Relapse and Acquired Rifampin Resistance in HIV-Infected Patients with Tuberculosis Treated with Rifampin- or Rifabutin-Based Regimens in New York City, 1997–2000

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Background. The relationship between rifamycin use and either relapse or treatment failure with acquired rifampin resistance (ARR) among human immunodeficiency virus (HIV)–infected patients with tuberculosis (TB) is not well understood.

Methods. We conducted a retrospective cohort study of HIV-infected and HIV-uninfected persons with rifampin-susceptible TB, (1) to compare relapse rates, ARR, and treatment failure, according to HIV serostatus; and (2) to examine whether and how use of rifamycin was associated with clinical outcomes of interest among HIV-infected patients with TB.

Results. HIV-infected patients were more likely to have ARR than were HIV-uninfected patients (0.9% vs. 0.1%; $P = .007$), and the association remained significant in multivariate analysis (adjusted odds ratio [OR], 5.5; 95% confidence interval [CI], 1.4–21.5). Among HIV-infected patients with TB, none of 57 patients treated with rifabutin-based regimens alone had ARR, and only 1 of 395 patients treated with rifabutin given in combination with a rifampin-based regimen had ARR, whereas 6 of 355 patients treated with a rifampin-based regimen alone had relapse and ARR. HIV-infected patients treated with rifampin-based regimens alone had a higher risk for relapse and development of rifampin resistance if intermittent dosing of rifampin was started during the intensive phase of treatment, compared with patients who did not receive intermittent dosing (hazard ratio [HR] for relapse, 6.7 [95% CI, 1.1–40.1]; HR for ARR, 6.4 [95% CI, 1.1–38.4]). This association remained when confined to patients with a $CD4^+$ T lymphocyte count of <100 lymphocytes/mm^3. Intermittent dosing started only after the intensive phase of treatment did not increase the risks of relapse and ARR among HIV-infected patients with TB.

Conclusion. The risk for ARR among HIV-infected persons with TB did not depend on the rifamycin used but, rather, on the rifampin dosing schedule in the intensive phase of treatment.

The use of rifampin is pivotal for the effective control of tuberculosis (TB) [1–3]. Since the mid-1990s, when HAART became available, rifabutin has been recommended in the United States as an alternative to rifampin for the treatment of TB when protease inhibitors (PIs) and nonnucleoside reverse-transcriptase inhibitors (NNRTIs) are being used concomitantly, because of the strong drug interaction between rifampin and PIs or NNRTIs [4–6]. In clinical trials, the efficacy of rifabutin administered daily or intermittently was similar to that of rifampin [7–9]. However, a recent clinical trial raised the question of whether the use of rifabutin, particularly when administered intermittently, was a cause of acquired rifampin resistance (ARR) in HIV-infected patients with TB who had low $CD4^+$ T lymphocyte counts [10]. Case reports and various studies have reported ARR in HIV-infected patients with TB [11–19]. In 2003, the Centers for Disease Control and Prevention (CDC) revised the TB treatment guidelines on the basis of findings from recent clinical trials, and they recommended that highly intermittent dosing of rifamycins not be used for patients with TB who have advanced HIV infection [10, 20]. Nevertheless, whether the timing of intermittent dosing of rifamycins is

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associated with relapse or treatment failure and ARR among HIV-infected patients with TB is not well understood.

In New York City (NYC), directly observed therapy is the standard of care for TB treatment and is offered to all patients with TB. Directly observed therapy is mandatory if intermittent therapy is used. Standard treatment regimens are recommended for all patients [6]. Most patients receive therapy daily for 8 weeks and then receive a twice- or thrice-weekly regimen in the continuation phase of treatment. A small percentage of patients receive a twice-weekly regimen after receiving treatment daily for 2 weeks, and even fewer patients receive a thrice-weekly regimen throughout the treatment period. Intermittent treatment is not recommended for patients with organisms resistant to rifampin. The objectives of the present study were as follows: (1) to compare relapse, ARR, and treatment failure between HIV-infected and HIV-uninfected patients with TB; (2) to analyze the characteristics of HIV-infected patients with TB, as well as whether the time of initiation of intermittent dosing of rifamycin (rifampin and/or rifabutin) was associated with relapse, ARR, and treatment failure; and (3) to assess whether these associations were modified on the basis of $CD4^+$ T lymphocyte counts.

PATIENTS AND METHODS

Study patients. A retrospective cohort study was conducted. Patients of any age who were from NYC, who had growth of *Mycobacterium tuberculosis* from any anatomical site and had such growth verified between 1 January 1997 and 31 December 2000, and for whom results of drug susceptibility testing of isolates were available were included in the study. Patients were excluded from the study (1) if they received treatment for <6 months or if they received rifampin or rifabutin for <15 days, (2) if they had an unknown HIV serostatus, (3) if the initial isolate recovered (i.e., the "initial isolate") was resistant to rifampin, (4) or if the initial isolate was resistant to isoniazid and ethambutol, which would make the patients ineligible to receive a 6-month regimen.

Variables. The outcome variables of interest included relapse (defined by growth of *M. tuberculosis* from any anatomical site after completion of treatment), ARR (defined by the identification of isolates that were initially susceptible to rifampin but that subsequently developed resistance to rifampin after the patient received rifamycin-based treatment for ⩾15 days), and treatment failure (defined by a positive culture result after the patient received appropriate treatment for 4 months). The "relapse rate" was defined as the number of episodes of relapse divided by the number of person-years of follow-up after treatment ended. "ARR rate" was defined as the number of episodes of ARR divided by the number of person-years of follow-up from the date that the initial TB treatment was started to the date that the first rifampin-resistant specimen was collected or the censored date. Patients were observed for relapse or ARR until 15 April 2002. If no event occurred, patients were observed until the first occurrence of any of the following dates: the date of death, the date of a move out of NYC, the date that the patient was lost to follow-up before completing treatment, or 15 April 2002. Guidelines of the NYC Department of Health and Mental Hygiene recommend monthly collection of sputum until the conversion of a positive culture result to a negative culture result, as well as at the end of treatment to document cure. Posttreatment follow-up was performed through passive surveillance of laboratories and providers mandated to report *M. tuberculosis* cultures and patients receiving TB treatment, as well as through active surveillance of mycobacteriology laboratories, to identify *M. tuberculosis* cultures.

The exposure variable of interest was the use of rifamycins (rifampin and/or rifabutin). Treatment regimens were grouped into 3 categories, according to whether rifamycin treatment was rifampin based (i.e., rifampin, not rifabutin, was given), rifabutin based (i.e., rifabutin, not rifampin, was given), or rifabutin and rifampin based (i.e., rifabutin and rifampin were given at different times during the same course of treatment). Because most relapses or ARR occurred among patients who received a rifampin-based regimen, use of rifampin was further examined according to the frequency of dosing (either twice or thrice weekly) and whether treatment was begun in the intensive phase (i.e., during the first 2 months of treatment) or in the continuation phase (i.e., after the first 2 months of treatment), compared with patients who never received intermittent dosing. Because of the small number of events that occurred, we did not stratify regimens on the basis of the number of intermittent doses given per week in the present analysis. The $CD4^+$ T lymphocyte count determined within 6 months before or after initiation of TB treatment started was considered to be the baseline value. Nonadherence to treatment was defined either as <80% of the total number of expected doses having been taken under direct observation or as a treatment gap of >2 weeks occurring among patients receiving self-administered therapy. History of homelessness, injection drug use, alcohol abuse, and mental illness during the 12 months before diagnosis of TB was self-reported.

Data collection. Data on demographic and clinical characteristics, tuberculosis treatment, and bacteriologic monitoring were obtained from the NYC TB Registry. $CD4^+$ T lymphocyte counts were obtained from the NYC HIV/AIDS Surveillance Database. Patients who had not died during the TB treatment were matched with the Death Registry of the NYC Bureau of Vital Statistics; such matching yielded data on 139 additional deaths prior to 15 April 2002. The study protocol was approved by the institutional review board of the NYC Department of Health and Mental Hygiene, and it was reviewed and approved by the Office of the Associate Director for Science of the CDC.

Statistical analysis. Analyses were performed using SAS software, version 8.02 (SAS Institute). Either the Pearson χ^2 test or Fisher's exact test was used to test differences in categorical variables. The Wilcoxon rank-sum test was used for comparison of continuous variables. The association between HIV status and study outcomes was evaluated using bivariate and multivariate logistic regression [21]. In subanalyses of HIV-infected patients with TB, Cox proportional hazards methods [22] were used to determine the hazard ratio (HR) for relapse and ARR. The effect of the $CD4^+$ T lymphocyte count on the risks of relapse and ARR was examined by restricting analysis to patients with a $CD4^+$ T lymphocyte count of <100 lymphocytes/mm^3. Log(−Log [time to event/censoring]) curves were plotted according to the time that intermittent dosing was started, and they were found to be parallel, thereby confirming the assumption of proportionality of hazards. The association of treatment failure with the type of rifamycin regimen received was estimated from the ORs derived from logistic regression analysis [21].

RESULTS

A total of 4632 patients had ⩾1 *M. tuberculosis* isolate undergo drug susceptibility testing. Of these patients, 1771 were excluded from the study: 790 patients had an unknown HIV serostatus, 604 died before month 6 of treatment, 192 received

Table 1. Clinical characteristics of and outcomes for study subjects in New York City in 1997–2000, according to HIV status.

Characteristic or outcome	HIV-infected subjects (n = 807)	HIV-uninfected subjects (n = 2054)	P
Disease site			
Pulmonary only	490 (60.7)	1513 (73.7)	<.001
Extrapulmonary only	109 (13.5)	400 (19.5)	<.001
Pulmonary and extrapulmonary	208 (25.8)	141 (6.9)	<.001
Cavitary lesion[a]	53 (7.6)	491 (29.7)	<.001
Rifamycin received			
Rifampin only	355 (44.0)	2007 (97.7)	<.001
Rifabutin only	57 (7.1)	2 (0.1)	<.001
Rifampin and rifabutin	395 (48.9)	45 (2.2)	<.001
Death			
Before treatment completion	24 (3.0)	17 (0.8)	<.001
After treatment completion	146 (18.1)	104 (5.1)	<.001
Treatment duration,[b] months			
6–8	234 (30.9)	1202 (67.3)	<.001
9–12	312 (41.2)	428 (24.0)	<.001
>12	212 (28.0)	157 (8.8)	<.001
Nonadherence to treatment	376 (46.6)	773 (37.6)	<.001
Treatment failure	13 (1.6)	17 (0.8)	.035
Relapse	10 (1.2)	11 (0.5)	.048
Relapse rate, no. of cases/100 person-years	0.59	0.02	
Acquired rifampin resistance	7 (0.9)	3 (0.1)	.007[c]
With treatment failure and subsequent relapse	1 (14.3)[d]	0 (0.0)[d]	
With relapse only	5 (71.4)[d]	0 (0.0)[d]	
With treatment failure only	1 (14.3)[d]	1 (33.3)[d]	
With neither relapse nor treatment failure	0 (0.0)[d]	2 (66.7)[d]	
With initial isolate resistant to INH	1 (14.3)[d]	2 (66.7)[d]	
With initial isolate susceptible to INH	6 (85.7)[d]	1 (33.3)[d]	

NOTE. Data are no. (%) of study subjects, unless indicated otherwise. INH, isoniazid.

[a] Limited to any patients with pulmonary tuberculosis (n = 698 for HIV-infected patients; n = 1654 for HIV-uninfected patients).

[b] Limited to patients who completed treatment.

[c] As determined by Fisher's exact (2-tailed) test.

[d] The denominator is the total no. of cases of acquired rifampin resistance in the respective subject group (n = 7 for HIV-infected patients; n = 3 for HIV-uninfected patients).

Table 2. Selected clinical and treatment information for HIV-infected patients with tuberculosis (TB) who experienced relapse or had acquired rifampin resistance (ARR) develop.

Patient	Relapse	ARR	Age, years	Disease sites at initial diagnosis of TB[a]	Dosing of rifamycin, according to treatment phase		$CD4^+$T lymphocyte count at TB diagnosis,[b] cells/mm^3	Year HIV infection diagnosed/ year TB diagnosed	Duration of initial treatment, months
					Intensive phase	Continuation phase			
1	Yes	Yes	24	Soft tissue	Daily RIF	Daily RIF	25	1997/1997	8
2	Yes	Yes	46	Lungs, blood	Thrice-weekly RIF	Thrice-weekly RIF (for 2+ months); twice-weekly RIF (for 3+ months)	34	1992/1997	9
3	Yes	No	33	Lungs	Daily RIF	Daily RIF	207	1993/1997	10
4	Yes	Yes	32	Lungs, lymph nodes	Daily RIF (during first month); daily RBT (during second month)	Daily RBT (for 1 month); daily RIF (for 1 month); twice-weekly RIF (for 3 months); twice-weekly RBT (for 2 months); daily RBT (for 1 month)	37	1993/1997	11
5	Yes	Yes	34	Lungs, lymph nodes	Daily RIF (for 3 weeks); twice-weekly RIF (for 5 weeks)	Twice-weekly RIF (for 5 months); daily RIF (for 2 months); twice-weekly RIF (for 3+ months)	20	1997/1997	17
6	Yes[d]	Yes[d]	39	Lungs	Daily RIF	Daily RIF	9	1990/1998	16
7	Yes	No	49	Lungs	Daily RIF	Daily RIF (for 7 months); daily RBT (for 1+ month)	80	1992/1998	11
8	Yes	Yes	39	Lungs	Daily RIF	Thrice-weekly RIF	36	1998/1998	7
9	Yes	No	33	Lungs, genito-urinary tract	Daily RIF	Daily RIF (for 3 months); twice-weekly RIF (for 1 month)	145	1998/1998	6
10	No	Yes[d]	36	Lungs, lymph nodes	Daily RIF (during first month; stopped during second month)	Restarted RIF during ninth month	20	1980s/1998	26
11	Yes	No	38	Lymph nodes	Daily RBT	Daily RBT	215	1990/1999	7

NOTE. Continuation phase, period after the first 2 months of treatment; d4T, stavudine; INH, isoniazid; intensive phase, the first 2 months of treatment; LFT, liver function test; NA, not available; Nfv, nelfinavir; RBT, rifabutin; RIF, rifampin; Rtv, ritonavir; Stm, streptomycin; 3TC, lamivudine; Zdv, zidovudine.

[a] According to positive culture results.
[b] Count was obtained nearest to the time of diagnosis of TB.
[c] Count was obtained nearest to the time of relapse of TB.
[d] Also experienced treatment failure.
[e] The patient was completely adherent to daily and twice-weekly therapy until the eighth week after treatment started.

treatment for <6 months, 140 had initial isolates that were resistant to rifampin, 24 had initial isolates that were resistant to isoniazid and ethambutol, and 21 did not receive a rifamycin. Of the 2861 patients who were still included in the analysis, 807 were HIV infected, and 2054 were HIV uninfected.

HIV-infected versus HIV-uninfected patients. Compared with HIV-uninfected patients, HIV-infected patients with TB were more likely to be older (median age, 41 vs. 39 years; $P = .003$), male (68% vs. 62%), born in the United States (69% vs. 34%), of non-Hispanic black race/ethnicity (62% vs. 34%), homeless (9% vs. 4%), an injection drug user (12% vs. 2%), and an alcohol abuser (19% vs. 11%) and to have mental illness (7% vs. 3%). There were significant differences in the clinical characteristics of and outcome for patients, according to HIV serostatus (table 1). According to univariate analysis, HIV-infected patients were more likely to have treatment failure, relapse, and ARR. In the multivariate analyses that adjusted for site of disease and nonadherence to treatment, HIV status was strongly associated with ARR (adjusted OR, 5.5; 95% CI, 1.4–21.5) but not with treatment failure or relapse.

HIV-infected patients. The association of relapse, treatment failure, and ARR with rifamycin use was examined for 807 HIV-infected patients; 737 patients (91.3%) had initial isolates that were fully susceptible, and 70 (8.7%) had initial isolates that were drug resistant. Compared with patients with initial isolates that were drug susceptible, patients with initial isolates that were drug resistant were no more likely to have relapse (2.9% vs. 1.1%; $P = .21$) or ARR (1.4% vs. 0.8%; $P = .60$). $CD4^+$ T lymphocyte counts were available for 47.3% of HIV-infected patients (median count, 59 cells/mm^3; range, 0–500 cells/mm^3). The timing of determination of the $CD4^+$ T lymphocyte count at diagnosis of TB was similar in the rifampin- and rifabutin-based, rifabutin-based, and rifampin-based treatment groups (median no. of days before or after

Nonadherence to treatment		Time from start of initial treatment to ARR, months	Time from completion of initial treatment to first culture-positive relapse	$CD4^+$ T lymphocyte count at relapse,[c] cells/mm^3	Initial drug resistance	Drug-resistance pattern at the time of ARR	Antiretroviral therapy received, according to TB episode	
During the first 2 months after initiation	During the entire treatment period						Initial	Relapse
No	No	13.3	5.8	39	…	RIF	No	Zdv
No	Yes	11.0	1.7	49	INH	RIF, INH, Stm	d4T and 3TC	Unknown
No	No	NA	14.4	NA	…	…	Refused	Unknown
No	Yes	12.7	2.0	50	…	RIF	Refused	d4T and 3TC
Yes[e]	Yes	20.9	4.0	33	…	RIF	Refused	3TC, abacavir, and Rtv
No	No	19.5	3.1	4	…	RIF	Refused	Unknown
Yes	Yes	NA	14.9	NA	INH	…	No	No
No	No	19.9	6.4	NA	…	RIF	No	d4T, 3TC, and Rtv
No	Yes	NA	6.5	54	…	…	No	3TC/Zdv
No	Yes	18.1	NA	21	…	RIF	Nfv and 3TC/Zdv	No (because of a poor LFT result)
No	No	NA	6.0	81	…	…	d4T and 3TC	d4T, 3TC, and Rtv

diagnosis of TB when the lymphocyte count was determined, 22, 30, and 19 days, respectively; $P = .84$).

Of 807 HIV-infected patients, 10 (1.2%) experienced relapse. Of these 10 patients, 6 had ARR and 1 had ARR with treatment failure but without relapse; thus, a total of 7 patients (0.9%) had ARR. The median time from treatment completion to relapse was 0.49 years (range, 0.14–1.24 years), and the median time from initiation of treatment to development of ARR was 1.15 years (range, 0.91–1.73 years). The clinical characteristics of patients with relapse or ARR are shown in table 2. All 7 patients with ARR had a $CD4^+$ T lymphocyte count of <50 lymphocytes/mm^3 at the time of diagnosis of TB. Results of IS*6110*-based RFLP analysis and spoligotyping were available for initial and event (i.e., relapse and/or ARR) isolates recovered from 5 of 10 patients who experienced a relapse and from 4 of 7 patients who developed ARR; the DNA pattern of all event isolates matched that of the initial isolate.

The rates of relapse and ARR, stratified according to the characteristics of all HIV-infected patients with TB, are shown in figure 1. The rate of ARR among such patients with a $CD4^+$ T lymphocyte count of <100 lymphocytes/mm^3 was 0.89 episode of ARR/100 person-years, and, for patients with either a $CD4^+$ T lymphocyte count of ⩾100 lymphocytes/mm^3 or an unknown $CD4^+$ T lymphocyte count, the rate of ARR was 0 episodes of ARR/100 person-years. However, the rate of relapse among patients with a $CD4^+$ T lymphocyte count of <100 lymphocytes/mm^3 was not much higher than that for patients with a $CD4^+$ T lymphocyte count of ⩾100 lymphocytes/mm^3. Patient characteristics, outcomes, and use of intermittent dosing, according to the type of regimen received, are shown in table 3. Patients treated with rifampin-based regimens did not differ from patients treated with rifabutin-based regimens, according to age, sex, treatment adherence, medical provider, and use of intermittent dosing of rifamycins.

For patients who received rifampin-based regimens alone, the risk of relapse was not statistically different from that for patients who received rifampin- and rifabutin-based regimens or rifabutin-based regimens alone (table 4). The risk of relapse was significantly higher for patients who started intermittent dosing of rifampin during the intensive phase of treatment. When the latter analysis was restricted to patients with a $CD4^+$ T lymphocyte count of <100 lymphocytes/mm^3, intermittent dosing of rifampin during the intensive phase was associated with relapse (adjusted HR, 9.8; 95% CI, 1.4–70.3) (table 4).

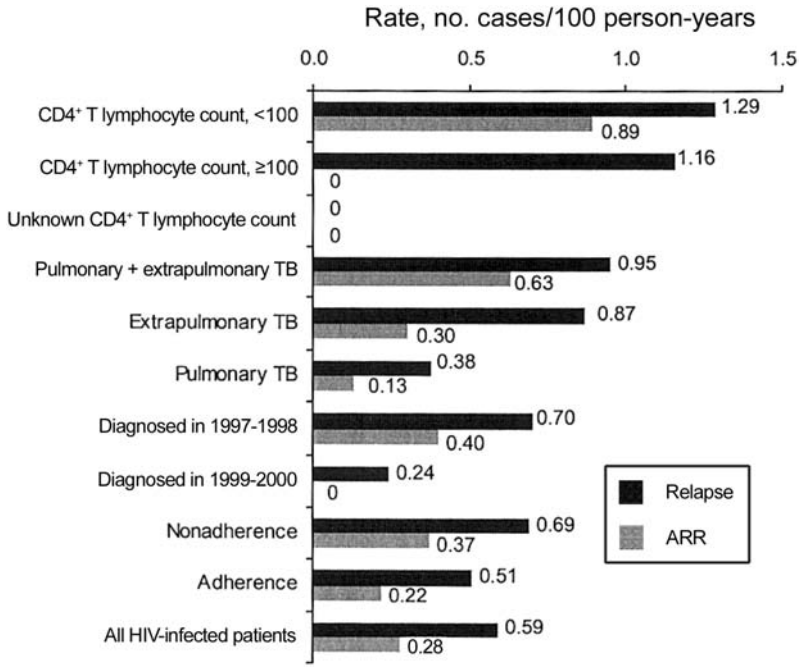

Figure 1. Rates of relapse and acquired rifampin resistance (ARR), according to selected characteristics of HIV-infected patients with tuberculosis (TB) in New York City in 1997–2000. $CD4^+$ T lymphocyte counts were expressed as the no. of lymphocytes per cubic milliliter. (The rates of relapse and ARR were not significantly different according to age, sex, country of birth, homelessness, alcohol abuse, injection drug use, mental illness, nonadherence to treatment, duration of treatment, the resistance pattern of the initial isolate, presence of acid-fast bacilli on sputum microscopy, and presence of cavitary lesions on a chest radiograph. Thus, these rates are not presented in the figure.)

Unlike the risk of relapse, the risk of ARR was significantly associated with receipt of rifampin-based regimens when analysis was restricted to patients with a $CD4^+$ T lymphocyte count of <100 lymphocytes/mm^3 (adjusted HR, 8.5; 95% CI, 1.03–70.9) (table 5). Among patients who received rifampin-based regimens alone, patients who began receiving intermittent dosing during the intensive phase of treatment had an increased risk of ARR (crude HR, 6.4; 95% CI, 1.1–38.44), compared with patients who did not receive intermittent dosing of rifampin. This association remained significant when analysis was restricted to patients with a $CD4^+$ T lymphocyte count of <100 lymphocytes/mm^3 (adjusted HR, 6.2; 95% CI, 1.03–36.9). Only 20 patients received rifampin intermittently in the intensive phase; 2 of these patients with ARR experienced a relapse (patients 2 and 5; table 2). The initial treatment regimens received by both of these patients involved isoniazid, rifampin, ethambutol, and pyrazinamide. Patient 2 had isoniazid discontinued after the first month of treatment, because the initial isolate was resistant to isoniazid. Starting intermittent dosing of rifampin during the continuation phase of treatment did not increase the risk of ARR.

Treatment failure was not associated with the type of rifamycin regimen received. Thirteen (1.6%) of 807 HIV-infected patients with TB experienced treatment failure; none received a rifabutin-based regimen alone. Treatment failure was not associated with the type of regimen received (OR, 1.8; 95% CI, 0.6–5.5; $P = .31$). Treatment failure also was not affected for patients receiving intermittent dosing of rifampin either during the intensive phase (OR, 1.4; 95% CI, 0.2–11.1; $P = .75$) or during the continuation phase (OR, 0.4; 95% CI, 0.1–2.8; $P = .32$), compared with patients who never received an intermittently administered regimen.

CONCLUSIONS

Two major findings from this study are noteworthy. First, this is the largest cohort of HIV-infected patients treated with rifabutin, and the patients had good outcomes. No patient who was treated with a rifabutin-based regimen alone and 1 patient who was treated with a rifabutin- and rifampin-based regimen had ARR. This finding differs from the findings of previous studies in which intermittent dosing of rifabutin or previous treatment with rifabutin was suspected to be the probable cause of development of rifampin monoresistance [10, 11, 18]. The difference may be the result of the fact that none of the patients in the present study began receiving intermittent dosing with rifabutin during the intensive phase.

Second, intermittent rifampin therapy significantly increased the risk of ARR only when intermittent dosing was begun during the intensive phase. This elevated risk remained when analy-

Table 3. Selected characteristics of and outcomes and intermittent therapy for HIV-infected patients with tuberculosis (TB) in New York City in 1997–2000, according to the type of regimen received.

Finding	RIF-based regimen (n = 355)	RBT-based regimen (n = 57)	RIF- and RBT-based regimen (n = 395)		
			Entire regimen	RIF portion	RBT portion
$CD4^+$ T lymphocyte count					
Data available	153 (43.1)	20 (35.1)	209 (52.9)	…	…
Median lymphocytes/mm^3[a] (range)	63 (0–462)	58.5 (0–388)	57 (0–500)	…	…
Treatment provider					
Department of health clinics	136 (38.3)	27 (47.4)	124 (31.4)	…	…
Public health facility	76 (21.4)	9 (15.8)	81 (20.5)	…	…
Private sector	133 (37.5)	18 (31.6)	159 (40.3)	…	…
Other	10 (2.8)	3 (5.3)	31 (7.8)	…	…
Treatment failure	8 (2.3)	0 (0.0)	5 (1.3)	…	…
Relapse of TB	7 (2.0)	1 (1.8)	2 (0.5)	…	…
Acquired rifampin resistance	6 (1.7)	0 (0.0)	1 (0.3)	…	…
Started intermittent dosing of RIF					
In the intensive phase[b]					
Twice weekly	12 (3.4)	3 (5.3)	…	15 (3.8)	7 (1.8)
Thrice weekly	8 (2.3)	1 (1.8)	…	9 (2.3)	8 (2.0)
In the continuation phase[b]					
Twice weekly	111 (31.3)	18 (31.6)	…	38 (9.6)	83 (21.0)
Thrice weekly	42 (11.8)	4 (7.0)	…	12 (3.0)	25 (6.3)
Continued intermittent dosing of RIF in continuation phase[b,c]					
Twice weekly	10 (2.8)	3 (5.3)	…	11 (2.8)	7 (1.8)
Thrice weekly	7 (2.0)	1 (1.8)	…	4 (1.0)	6 (1.5)
Never received intermittent therapy	199 (56.1)	33 (57.9)	223 (56.5)	…	…

NOTE. Data are no. (%) of patients, unless indicated otherwise. Continuation phase, period after the first 2 months of treatment; intensive phase, first 2 months of treatment; RBT, rifabutin; RIF, rifampin.

[a] Based on available data.

[b] The nos. of patients were not exclusive.

[c] After intermittent dosing of RIF was started in the intensive phase.

sis was confined to patients with a $CD4^+$ T lymphocyte count of <100 lymphocytes/mm^3. A recent study of the US Public Health Service Tuberculosis Trials Consortium also had similar findings [10]. However, the present study also revealed that intermittent dosing that was initiated after the intensive phase of treatment did not increase the risk of ARR for HIV-infected patients with TB, even when they had a low $CD4^+$ T lymphocyte count. The findings of the present study support current CDC recommendations against the use of intermittent regimens during the intensive phase of treatment for patients with TB and advanced HIV infection [6, 20], and they also support the hypothesis that, for HIV-infected patients with TB, the critical time for development of resistance to rifampin may be in the first 2 months of treatment.

The present study also found that intermittent dosing of rifampin during the intensive phase of treatment also increased the risk of relapse. It is possible that this relationship could have been confounded by the development of ARR, because 6 of 10 patients who experienced relapse had ARR as well. However, because both relapse and ARR are equally important clinical outcomes, and because they tend to occur concurrently in HIV-infected patients, factors that predict ARR may also predict relapse.

Consistent with the findings of other studies [23–27], the relapse rate was low among HIV-infected patients with TB in the present study, and it was lower than that noted in our previous study [28]. This decrease in the relapse rate may explain why HIV infection was no longer associated with relapse in the present study, although it was a risk factor observed in our previous study [28]. The decrease in the relapse rate also demonstrates the effectiveness of TB-control efforts for HIV-infected patients with TB. In addition, most cases of relapse occurred in patients who received an initial diagnosis of TB in 1997 or 1998.

Although it would be useful to evaluate an association of ARR with treatment failure or relapse, the present study was

Table 4. Results of Cox proportional hazards analysis of the association of the use of rifamycin with the risk of development of relapse among 758 HIV-infected patients with tuberculosis (TB) in New York City in 1997–2000.

Variable	Total no. of patients	No. (%) of patients who experienced a relapse	Crude HR (95% CI)	HR (95% CI)[a]
Regimen				
RIF based	332	7 (2.1)	4.0 (0.8–19.2)	3.5 (0.7–18.2)
RBT based	55	1 (1.8)	3.6 (0.3–40.3)	NA[b]
RIF and RBT based	371	2 (0.5)	1.0	1.0
Started intermittent dosing of RIF[c]				
In intensive phase	19	2 (10.5)	6.7 (1.1–40.1)	9.8 (1.4–70.3)
In continuation phase	134	1 (0.7)	0.9 (0.1–5.3)	0.8 (0.1–8.6)
Never	179	4 (2.2)	1.0	1.0

NOTE. Included only patients who completed treatment and therefore were eligible for relapse analysis. Continuation phase, period after the first 2 months of treatment; HR, hazard ratio; intensive phase, first 2 months of treatment; RBT, rifabutin; RIF, rifampin.

[a] Analysis restricted to include only those patients who had a $CD4^+$ T lymphocyte count of <100 lymphocytes/mm^3.
[b] No patient who experienced relapse had a $CD4^+$ lymphocyte count of <100 lymphocytes/mm^3, and, therefore, this result is not available (NA).
[c] Limited to patients who received a RIF-based regimen only.

limited in that the number of events was too small to make this assessment. Incomplete data on the $CD4^+$ T lymphocyte count at the time of diagnosis of TB limited our ability to fully explore the effect of the $CD4^+$ T lymphocyte count on outcomes of interest. Use of HAART may have decreased the relapse rate for patients with TB diagnosed after 1998. Another potential limitation of the present study was an underestimation of events resulting from the exclusion of 24 HIV-infected patients and 91 HIV-uninfected patients who did not receive TB treatment for ⩾6 months; however, none of these patients had treatment failure or ARR. Last, we considered the likelihood of reinfection versus that of ARR or relapse. Other studies have shown that reinfection is unlikely in settings in which the incidence of TB is low [13, 14]. The findings of the present study also show a low likelihood of reinfection.

In summary, the present study suggests that the risk of ARR does not depend on the rifamycin used but, rather, on the dosing of rifampin during the intensive phase of treatment. This finding reiterates that patients who have coinfection with TB and HIV should not receive twice-weekly regimens during the intensive phase of treatment. In addition, the present study suggests that an increased risk of ARR is associated with thrice-weekly dosing of rifampin. This finding should be further examined, because it could have implications for TB treatment

Table 5. Results of Cox proportional hazards analysis of the association of rifamycin use with the risk of development of acquired rifampin resistance (ARR) among 807 HIV-infected patients with tuberculosis in New York City in 1997–2000.

Variable	Total no. of patients	No. (%) of patients with ARR	Crude HR (95% CI)	HR (95% CI)[a]
Regimen				
RIF based	355	6 (1.7)	6.9 (0.8–57.6)	8.5 (1.03–70.9)
RBT based	57	0	NA[b]	NA[b]
RIF and RBT based	395	1 (0.3)	1.0	1.0
Started intermittent dosing of RIF[c]				
In intensive phase	20	2 (10.0)	6.4 (1.1–38.4)	6.2 (1.03–36.9)
In continuation phase	136	1 (0.7)	0.4 (0.1–4.3)	0.6 (0.1–5.4)
Never	199	3 (1.5)	1.0	1.0

NOTE. Continuation phase, period after the first 2 months of treatment; HR, hazard ratio; intensive phase, first 2 months of treatment; RBT, rifabutin; RIF, rifampin.

[a] Analysis restricted to include only those patients who had a $CD4^+$ T lymphocyte count of <100 lymphocytes/mm^3.
[b] No patients who received a rifabutin-based regimen experienced relapse; therefore, this result is not available (NA).
[c] Limited to patients who received a RIF-based regimen only.

guidelines globally. Use of thrice-weekly regimens during the intensive phase of treatment is recommended by the World Health Organization and the International Union Against Tuberculosis and Lung Disease for TB treatment, regardless of the HIV status of patients [29, 30]. Rifabutin-based regimens were quite effective. Although relapse rates were low, the majority of patients with relapse had ARR. Clinicians should expect and provide treatment for resistance to rifampin until susceptibility is confirmed in HIV-infected patients suspected of having relapse of TB.

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