectiveness of the host immune response, and adherence to the regimen play a role in the outcome of treatment. Therefore, it is unlikely that any serum concentration range will be therapeutic for all patients. The current normal ranges provide the best available reference regarding the completeness of drug absorption [26–28]. In summary, in a cohort of ambulatory pa-

Figure 4. Ethambutol serum concentrations for healthy volunteers from the United States (Vols), intensively sampled HIV-negative US patients with tuberculosis (TB) (NIH A), sparsely sampled HIV-negative US patients with TB (NIH B), and patients with TB from Botswana who were HIV infected (HIV+) or non–HIV infected (HIV−).

tients with TB in Botswana, low serum concentrations of the antimycobacterial drugs were common, and patients with low concentrations of those drugs could not be reliably identified using clinical and epidemiologic information.

Acknowledgments

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