Treatment Outcomes of Patients with HIV and Tuberculosis

Payam Nahid^{1,2}, Leah C. Gonzalez¹, Irina Rudoy^{1,2}, Bouke C. de Jong³, Alon Unger¹, L. Masae Kawamura^{1,2}, Dennis H. Osmond¹, Philip C. Hopewell^{1,2}, and Charles L. Daley⁴

¹Division of Pulmonary and Critical Care Medicine, San Francisco General Hospital, University of California, San Francisco, San Francisco, California; ²The Tuberculosis Control Section, Department of Public Health, San Francisco, California; ³Stanford University, Stanford, California; and ⁴Division of Mycobacterial and Respiratory Infections, National Jewish Medical and Research Center, Denver, Colorado

Rationale: The optimal length of tuberculosis treatment in patients coinfecting with HIV is unknown.

Objectives: To evaluate treatment outcomes for HIV-infected patients stratified by duration of rifamycin-based tuberculosis therapy.

Methods: We retrospectively reviewed data on all patients with tuberculosis reported to the San Francisco Tuberculosis Control Program from 1990 through 2001. Patients were followed for up to 12 months after treatment completion.

Measurements and Main Results: Of 700 patients, 264 (38%) were HIV infected, 315 (45%) were not infected, and 121 (17%) were not tested. Mean duration of treatment was extended to 10.2 months for HIV-infected patients versus 8.4 months for uninfected/unknown patients ($p < 0.001$). Seventeen percent of the HIV-infected and 37% of the HIV uninfected/unknown patients received 6 months of rifamycin-based therapy. The relapse rate among HIV-infected was 9.3 per 100 person-years versus 1.0 in HIV-uninfected/unknown patients ($p < 0.001$). HIV-infected individuals who received a standard 6-month rifamycin-based regimen were more likely to relapse than those treated longer (adjusted hazard ratio, 4.33; $p = 0.02$). HIV-infected individuals who received intermittent therapy were also more likely to relapse than those treated on daily basis (adjusted hazard ratio, 4.12; $p = 0.04$). The use of highly active antiretroviral therapy was associated with more rapid conversion of smears and cultures and with improved survival.

Conclusions: HIV-infected patients who received a 6-month rifamycin-based course of tuberculosis treatment or who received intermittent therapy had a higher relapse rate than HIV-infected subjects who received longer therapy or daily therapy, respectively. Standard 6-month therapy may be insufficient to prevent relapse in patients with HIV.

Keywords: tuberculosis; recurrence/relapse; rifampin; HIV/AIDS; HAART

The preferred regimen for the treatment of drug-susceptible tuberculosis in HIV-uninfected individuals is a 6-month, rifamycin-based regimen that includes pyrazinamide during the initial 2-month phase (1, 2). There continues to be controversy about the optimal duration of treatment for tuberculosis in HIV-infected patients (3–5). Although several prospective trials have attempted to address this issue, significant variations in design between them have hindered our ability to draw concrete con-

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

The optimal length of tuberculosis treatment in patients coinfecting with HIV is unknown.

What This Study Adds to the Field

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clusions (6). In general, treatment outcomes of conventional 6-month, rifamycin-based regimens for tuberculosis are reported as being equivalent in HIV-infected and HIV-uninfected individuals (7–12). As a consequence, current guidelines recommend a 6-month, rifamycin-based course for all patients with drug-susceptible tuberculosis regardless of their HIV serostatus (2). Since 1990, the San Francisco Tuberculosis Control Program has initiated the same 6-month treatment regimen for drug-susceptible tuberculosis in all cases regardless of HIV serostatus. To determine how treatment outcomes of a 6-month, rifamycin-based regimen in HIV-infected patients compare with those in HIV-uninfected patients, we conducted a retrospective cohort study of 700 patients with culture-positive tuberculosis. Our objective was to evaluate treatment outcomes in a low-incidence setting, where patients were managed at a tuberculosis control program without significant resource limitations.

METHODS

Study Population and Setting

We reviewed all tuberculosis cases reported to the San Francisco Tuberculosis Control Program from January 1, 1990, through December 31, 2001. Cases with initial drug resistance and those who were culture negative or noncultured, treated outside the Department of Health, and younger than 18 years of age and cases diagnosed at autopsy were excluded. Foreign-born patients of Asian race were excluded due to their low HIV-seroprevalence rate in addition to their social and demographic differences (see online supplement). Thus, the study population was comprised of a cohort of 700 patients with culture-positive tuberculosis.

HIV status was unknown in 121 patients (17.3%). The demographics and clinical data of these patients were further scrutinized to determine whether combining them with the HIV-uninfected cohort for analyses would result in a misclassification error. First, significant sociodemographic differences from the HIV-infected and uninfected cohorts were identified. These differences reflected the predominant reasons why HIV testing was not offered to them, namely that the subjects without

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Correspondence and requests for reprints should be addressed to Payam Nahid, M.D., M.P.H., University of California, San Francisco, San Francisco General Hospital, 1001 Potrero Avenue, Sk1, San Francisco, CA 94110. E-mail: pnahid@ucsf.edu

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known HIV status were significantly older than both groups (mean age 49.3 vs. 37.3 yr in HIV-infected and 41.1 yr in HIV-uninfected subjects; $p < 0.001$) and that they had the lowest proportion of homelessness and substance abuse of the three groups ($p \leq 0.02$). Second, analyses with the HIV-unknown cohort included and then excluded resulted in no significant changes in tuberculosis outcomes. Third, chart review was undertaken to confirm that these cases had no identifiable risk factors for HIV. Consequently, the HIV-unknown cohort was combined with the uninfected cohort for all analyses; this cohort is named HIV-uninfected/unknown (see Table E1 in the online supplement).

Study Design

A retrospective cohort study design was used to evaluate tuberculosis treatment outcomes. A standard data collection form was used to record information extracted from patient records.

Patients were considered cured if they completed all prescribed doses, converted their cultures to negative (when available), and had resolution of symptoms. For 68 patients in whom subsequent microbiologic confirmation of cure was unattainable, cure was defined as having resolution of signs and symptoms in conjunction with completion of all prescribed doses. Treatment failure was defined by positive cultures after 4 months of treatment (2). Recurrence was defined by evidence of a second episode of tuberculosis after a patient had completed treatment and had been deemed cured of tuberculosis. If isolates from a second episode had the same genotype pattern as the initial pretreatment isolates, the patient was considered to have relapsed. When genotype data were not available, recurrent cases were categorized as relapses if they had the same drug susceptibility pattern or had acquired resistance to only one drug. Cause of death was assessed by review of available charts, death certificates, and autopsy information.

The majority of patients received directly observed therapy throughout treatment or at minimum during the intensive phase of treatment (see online supplement). Rifabutin was prescribed ($n = 32$) in place of rifampin in patients receiving highly active antiretroviral treatment (HAART) per recommendations (2).

Patients who received once-, twice-, or thrice-weekly dosing were categorized as having received intermittent therapy, and those who received therapy 5 to 7 days per week dosing were categorized as having received daily therapy. We were unable to establish dosing frequency in 13 cases. All 13 of these cases completed treatment and none relapsed. Sensitivity analyses (in which all analyses were repeated with the 13 cases excluded, included as daily, or included as intermittent) confirmed that the predictors of relapse did not change. Consequently, we selected the most conservative categorization and classified the 13 cases as having received intermittent dosing.

The San Francisco Tuberculosis Control Program invests significant resources into assuring follow-up 6 and 12 months after treatment completion. Despite this, a significant number of patients ($n = 252$) had 11 months or less of follow-up after completing treatment. Moreover, there was a significant differential in follow-up between HIV-infected and uninfected/unknown patients. Several analyses were pursued to address potential biases this differential in follow-up may have caused. These analyses confirmed that our findings on the predictors of relapse are valid (see online supplement).

Genotypic analysis of *Mycobacterium tuberculosis* isolates was performed using previously described methods (13, 14). The study protocol was approved by the Committee on Human Research of the University of California, San Francisco.

Statistical Analysis

Statistical analyses were performed using SAS version 9.1 software (SAS Institute, Inc., Cary, NC). Rates per person-year were calculated to adjust for differing follow-up times, and rate ratios were tested assuming a Poisson distribution for differences between groups (see online supplement). Multivariate Cox proportional-hazards regression analysis was used to assess risk factors for relapse, with selection of factors associated ($p < 0.20$) with relapse on univariate Cox analysis.

RESULTS

Study Population Demographics and Clinical Characteristics

A total of 700 patients with culture-proven tuberculosis met inclusion criteria for the study. Of the 700 patients, 264 (37.7%)

were infected with HIV, 315 (45%) were not infected with HIV, and 121 (17.3%) had no risk factors identified for HIV (15, 16) and were not offered HIV testing (see METHODS). The baseline clinical and demographic data of individuals according to HIV infection are shown in Table 1.

At presentation, HIV-infected and HIV-uninfected/unknown patients did not show any significant differences in rates of smear- and culture-positive sputa. However, the HIV-infected cohort was significantly more likely to have extrapulmonary in addition to pulmonary involvement at the time of diagnosis but significantly less likely to have cavitary disease on initial chest radiograph as compared with the HIV-uninfected/unknown cohort (all $p < 0.001$). Finally, HIV-infected patients were more likely to be treated for more than 6 months ($p < 0.001$), but there were no significant differences by HIV status in tuberculosis treatment regimens, intermittency of dosing, or adherence. Patient status at end of therapy and at 12-month follow-up is displayed in Figure 1.

Outcomes by HIV Status

Of those who completed therapy, recurrence occurred in 13 of 196 HIV-infected patients (6.6%), a rate of 9.31 per 100 person-years, and in 3 of 362 HIV-uninfected/unknown patients (0.8%), a rate of 0.97 per 100 person-years ($p < 0.001$) (Table 2) with a rate ratio of 9.64 (see Table E2 for characteristics of all 16 individuals whose tuberculosis recurred). Molecular genotyping was available on 8 of 13 HIV-infected recurrent cases and one of three HIV-uninfected cases; comparison to the original genotypes confirmed that all were true relapses. Of the five HIV-infected and two HIV-uninfected patients who did not have recurrent isolates available for genotyping, all recurred within 12 months of the end of therapy, and six patients (four HIV-infected and two HIV-uninfected) had the same drug susceptibility pattern. In one HIV-infected case whose tuberculosis recurred 8 months after treatment completion, the recurrent isolate had acquired partial isoniazid resistance ($> 50\%$ growth at a concentration of $0.2 \mu\text{g/ml}$). Based on the available molecular genotyping data and drug susceptibility patterns, it is unlikely that any of the recurrent cases were due to reinfection, particularly given the low-incidence setting of our study. Consequently, all 16 recurrent episodes of tuberculosis in this study are referred to as relapses.

Given that there were significant sociodemographic and clinical differences between the HIV-infected cohort and the HIV-uninfected/unknown cohort that could potentially influence the outcome variable, multivariate analyses were performed on the entire cohort with 16 relapses, and, after adjusting for potential confounders, HIV status remained independently predictive of relapse ($p = 0.003$). Receiving a regimen that was intermittently dosed independently predicted relapse ($p = 0.004$). Other variables predictive of relapse in prior publications (2, 17–19), including culture status at 2 months, cavitation on chest radiography, having bilateral pulmonary involvement, and being a non-Hispanic white person, did not predict relapse in our population (all $p > 0.20$). Intermittent rifabutin-based therapy has also been associated with increased risk of relapse (20); however, rifabutin was not prescribed in the treatment of any of our cases whose tuberculosis relapsed. The finding that HIV serostatus independently predicted relapse was particularly notable given that HIV-infected patients were treated on average for a significantly longer duration than HIV-uninfected/unknown patients (10.2 mo vs. 8.4 mo; $p < 0.001$) (Table 2). In these patients, prolongation of treatment was a reflection of more doses being administered rather than merely administering the same number of doses over a longer period of time (see online supplement).

TABLE 1. DEMOGRAPHIC, CLINICAL, AND TREATMENT CHARACTERISTICS OF PATIENTS BY HIV STATUS (N = 700)

Characteristic	HIV Infected (n) (%)	HIV Uninfected/Unknown (n) (%)	p Value
No.	264	436	
Demographic data			
Age at diagnosis, yr (mean $\pm$ SD)	37.3 $\pm$ 8.7	43.4 $\pm$ 15.6	< 0.001
Race			0.22
White	158 (59.9)	267 (61.2)	
Black	100 (37.9)	149 (34.2)	
Other	6 (2.3)	20 (4.6)	
Hispanic ethnicity	63 (23.9)	136 (31.2)	0.04
Male sex	232 (87.9)	328 (75.2)	< 0.001
Foreign born	44 (16.7)	156 (35.8)	< 0.001
Homeless	76/168 (45.2)	123/298 (41.3)	0.41
Substance abuse	134 (50.8)	186 (42.7)	0.04
Clinical data			
Initial sputum smear positive	132 (50.0)	198 (45.4)	0.24
Initial sputum culture positive	244 (92.4)	384 (88.1)	0.07
Pulmonary and extrapulmonary disease	95 (38.6)	37 (9.5)	< 0.001
Solely extrapulmonary disease	18 (6.8)	46 (10.6)	0.10
Chest radiograph			
Normal	12 (4.6)	26 (6.0)	0.42
Cavitary	25 (9.5)	132 (30.3)	< 0.001
Infiltrate	164 (62.1)	326 (74.8)	< 0.001
Miliary	31 (11.7)	6 (1.4)	< 0.001
Intrathoracic adenopathy	71 (26.9)	25 (5.7)	< 0.001
Pleural effusion	42 (15.9)	68 (15.6)	0.91
CD4 ⁺ T-lymphocyte count			
$\leq$ 200 cells/mm ³	162/219 (74.0)	—*	
Mean $\pm$ SD	157 $\pm$ 170	—	
Median (range)	96 (0–1,011)	—	
Treatment data			
Standard treatment regimen [†]	260 (98.5)	426 (97.7)	0.48
DOT (four missing)			0.003
Received DOT for all doses	149 (56.9)	211 (48.6)	
Received partial DOT	52 (19.9)	68 (15.7)	
Self-administered therapy for all doses	61 (23.3)	155 (35.7)	
Adherent to drug regimen	127/256 (49.6)	240/431 (55.7)	0.12
Received ART during tuberculosis therapy			
HAART	32 (12.1)	—	
Single or dual drug ART	106 (40.2)	—	
None	126 (47.7)	—	
Received 6 mo of therapy (vs. > 6 mo)	71 (26.9)	189 (43.4)	< 0.001
Received therapy intermittently	56/255 (22.0)	109/431 (25.3)	0.32
Hospitalized for tuberculosis	169/264 (64.0)	192/433 (44.3)	< 0.001

Definition of abbreviations: ART = antiretroviral therapy; DOT = directly observed therapy; HAART = highly active antiretroviral therapy.

* CD4⁺ T-lymphocyte count was not measured in HIV-uninfected/unknown individuals, and ART was not indicated.

[†] All 700 cases received a rifamycin-based regimen. Standard regimen defined as isoniazid, rifampin, and pyrazinamide $\pm$ ethambutol depending on whether drug susceptibility results were known, as recommended by the American Thoracic Society, Centers for Disease Control and Prevention, and Infectious Diseases Society of America (10).

A significantly larger percentage of the HIV-infected patients died than the HIV-uninfected/unknown patients. Overall, 85 HIV-infected patients died during treatment or at any time in the 12 months of follow-up (a rate of 23.5 per 100 person-years) versus 27 HIV-uninfected/unknown patients (a rate of 4.5 per 100 person-years) (relative risk [RR], 5.19; 95% confidence interval [CI] 3.37–8.00; $p < 0.001$). HIV-related death was the predominant reason for the difference in the mean duration of follow-up of 8.4 months in HIV-infected and 10.1 months in HIV-uninfected/unknown patients ($p = 0.005$) (Table 2) (see METHODS and online supplement for measures taken to address differences in follow-up). The use of HAART during treatment for tuberculosis significantly protected against mortality when compared with HIV-infected patients who did not receive antiretroviral medications or who received regimens other than HAART (RR, 0.36; 95% CI, 0.14–0.91; $p = 0.01$). Furthermore, HIV-infected patients who received HAART during tuberculosis

treatment converted their sputum smears and cultures to negative significantly faster than those not treated with HAART (mean, 3.5 vs. 5.9 wk [$p = 0.01$] and 5.1 vs. 8.7 wk [$p = 0.003$], respectively). Analysis of the effect of HAART on other tuberculosis outcomes, such as relapse, was not feasible given the small sample of patients receiving HAART (32 out of 73 diagnosed during or after 1996). Moreover, none of the 13 HIV-infected patients whose tuberculosis relapsed had received HAART.

HIV-infected patients were significantly more likely to experience adverse reactions to antituberculosis medications and to acquire drug resistance as compared with the HIV-uninfected/unknown subjects (21.3% versus 12.4% and 4.2% versus 0.5%, respectively; all $p < 0.005$). Administration of HAART with tuberculosis treatment was not associated with the occurrence of adverse drug reactions. The predominant medications to which resistance was acquired by HIV-infected patients were rifampin

Figure 1. Study profile with status at end of therapy and at 12-month follow-up by HIV status.

and isoniazid; 7 of 11 cases acquired resistance to rifampin alone, two cases acquired resistance to rifampin and isoniazid, and two cases acquired resistance to isoniazid alone. Because of the retrospective nature of the study, information on other adverse events, such as immune reconstitution syndromes, was limited and thus could not be analyzed.

Outcomes by Duration and Administration of Treatment

Within the HIV-infected cohort, when treatment duration was compared (Table 3), there was a significantly higher relapse rate

among those who completed tuberculosis treatment within a 6-month period (23.4 per 100 person-years [5 of 33 cases] vs. 7.0 per 100 person-years [8 of 163 cases] for patients treated longer; $p = 0.04$). Those who completed tuberculosis treatment within a 6-month period had associated characteristics that would identify them as being ideal candidates for a short-course regimen and of lower risk for relapse (i.e., they were adherent, they converted their cultures sooner, and they had few side-effects). Nonuniform loss to follow-up was not a factor in the difference in relapse rate because the mean duration of follow-up after treatment

TABLE 2. TREATMENT OUTCOMES OF PATIENTS ACCORDING TO HIV STATUS

Outcomes	HIV Infected (n) (%)	HIV Uninfected/Unknown (n) (%)	Relative Risk (95% CI)	p Value
No. of subjects	264	436		
Treatment duration				
Months on treatment, mean $\pm$ SD	10.2 $\pm$ 4.9	8.4 $\pm$ 3.5		< 0.001
Received 6 mo of treatment (vs. > 6 mo)	33/196 (16.8)	133/362 (36.7)	0.46 (0.33–0.64)	< 0.001
Bacteriologic outcomes				
Weeks to sputum smear negative, mean $\pm$ SD	5.5 $\pm$ 5.6	5.6 $\pm$ 5.4		0.85
Weeks to sputum culture negative, mean $\pm$ SD	8.2 $\pm$ 12.4	8.0 $\pm$ 7.3		0.86
Converted cultures in 8 wk	129/174 (74.1)	197/303 (65.0)	1.14 (1.01–1.29)	0.04
Outcomes				
All failures	15/202 (7.4)	15/365 (4.1)	1.81 (0.90–3.62)	0.09
All relapses (rate per 100 person-years)	13 (9.31)	3 (0.97)	9.64 (2.75–33.8)	< 0.001
Acquired drug resistance	11 (4.2)	2 (0.5)	9.08 (2.03–40.7)	< 0.001
Adverse drug reaction to treatment	55/258 (21.3)	54/434 (12.4)	1.71 (1.22–2.41)	0.002
Received therapy intermittently	56/255 (22.0)	109/431 (25.3)	0.87 (0.65–1.15)	0.32
Months of follow-up after treatment completion				
Mean $\pm$ SD	8.4 $\pm$ 6.8	10.1 $\pm$ 5.7		0.005
Median (range)	8.5 (0–34.5)	12.0 (0–26.0)		
Died during treatment or follow-up (rate per 100 person-years)	85 (23.5)	27 (4.5)	5.19 (3.37–8.00)	< 0.001
Death due to tuberculosis	13/85 (15.3)	2/27 (7.4)	2.06 (0.50–8.58)	0.52

Definition of abbreviations: CI = confidence interval.

TABLE 3. TREATMENT OUTCOMES OF HIV-INFECTED PATIENTS ACCORDING TO TREATMENT DURATION

Outcomes	Completed in 6 mo (n) (%)	Completed in > 6 mo (n) (%)	Relative Risk (95% CI)	p Value
No. of subjects	33	163		
Characteristics				
CD4 ⁺ T lymphocyte count $\geq$ 200 cells/mm ³ (28 missing)	19/31 (61.3)	97/137 (70.8)	0.87 (0.64–1.17)	0.30
Received ART during tuberculosis therapy				
HAART	2 (6.1)	28 (17.2)	0.33 (0.07–1.55)	0.16
Single- or dual-drug ART	16 (48.5)	65 (39.9)	1.15 (0.53–2.51)	0.73
None	15 (45.5)	70 (42.9)	(Reference)	1.00
Opportunistic infection	24 (72.7)	84 (51.5)	1.41 (1.09–1.82)	0.03
Cavitary disease	2 (6.1)	16 (9.8)	0.62 (0.15–2.56)	0.74
Received any directly observed therapy	21 (63.6)	128 (78.5)	0.81 (0.62–1.06)	0.07
Adherent to drug regimen	32 (97.0)	70 (42.9)	2.26 (1.87–2.72)	< 0.001
Substance abuse	12 (36.4)	85 (52.2)	0.70 (0.43–1.12)	0.10
Bacteriologic outcomes				
Weeks to sputum smear negative, mean $\pm$ SD	5.4 $\pm$ 4.2	5.5 $\pm$ 5.7		0.93
Weeks to sputum culture negative, mean $\pm$ SD	5.8 $\pm$ 2.5	8.9 $\pm$ 14.5		0.03
Converted cultures in 8 wk	21/25 (84.0)	86/121 (71.1)	1.18 (0.96–1.45)	0.18
Outcomes				
All failures	0	9 (5.5)	0.25 (0.02–4.26)*	0.36
All relapses (rate per 100 person-years)	5 (23.4)	8 (7.04)	3.32 (1.09–10.2)	0.04
Acquired drug resistance	1 (3.0)	4 (2.5)	1.23 (0.14–10.7)	1.00
Adverse drug reaction to treatment	1 (3.0)	36 (22.1)	0.14 (0.02–0.97)	0.01
Received therapy intermittently	7 (21.2)	43 (26.4)	0.80 (0.40–1.63)	0.53
Months of follow-up after treatment completion				
Mean $\pm$ SD	7.8 $\pm$ 5.4	8.6 $\pm$ 7.1		0.55
Median (range)	7.6 (0–16.6)	8.6 (0–34.5)		
Died during follow-up [†] (rate per 100 person-years)	9 (38.0)	37 (30.3)	1.25 (0.60–2.59)	0.55
Death due to tuberculosis	1/9 (11.1)	2/37 (5.4)	2.06 (0.21–20.2)	0.49

Definition of abbreviations: ART = antiretroviral therapy; CI = confidence interval; HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus.

* Estimated 0.5 for every cell with a zero.

[†] Three cases relapsed before death during follow-up.

completion was not significantly different between the two groups (7.8 mo versus 8.6 mo, respectively; $p = 0.55$). Additional analyses were pursued to determine if there were differences between those who did and did not complete follow-up in terms of predicting relapse. These analyses showed that HIV-infected individuals who did not complete follow-up had significantly lower mean CD4⁺ T-lymphocyte counts ($p = 0.004$), with a significantly larger proportion of them having had an opportunistic infection before their tuberculosis diagnosis ($p < 0.001$). Almost half of the HIV-infected individuals who did not complete follow-up died from HIV-related causes. There were no significant differences in characteristics associated with relapse (including the proportion receiving a 6-mo regimen) between those who did and did not complete follow-up.

In univariate analyses, only the duration of treatment of tuberculosis was significantly predictive of relapse in the HIV-infected cohort ($p = 0.02$) (Table 4). None of the HIV-infected individuals whose tuberculosis relapsed had cavitary disease on initial chest radiograph, and none received HAART; thus, these variables could not be analyzed further. Culture status at 2 months of treatment was not associated with relapse in univariate analysis ($p = 0.41$) and was not included in multivariate models. Other predictors of relapse (i.e., self-administration of medications, intermittent dosing, and hospitalization) did not reach statistical significance but were included in multivariate models (all characteristics with p values ≤ 0.20).

Using multivariate Cox proportional-hazards analysis, we identified two factors as being independently associated with relapse during the follow-up period in HIV-infected individuals: receiving 6 months' duration of treatment (5 of 13 relapses;

hazard ratio, 4.33; $p = 0.02$) and receiving therapy intermittently (5 of 13 relapses; hazard ratio, 4.12; $p = 0.04$).

DISCUSSION

In this study, we have shown that HIV-infected patients with tuberculosis are significantly more likely to relapse after completion of a rifamycin-based regimen than HIV-uninfected/unknown patients. Of five prior publications in which recurrence data were compared and reported, none showed a statistically significant difference between HIV-infected and HIV-uninfected/unknown patients (8–12). The recurrence rate in HIV-infected individuals treated for tuberculosis was around 5% in all of these studies except one, which was located in an area of endemic tuberculosis and reported a high recurrence rate of 9% (11). Because this latter study did not have access to molecular genotyping, no distinction could be made between recurrence from relapse or reinfection (21). A recent follow-up (22) of an observational cohort study originally published in 1999 (12) that included molecular genotyping showed findings similar to ours: HIV-infected patients were five times more likely to recur. In studies reporting tuberculosis outcomes in HIV-infected individuals only (23–27), designed primarily to compare various treatment regimens, relapse rates ranged from 0% in one study in which the continuation phase was extended to 7 months (26) to 10% in a study using twice-weekly isoniazid and rifampin during the continuation phase (27). Thus, our finding that 6.6% of our HIV-infected cohort experienced a second episode of tuberculosis, representing a relapse rate of 9.3 per 100 person-years, is at the higher end of the range reported for rifamycin-based regimens. Moreover, it is significantly greater than the relapse rate of 1.0 per 100 person-years in our

TABLE 4. RISK FACTORS FOR RELAPSE (n = 13) IN 196 HIV-INFECTED INDIVIDUALS WHO COMPLETED THERAPY

Characteristic	Unadjusted Hazards Ratio (95% CI)	p Value	Adjusted Hazards Ratio (95% CI)	p Value
Treatment characteristics				
Treated for 6 mo (vs. > 6 mo)	4.19 (1.28–13.8)	0.02	4.33 (1.26–14.8)	0.02
Self-administered therapy (no DOT)	2.80 (0.93–8.42)	0.07	3.11 (0.81–11.9)	0.10
Received therapy intermittently*	2.54 (0.83–7.78)	0.10	4.12 (1.09–15.6)	0.04
Hospitalized for tuberculosis	3.01 (0.83–11.0)	0.09	3.60 (0.96–13.5)	0.06
Nonadherent to drug regimen	0.71 (0.23–2.20)	0.56		
Adverse reaction	0.19 (0.02–1.61)	0.13	0.40 (0.04–4.05)	0.43
Sociodemographic characteristics				
History of opportunistic infection	1.81 (0.59–5.54)	0.30		
Substance abuse within 6 mo of treatment start	0.78 (0.24–2.48)	0.67		
Non-Hispanic white	1.59 (0.52–4.87)	0.42		
Clinical and bacteriologic characteristics				
Sputum smear positive	0.63 (0.20–2.06)	0.45		
Culture positive at 2 mo of treatment†	0.42 (0.05–3.39)	0.41		
CD4 ⁺ T-lymphocyte count ≤ 200 cells/mm ³ (28 missing, four of whom relapsed)	2.12 (0.44–10.3)	0.35		
Cavitary disease	—‡			
Bilateral disease	0.39 (0.05–3.02)	0.37		

Definition of abbreviations: CI = confidence interval; DOT = directly observed therapy.

* Three cases who received therapy three times per week were classified as receiving intermittent therapy. In a separate sensitivity analysis, these three cases were reclassified as receiving daily therapy, and the unadjusted hazard ratio was 2.01 (0.62–6.54) ($p = 0.25$).

† We were unable to document 2-month culture status in 50 cases; 16 had solely extrapulmonary disease, of whom all were cured, and 34 did not have cultures at 2 months, of whom 4 relapsed.

‡ Zero relapsed cases had cavitary disease; hazard ratio is incalculable.

HIV-uninfected/unknown cohort. Whether this is a result of extraordinary successes in the HIV uninfected/unknown or of the inherent complexities of treating HIV and tuberculosis coinfecting patients cannot be readily determined from a retrospective study.

In this study, we have also shown that duration of tuberculosis treatment and intermittent dosing were strong independent predictors of relapse in HIV-infected patients. Patients who received 6 months of a rifamycin-based tuberculosis regimen were four times more likely to relapse than those treated longer than 6 months, and patients who received intermittent dosing were four times more likely to relapse than those who had daily dosing (Table 4). Although the association of relapse with intermittent therapy is in line with recent publications (20, 28), the importance of the duration of treatment in our study is not. A recent meta-analysis of prospective clinical trials reported no significant difference in risk of recurrence between HIV-infected patients who received 5 to 6 months of rifampin-based therapy and those who received 7 months or longer (29). This finding may reflect the fact that our study was a review of tuberculosis management outside the controlled context of a clinical trial. Indeed, a study of tuberculosis outcomes in HIV-uninfected patients also under program settings showed that extension of intensive phase and overall treatment protected against relapse (19). Being hospitalized for tuberculosis, which is possibly a marker of severity of disease and immunosuppression, was the only other predictor of relapse in our HIV-infected cohort, with a p value close to statistical significance. Several characteristics were exclusively associated with HIV-infected individuals whose tuberculosis relapsed and thus could not be entered into multivariate regression models: All 13 HIV-infected-associated relapses presented with noncavitary disease on plain radiograph, and none received HAART during the study period. To our knowledge, a potential link between receiving HAART and lower risk for tuberculosis relapse has not been noted in the literature. Although prior publications have reported that the risk of progression to tuber-

culosis is significantly reduced among HIV-infected individuals receiving HAART (30–32), none have reported a beneficial effect of HAART on tuberculosis outcomes (33). Initial CD4⁺ T-lymphocyte count did not predict relapse in our HIV-infected cohort, in contrast to a prior publication in which a low median initial CD4⁺ T-lymphocyte count was reported as being the sole predictor of relapse (22). However, mortality during follow-up was associated with having a low initial CD4⁺ T-lymphocyte count, and this relationship may have masked the presence of a possible association between CD4⁺ T-lymphocyte count and relapse.

We have shown that the use of HAART during treatment for tuberculosis significantly protected against mortality when compared with HIV-infected patients who received no antiretroviral medication or antiretroviral regimens other than HAART (RR, 0.36; 95% CI, 0.14–0.91; $p = 0.01$). Furthermore, HIV-infected patients who received HAART during their tuberculosis treatment converted their sputum smears and cultures to negative significantly faster than those not treated with HAART (mean of 3.5 vs. 5.9 wk [$p = 0.01$] and mean of 5.1 vs. 8.7 wk [$p = 0.003$], respectively). However, the administration of HAART was associated with a significant prolongation of tuberculosis treatment for unclear reasons. Despite the apparent benefits associated with HAART, only 32 (44%) of the 73 HIV-infected patients treated for tuberculosis during or after 1996 received HAART. This was likely due to the lack of an expert consensus about whether and when HAART should be initiated during the treatment of HIV-related tuberculosis—an issue that remains controversial (34). Even though delaying HAART until the end of tuberculosis treatment simplifies the management of the two diseases, our results are in line with recent literature (35) and provide compelling evidence to warrant the initiation of HAART during tuberculosis treatment in select patients. Until there is further information from prospective clinical trials about the optimal time to initiate HAART, the current World Health Organization recommendations remain our best guide (36).

Our study was limited by potential biases. The effect of physician preference for prolonging treatment in HIV-infected patients proved to be difficult to control. Throughout chart reviews, it was evident that certain cases had treatment prolonged by their physician due to profound HIV-mediated immunosuppression rather than due to the standard reasons for prolonging therapy. Determining cause of death also proved difficult. We reviewed all available charts, computer records, death certificates, and autopsy information to determine cause of death; however, only a minority of cases had *post mortem* analyses. The retrospective cohort design of this study precluded analysis of the effects of the timing of initiating HAART on tuberculosis outcomes and time-matched comparisons of CD4⁺ T-lymphocyte count and viral load in those receiving various antiretroviral regimens versus those receiving none. To determine the optimum duration of therapy for tuberculosis in an era of HAART and to determine the optimum time to initiate HAART would require a large randomized clinical trial. The database for this cohort was initiated in the early 1990s when the immune reconstitution syndrome in HIV-infected patients was starting to be described (37, 38); therefore, our data on this syndrome are limited. There was differential attrition in the two groups. However, most of the attrition in the HIV-infected patients was due to HIV-related death. Had these patients lived longer, the relapse rate would have likely been even higher.

In summary, we have shown in this study that HIV-infected patients who successfully completed a rifamycin-based course of therapy, regardless of its duration, were more likely to relapse in follow-up when compared with HIV-uninfected patients. We have also shown that HIV-infected patients who received a 6-month, rifamycin-based course of tuberculosis treatment or who were treated intermittently had a relapse rate that was significantly higher than HIV-infected individuals who received a longer duration of therapy or were treated with daily dosing, respectively. Despite the varying recurrence rates noted in the literature, the generally recommended treatment for HIV-infected patients with tuberculosis is 6 months of a rifamycin-based regimen (2). Based on our findings, we recommend that further research is warranted to identify the most efficacious duration of therapy and the optimum timing for HAART in the treatment of HIV-related tuberculosis.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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