Pharmacokinetics of Antimycobacterial Drugs in Patients with Tuberculosis, AIDS, and Diarrhea

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To test the hypothesis that antituberculous drug disposition is altered in patients with AIDS, we studied the steady-state pharmacokinetics of isoniazid (300 mg/d), rifampin (600 mg/d), and pyrazinamide (1,500 mg/d) in 29 adults (14 patients infected with human immunodeficiency virus [HIV] and 15 non-HIV-infected patients) with tuberculosis in Nairobi, Kenya. Intestinal integrity was assessed with xylose. Neither HIV infection nor diarrhea accounted for the interpatient variability in the area-under-the-plasma concentration vs. time curve (AUC), the maximum concentration, or the terminal half-life (t1/2) of isoniazid, rifampin, and pyrazinamide. No significant association between HIV infection or diarrhea and pharmacokinetics was seen for any of the compounds. In addition, neither the AUC nor the t1/2 of any of these drugs reflected interpatient differences in CD4 lymphocyte counts. Xylose absorption was uniformly low. We did not demonstrate that HIV infection, diarrhea, or CD4 lymphocyte counts contributed significantly to the variability in pharmacokinetics of isoniazid, rifampin, and pyrazinamide in TB patients in Nairobi.

Although most HIV-infected patients with tuberculosis (TB) respond well to rifampin-based antimycobacterial drug regimens [1–8], recent reports suggest that malabsorption of antimycobacterial drugs occurs in selected HIV-infected patients with TB—particularly those with advanced HIV infection [9–13]. In case reports involving a total of 34 patients with AIDS and TB and in two case series (one involving 26 patients with AIDS and TB and another involving 15 patients with AIDS and disseminated Mycobacterium avium complex disease), malabsorption of antimycobacterial drugs was suggested by much-reduced serum levels, which were measured 2 hours after oral administration of the drugs [9–13]. The timing of such screening relative to dosing was based on data for non-HIV-infected patients, and the possibility of delayed absorption was not taken into account.

Serial measurements allowing determination of standard pharmacokinetic parameters (area-under-the-plasma concentration vs. time curve [AUC], the maximum plasma concentration [Cmax], and time to maximum plasma concentration [Tmax]) are more accurate measures of drug bioavailability but have been reported for only one HIV-infected patient with TB [11]. Existing dose-response data and serum-concentration response data [14–17] suggest that reduced bioavailability of antimycobacterial drugs could have serious consequences for HIV-infected patients with TB, such as delayed or incomplete response to treatment or selection for drug resistance.

Our objectives were to study the pharmacokinetics of three antimycobacterial drugs—isoniazid, rifampin, and pyrazinamide—in HIV-infected and non-HIV-infected patients with TB to determine if HIV infection alters the bioavailability of these drugs and to determine whether altered bioavailability is related to the stage of HIV infection, as measured by CD4 lymphocyte counts, and the presence or absence of diarrhea. The relationship between the absorption of antituberculous drugs and that of xylose, a sugar commonly used to measure intestinal integrity, was also evaluated.

Methods

Over a 1-year period beginning on 1 November 1994, all adults (i.e., patients ≥17 years of age) who presented to the Infectious Disease Hospital in Nairobi, Kenya, with sputum smear–positive pulmonary TB and who were not prisoners were evaluated prospectively for entry into a study of antimycobacterial-drug pharmacokinetics. Patients were required to meet all of the following criteria: (1) no current ingestion of antimycobacterial drugs; (2) no current ingestion of antifungal drugs; (3) no coexisting medical illness that may interfere with drug pharmacokinetics, apart from HIV infection or diarrhea; (4) no significant hepatic or renal dysfunction (levels of transaminases, alkaline phosphatase, and total bilirubin <3 times normal and normal levels of urea and creatinine); (5) no previous gastrointestinal surgery; (6) willingness to give informed consent.

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All patients meeting these criteria were admitted to the hospital, and baseline demographic, clinical, and laboratory data were collected. Oral first-line antimycobacterial drug therapy with isoniazid (300 mg/d), rifampin (600 mg/d [or 450 mg/d if the patient weighed less than 45 kg]), ethambutol (800 mg/d), and pyrazinamide (1,500 mg/d) was prescribed. Steady-state pharmacokinetic studies of isoniazid, rifampin, and pyrazinamide were performed on day 14.

**Demographic, clinical and laboratory data.** For each patient, the age at diagnosis of TB and sex were recorded. Height (m) and weight (kg) were measured, and the body mass index (kg/m²) was calculated. Note was made of any drugs other than antimycobacterial drugs being administered, and the presence or absence of diarrhea (three or more unformed stools per day for ≥3 days) and wasting (involuntary weight loss of >10% of baseline body weight) was also noted.

Stool samples were cultured for bacterial enteropathogens and examined for ova and parasites (by means of wet mount, trichrome staining, and modified acid-fast staining for cryptosporidia) at the Kenmi Microbiology Laboratories, Nairobi. Testing for antibodies to HIV (two independent ELISAs were performed, with pretest and posttest counseling) and a lymphocyte subset analysis (Becton Dickinson, Mississauga, Ontario, Canada) were performed at the World Health Organization Collaborative Centre for STD and HIV Control, Nairobi.

**Pharmacokinetic protocol.** Patients were not allowed to receive anything by mouth after midnight of day 13, and on day 14, heparin locks were established. At 0700, each patient was given 5 g of xylose in 100 mL of water. At 0800 (time 0), antimycobacterial drugs were administered with 150 mL of water while the patients were in upright positions. Patients were not permitted to eat or assume a completely recumbent position for 2 hours after ingestion of the drugs. Blood samples were obtained just before drug ingestion at time 0 (trough) and at 30 minutes, 60 minutes, 90 minutes, 120 minutes, 4 hours, 6 hours, 8 hours, and 12 hours after drug ingestion. Ascorbic acid was added to the blood tubes before the specimens were centrifuged, and the plasma was stored at −70°C.

**Pharmaceutical assays and assay of xylose.** All samples remained frozen until assay. Plasma levels of the three antimycobacterial drugs (isoniazid, rifampin, and pyrazinamide) were measured in the Clinical Investigation Unit of the Ottawa General Hospital, Ottawa, Ontario, Canada. Assays were performed in a blinded fashion with use of high-performance liquid chromatography (HPLC).

The HPLC method used to measure levels of isoniazid and its acetyl metabolite was that described by Hutchings et al. [18] and modified by Gallicano et al. [19]. Patients were classified as fast acetylators on the basis of an isoniazid t₁/₂ (terminal half-life) of <130 minutes [20]. The HPLC assays used to measure levels of rifampin and pyrazinamide were those described by Swart and Papgis [21], and Brouard et al. [22], respectively.

All assays had previously been validated and approved by Health Canada (Ottawa, Ontario, Canada) and were specific for the drugs of interest in the presence of nonantimycobacterial drugs used by the patients. In addition, all assays complied with the College of American Pathologists guidelines for reproducibility and quality control.

Xylose was measured in serum drawn at time 0 (1 hour after xylose ingestion) by a colorimetric method [23]. On the assumption that xylose does not occur naturally and in an effort to minimize sampling blood loss, baseline xylose levels were not measured.

**Pharmacokinetic data analysis.** Appropriate ‘‘model-independent’’ pharmacokinetic parameters were determined from the plasma concentration-time profiles for each participant drug. The highest plasma drug concentration observed over the dose interval at steady-state (Cₘₐₓ) and the time at which it occurred (Tₘₐₓ) were determined. The AUC was determined over a dosing interval by using the trapezoidal rule. The terminal elimination rate constant was calculated by least squares regression of the natural logarithm of the plasma drug concentration vs. time for the terminal linear portion. The t₁/₂ was calculated by dividing the terminal disposition rate constant into 0.693 [24]. The AUC and Cₘₐₓ were normalized to a body dose interval at steady-state (Cₘₐₓ) and the time at which it occurred (Tₘₐₓ) were determined. The AUC was determined over a dosing interval by using the trapezoidal rule. The terminal elimination rate constant was calculated by least squares regression of the natural logarithm of the plasma drug concentration vs. time for the terminal linear portion. The t₁/₂ was calculated by dividing the terminal disposition rate constant into 0.693 [24]. The AUC and Cₘₐₓ were normalized to a body weight of 70 kg and to doses of 300 mg for isoniazid, 600 mg for rifampin, and 1,500 mg for pyrazinamide. The code was broken after completion of the analytical and pharmacokinetic analyses.

Analysis of variance (ANOVA) (SYSTAT; SYSTAT Inc., Evanston, IL [25]) was used to assess the potential for HIV infection, diarrhea, or an association between them to account for interpatient variability in AUC, Cₘₐₓ, and t₁/₂. ANOVA was also used to assess the potential for CD4 lymphocyte counts to account for interpatient variability in AUC and t₁/₂ [25]. The influence of acetylator status on AUC and t₁/₂ of isoniazid was included in the ANOVA model. The Bonferroni correction factor was applied to control for the type I error rate, resulting in a P value of .05 indicating significance. The χ² test and the Student’s t test were applied to determine the significance between discrete and continuous variables, respectively, with use of SYSTAT [25]. Differences (P < .05) for two-tailed tests were considered significant.

**Results**

Over the 1-year study period, 465 patients with sputum smear–positive pulmonary TB presented to the Infectious Disease Hospital. Of these patients, 30 adults met the study entry criteria and were admitted to the hospital for baseline data collection and administration of antimycobacterial drugs. The pharmacokinetics of the drugs could not be studied in one patient who died while receiving treatment. The baseline demographic, clinical, and laboratory data on the remaining 29 patients (14 HIV-infected patients and 15 non-HIV-infected patients) are shown in table 1.
T lymphocyte subset analyses were not performed for eight patients (three, HIV-infected; five, non-HIV-infected). HIV-infected and noninfected patients did not differ significantly with respect to age, sex, body mass index, wasting, or CD8 lymphocyte counts. Diarrhea was significantly more common among HIV-infected patients (50%) than among non-HIV-infected patients (27%), and CD4 lymphocyte counts and CD4/CD8 ratios were significantly lower among HIV-infected patients than among non-HIV-infected patients (155/mm³ vs. 556/mm³ and 0.24 vs. 0.97, respectively). (P < .05). Eight (all HIV-infected) of the 21 patients for whom lymphocyte subset analyses were performed had CD4 lymphocyte counts of <200/mm³. Stool cultures for enteropathogens and stool examinations for ova and parasites were negative for all 29 patients.

Three patients were taking nonantimycobacterial drugs; one non-HIV-infected patient was taking indomethacin, and another was taking trimethoprim-sulfamethoxazole; one HIV-infected patient was taking amoxicillin, metronidazole, and N-butylscopolammonium bromide (Buscopan).

Standard doses of antimycobacterial drugs were administered to all but nine patients (four, HIV-infected; five, non-HIV-infected). These patients weighed <45 kg at baseline and thus received 450 mg of rifampin. The plasma concentration-time data allowed for a complete determination of the pharmacokinetics of isoniazid in 25 patients, rifampin in 29 patients, and pyrazinamide in 26 patients.

Determinations of isoniazid pharmacokinetics were incomplete for two patients. For isoniazid, the acetylator status was determined in 25 of the 29 patients; incomplete pharmacokinetic data precluded acetylator phenotyping in four patients. There were five fast acetylators (four, HIV infected) and 20 slow acetylators (eight, HIV infected). ANOVA showed no association of acetylator status with any pharmacokinetic parameters. As expected, the effects of acetylator status were significant for the AUC and t½, with a shorter mean isoniazid t½ (±SD) observed for fast acylators (1.74 ± .23 hours) than for slow acylators (3.57 ± 1.12 hours) and a lower mean AUC (±SD) observed for fast acylators (4.05 ± 1.85 mg/[L·h]) than for slow acylators (12.02 ± 8.69 mg/[L·h]) (P < .05).

The pharmacokinetic characteristics of isoniazid, rifampin, and pyrazinamide, according to the presence or absence of HIV infection and diarrhea, are given in Table 2. Neither diarrhea nor HIV infection accounted for the interpatient variability in AUC or Cmax of isoniazid, rifampin, or pyrazinamide; the mean AUC (±SD) (mg/[L·h]) and the mean Cmax (±SD) (mg/L) were not significantly different for HIV-infected patients than for non-HIV-infected patients or those with or without diarrhea. In addition, no significant association between the presence of HIV or diarrhea and pharmacokinetic properties was seen for any of the compounds. The nonnormalized Cmax for isoniazid was <3 mg/L in 24 (89%) of 27 patients; for rifampin, <8 mg/L in 26 (90%) of 29 patients; and for pyrazinamide, <30 mg/L in 2 (8%) of 26 patients.

The t½ data supported the conclusion that drug disposition was unaffected by HIV infection or diarrhea; there was no significant difference in the t½ (hours) of isoniazid, rifampin, or pyrazinamide in HIV-infected patients vs. non-HIV-infected patients or in patients with or without diarrhea. No association with HIV infection or diarrhea was reflected in the t½ data for isoniazid, rifampin, or pyrazinamide.

The mean time (±SD) to achieve Cmax (Tmax) was also not significantly different in HIV-infected patients (isoniazid, 2.3 ± 1.6 hours; rifampin, 2.4 ± 1.5 hours; and pyrazinamide, 2.1 ± 0.5 hours). These times are not significantly different from the mean values in non-HIV-infected patients (isoniazid, 2.4 ± 1.2 hours; rifampin, 1.9 ± 0.9 hours; and pyrazinamide, 1.6 ± 0.7 hours). Thus, HIV infection and diarrhea did not affect the bioavailability of isoniazid, rifampin, or pyrazinamide, as measured by AUC or Cmax, the elimination phase rate constant k (h⁻¹), and the half-life t½ (hours) of the isoniazid, rifampin, or pyrazinamide in HIV-infected patients (isoniazid, 2.3 ± 1.6 hours; rifaprim, 2.4 ± 1.5 hours; and pyrazinamide, 2.1 ± 0.5 hours).

<table>
<thead>
<tr>
<th>Variable</th>
<th>HIV-infected (n = 14)</th>
<th>Non-HIV-infected (n = 15)</th>
<th>Total (n = 29)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (y) ± SD</td>
<td>34.3 ± 7.1</td>
<td>28.9 ± 7.2</td>
<td>31.5 ± 7.5</td>
<td>.054</td>
</tr>
<tr>
<td>No. of indicated sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
<td>12</td>
<td>21</td>
<td>NS</td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
<td>3</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Mean BMI ± SD (kg/m²)</td>
<td>17.3 ± 1.9</td>
<td>16.7 ± 2.3</td>
<td>17.0 ± 2.1</td>
<td>NS</td>
</tr>
<tr>
<td>No. with diarrhea*</td>
<td>7</td>
<td>4</td>
<td>11</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>No. without diarrhea</td>
<td>7</td>
<td>11</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>No. with wasting*</td>
<td>13</td>
<td>12</td>
<td>25</td>
<td>NS</td>
</tr>
<tr>
<td>No. without wasting</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Mean CD4 lymphocyte count ± SD (mm³)</td>
<td>155 ± 150</td>
<td>556 ± 213</td>
<td>346 ± 272</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean CD8 lymphocyte count ± SD (mm³)</td>
<td>632 ± 356</td>
<td>616 ± 243</td>
<td>624 ± 300</td>
<td>NS</td>
</tr>
<tr>
<td>Mean CD4/CD8 lymphocyte ratio ± SD</td>
<td>.24 ± .20</td>
<td>.97 ± .45</td>
<td>.59 ± .50</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

NOTE. BMI = body mass index; NS = not significant.
* See text for definitions of diarrhea and wasting
† Lymphocyte subset analyses were not available for eight patients (three, HIV-infected; five, non-HIV-infected).
Table 2. Pharmacokinetics of isoniazid, rifampin, and pyrazinamide, according to the presence or absence of HIV infection and diarrhea.

<table>
<thead>
<tr>
<th>Drug, pharmacokinetic data</th>
<th>Patients with HIV infection</th>
<th>Patients without HIV infection</th>
<th>Patients with diarrhea</th>
<th>Patients without diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC (mg/[L·h])</td>
<td>7.9 ± 7.3</td>
<td>6.3 ± 3.5</td>
<td>8.8 ± 6.3</td>
<td>5.7 ± 4.8</td>
</tr>
<tr>
<td>C_{max} (mg/L)</td>
<td>1.4 ± 0.8</td>
<td>1.1 ± 0.4</td>
<td>1.3 ± 0.5</td>
<td>1.2 ± 0.7</td>
</tr>
<tr>
<td>T_{1/2} (h)</td>
<td>3.2 ± 1.6</td>
<td>3.3 ± 0.9</td>
<td>3.5 ± 1.4</td>
<td>2.9 ± 1.1</td>
</tr>
<tr>
<td>Rifampin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC (mg/[L·h])</td>
<td>23.1 ± 12.9</td>
<td>19.6 ± 10.6</td>
<td>24.0 ± 13.9</td>
<td>19.3 ± 9.9</td>
</tr>
<tr>
<td>C_{max} (mg/L)</td>
<td>4.1 ± 2.0</td>
<td>4.3 ± 2.4</td>
<td>4.2 ± 2.1</td>
<td>4.1 ± 2.3</td>
</tr>
<tr>
<td>T_{1/2} (h)</td>
<td>2.8 ± 1.2</td>
<td>2.0 ± 0.7</td>
<td>2.8 ± 1.4</td>
<td>2.1 ± 0.6</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC (mg/[L·h])</td>
<td>350 ± 111</td>
<td>382 ± 143</td>
<td>407 ± 148</td>
<td>336 ± 103</td>
</tr>
<tr>
<td>C_{max} (mg/L)</td>
<td>32.1 ± 8.8</td>
<td>33.1 ± 8.2</td>
<td>33.9 ± 9.0</td>
<td>31.7 ± 8.1</td>
</tr>
<tr>
<td>T_{1/2} (h)</td>
<td>7.4 ± 1.6</td>
<td>6.9 ± 2.1</td>
<td>7.8 ± 1.9</td>
<td>6.7 ± 1.8</td>
</tr>
</tbody>
</table>

NOTE. Data (mean value ± SD) were normalized to a 300-mg dose of isoniazid, a 600-mg dose of rifampin, a 1,500-mg dose of pyrazinamide, and 70 kg of body weight. AUC = area under the plasma concentration vs. time curve; C_{max} = maximum concentration; T_{1/2} = terminal half-life.

2.2 ± 1.5 hours) than in non-HIV-infected patients (isoniazid, 2.3 ± 1.4 hours; rifampin, 2.3 ± 0.9 hours; and pyrazinamide, 2.2 ± 1.1 hours) or in those with diarrhea (isoniazid, 2.5 ± 1.8 hours; rifampin, 2.8 ± 1.5 hours; and pyrazinamide, 2.4 ± 1.6 hours) or without diarrhea (isoniazid, 2.1 ± 1.2 hours; rifampin, 2.0 ± 0.8 hours; and pyrazinamide, 2.0 ± 1.1 hours).

The relationship between the bioavailability (AUC) and elimination (T_{1/2}) of isoniazid, rifampin, and pyrazinamide and the CD4 cell count are plotted in figures 1, 2, and 3. Neither the AUC nor the T_{1/2} of isoniazid, rifampin, and pyrazinamide was affected by interpatient differences in CD4 cell counts.

Xylose was measured in the trough blood samples of 20 patients (12 HIV-infected and eight non-HIV-infected). For nine patients, there was an insufficient amount of plasma to complete the assay. After correction for body surface area, we found that all but four patients had xylose levels of <0.1 mmol/L.

One non-HIV-infected patient had a xylose level of 0.1 mmol/L, and three HIV-infected patients had levels of 0.17 mmol/L. None of the patients had a level that was in the normal range, according to our hospital (i.e., 0.6–1.3 mmol/[L·1.73 m^2]; Department of Clinical Chemistry, Health Sciences Centre, Winnipeg, Manitoba, Canada).

Discussion

Provided HIV-infected patients with TB are treated with a rifampin-based instead of a thiacetazone-based regimen (the
Figure 2. The relationship between the rifampin area under the plasma concentration vs. time curve (AUC) normalized to 70 kg of body weight (A) and terminal half-life ($t_{1/2}$) (B) and the CD4 cell count. $\bullet$ = HIV-infected patients; $\circ$ = non-HIV-infected patients. Normal mean rifampin AUC $\pm$ SE, 49.7 $\pm$ 10.2; normal mean $t_{1/2}$ $\pm$ SE, 1.4 $\pm$ 0.3; normal CD4 cell count, 546–1,276/mm$^3$.

latter has been associated with a higher relapse rate), response to antitubercular therapy is generally good and comparable to that of non-HIV-infected patients [1–8]. In a joint statement by members of the American Thoracic Society and investigators at the Centers for Disease Control and Prevention on the treatment of TB and TB infection in adults and children, a three-drug (initial phase), 6-month regimen for both HIV-infected and non-HIV-infected persons with drug-susceptible disease is recommended [26].

Nevertheless, it appears that in some HIV-infected patients with TB (particularly those with advanced HIV infection who malabsorb their antitubercular drugs), concentrations of many drugs including isoniazid, rifampin, and, to a lesser extent, pyrazinamide in blood drawn 2 hours after oral ingestion—an approximation of peak concentrations or $C_{\text{max}}$—are often well below the expected normal range (i.e., isoniazid, 3–5 mg/L; rifampin, 8–24 mg/L; and pyrazinamide, 30–40 mg/L) [27, 28]. These low levels were measured in patients who were determined to have AIDS on the basis of the pre-1993 definition (i.e., they had advanced HIV infection associated with either extrapulmonary TB or disseminated $M. avium$ complex, or they had TB plus another AIDS-defining illness). In 1993, the surveillance case definition of AIDS was modified to include pulmonary TB [29, 30].

Whether such low “peak” drug levels truly represent a low $C_{\text{max}}$ and AUC that threaten the adequacy of standard therapy and whether low levels correlate with the degree of immunosuppression (CD4 cell counts) or the presence of diarrhea is un-

Figure 3. The relationship between the pyrazinamide area under the plasma concentration vs. time curve (AUC) normalized to 70 kg of body weight (A) and terminal half-life ($t_{1/2}$) (B) and the CD4 cell count. $\bullet$ = HIV-infected patients; $\circ$ = non-HIV-infected patients. Normal mean pyrazinamide AUC $\pm$ SE, 544.9 $\pm$ 42.3; normal mean $t_{1/2}$ $\pm$ SE, 8.1 $\pm$ 0.6; normal CD4 cell count, 546–1,276/mm$^3$. 
known. Dose-response data [14–17] and the findings in recent case reports [11] suggest that low concentrations may indeed lead to therapeutic failures and/or drug resistance. Pharmacokinetic studies in HIV-infected patients from North America without TB suggest that malabsorption of antimycobacterial drugs increases as HIV disease becomes more advanced (as determined by lower CD4 cell counts and the presence of diarrhea) [31].

In the present study, we measured the pharmacokinetic parameters of orally administered isoniazid, rifampin, and pyrazinamide in 29 patients with TB, 14 of whom were infected with HIV and 15 of whom were not infected with the virus. This study was performed in Africa, where as many as 90% of patients with AIDS are reported to have gastrointestinal dysfunction [32]. We found that neither diarrhea nor HIV accounted for the interpatient variability in the AUC, \( C_{\text{max}} \), or \( t_{1/2} \) of isoniazid, rifampin, and pyrazinamide. Furthermore, no significant association between the presence of HIV or diarrhea and pharmacokinetics was seen for any of the compounds, and neither the variability in bioavailability (AUC) nor the variability in elimination (\( t_{1/2} \)) of isoniazid, rifampin, and pyrazinamide was explained by interpatient differences in CD4 cell counts.

Although four antimycobacterial drugs (isoniazid, rifampin, pyrazinamide, and ethambutol) were administered to each patient (initial coverage allowed for the possibility of drug resistance), our analysis was limited to the study of isoniazid, rifampin, and pyrazinamide, as a parental alternative is available for ethambutol (streptomycin), and we wished to keep sampling blood loss at a minimum.

Because testing for antibodies to HIV is not routinely performed for TB patients in Nairobi and because most TB patients who presented to the hospital were excluded from the study either because they were prisoners or because they refused to consent to the necessary 2-week hospitalization, it is possible that our study included a more debilitated subset of both HIV-infected and non-HIV-infected patients.

Variation in the rate of elimination of isoniazid is a function of metabolism and is known to have a bimodal distribution, which is primarily based on an individual’s genetically controlled acetylator phenotype [28]. As expected, the effects of acetylator status were significant for the AUC and \( t_{1/2} \), with shorter half-lives and lower AUC values observed in fast acetylators than in slow acetylators. However, there was no association of acetylator status with any of the pharmacokinetic parameters measured.

When we compared the absolute values of the observed \( (C_{\text{max}}, T_{\text{max}}) \) and calculated \( (AUC, t_{1/2}) \) pharmacokinetic parameters for isoniazid, rifampin, and pyrazinamide with the values cited in the literature on non-HIV-infected patients with TB [33], we noted across-the-board reduced bioavailability of isoniazid and, to a lesser extent, rifampin. This was true even when the raw, nonnormalized values were considered: e.g., the mean nonnormalized \( C_{\text{max}} \) (±SD) values for isoniazid and rifampin were 1.81 ± .88 mg/L and 5.16 ± 3.67 mg/L, respectively (values were normalized to 70 kg of body weight for purposes of comparing the pharmacokinetics).

On the other hand, the values for pyrazinamide were similar to those cited in the literature on non-HIV-infected patients with AIDS [33] and were consistent with many of the values cited in recent TB-AIDS case reports where the absorption of isoniazid, rifampin, and other antituberculous drugs appeared to be reduced, whereas pyrazinamide absorption was relatively well preserved.

Why isoniazid and rifampin bioavailability was reduced in our non-HIV-infected TB patients as well as in our HIV-infected TB patients is unclear. Significantly reduced antitubercular drug levels have not been reported in other non-HIV-infected patients with TB. We speculate that population differences—our patients were East African, and almost all were cachectic (93% of our HIV-infected patients and 80% of our non-HIV-infected patients had severe wasting)—resulted in the across-the-board reduced bioavailability of isoniazid and rifampin. Perhaps severe wasting is a predictor of drug malabsorption in both HIV-infected and noninfected patients. Wasting or malnutrition sufficient to cause small-bowel edema, villous atrophy, or bacterial overgrowth might be expected to result in malabsorption [34].

We have no reason to think that the isoniazid and rifampin formulations were substandard, and although the stability of rifampin may be problematic in the tropics, there is no reason to question the stability of isoniazid. The lack of any effect of CD4 cell counts or diarrhea on drug bioavailability within our HIV-infected group (as has been reported for HIV-infected North American patients without TB [31]) may have been because of the small number of patients or the overriding influence of cachexia.

Our xylose measurements suggest that a component of altered absorption may indeed have contributed to our results; the levels were low in all patients (12 HIV-infected and eight non-HIV-infected patients) tested. A low xylose level indicates poor mucosal absorption or contamination of the jejunum by bacteria that metabolize the sugar before it can be absorbed.

Interactions between the four antimycobacterial drugs [27, 35, 36], the measurement of pharmacokinetic parameters at steady-state (rifampin induces its own hepatic metabolism, and the \( C_{\text{max}} \) and \( t_{1/2} \) of rifampin decline over the first 1–2 weeks of therapy) [37], and the use of HPLC assays, as opposed to bioassays (which may measure metabolites as well as parent compound) [23], were other factors that may have contributed to our finding of reduced bioavailability of isoniazid and rifampin, as compared with some, but not all, values cited in the literature [28, 33]. However, because all 29 patients underwent the same preparation and received the same treatment (nonantimycobacterial drugs administered to three of the patients are not known to influence the absorption or metabolism of isoniazid, rifampin, or pyrazinamide), our comparison of pharmacokinetic parameters between groups remains valid.

Even though our patients’ severe wasting may have reduced the bioavailability of isoniazid and rifampin, the fact that peak serum concentrations were still well above the MICs for *Mycobacterium tuberculosis* (i.e., ≤0.1 mg/L for isoniazid and ≤0.5...
mg/L for rifampin) in all patients [38] suggests that our patients—even those with HIV infection—might respond well to their antimycobacterial drugs. Extensive clinical experience with such patients supports this conclusion.

Our results do not explain why some patients with TB and AIDS who have been described in the literature had clinically important reductions in the peak concentration of their drugs (i.e., reductions that led to treatment failure or the selection of drug resistance [9, 11]), nor do they explain dose-response data for antituberculous drugs [14–17]. In conclusion, our study did not demonstrate an important contribution of HIV infection, diarrhea, or CD4 cell counts to the variable pharmacokinetics of isoniazid, rifampin, and pyrazinamide in TB patients in Nairobi.

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