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Outcomes of HIV-infected Patients Treated for Recurrent Tuberculosis with the Standard Retreatment Regimen

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Abstract

SETTING—AIDS and tuberculosis center in Port-au-Prince, Haiti.

OBJECTIVE—To measure the effectiveness of tuberculosis retreatment with the standard regimen (2HRZES/1HRZE/5HRE) in HIV-infected adults.

DESIGN—Cohort study.

RESULTS—Of 1,318 HIV-infected patients with access to antiretroviral therapy following World Health Organization guidelines, 56 were diagnosed with recurrent pulmonary tuberculosis and retreated with the standard regimen. Ten patients (18%) died during retreatment, 3 patients (5%) defaulted, and 2 patients (4%) failed. Forty-one patients (73%) had a good retreatment outcome (cure, treatment completed). Of these, 8 patients (20%) died during follow-up, 5 patients (12%) were lost, and 5 patients (12%) had a second recurrence of tuberculosis. Only 26 (46%) of the 56 patients remained alive, in-care, and TB-free after a median of 36 months follow-up.

CONCLUSION—HIV-infected patients treated for recurrent tuberculosis with the standard retreatment regimen have a high mortality and poor long-term outcomes.

Keywords

tuberculosis; retreatment; human immunodeficiency virus

INTRODUCTION

In resource-poor countries with a low prevalence of multidrug-resistant tuberculosis (MDR-TB) and limited capacity for drug susceptibility testing (DST), the World Health Organization (WHO) recommends that patients with recurrent tuberculosis (TB) receive a standard 8-month regimen of first-line drugs (2HRZES/1HRZE/5HRE)[1]. Patients infected with the human immunodeficiency virus (HIV) have high rates of recurrent TB[2]. Therefore, a significant number of HIV-infected patients in resource-poor countries are likely to receive the WHO recommended standard retreatment regimen.

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In our clinic, we noted a large number of deaths of HIV-infected patients receiving this regimen, even though they had access to antiretroviral therapy (ART). Surprisingly, we found very little data in the literature on TB retreatment outcomes in HIV-infected patients.

Outcomes of standard TB retreatment in HIV-infected individuals may not be adequately predicted by TB retreatment outcomes in HIV-uninfected patients. Patients with primary TB who are coinfected with HIV have higher mortality than patients without HIV, and primary TB patients who have HIV or who live in an HIV-prevalent setting have higher TB treatment failure and relapse rates than patients not living with the burden of HIV[1,3]. It is reasonable to expect that HIV-infection has an impact on mortality, failure, and relapse rates related to standard treatment of recurrent TB as well. WHO recommends HIV testing for all individuals with suspected or confirmed TB and increased frequency of standard treatment dosing for primary TB in HIV-infected patients and in patients in high HIV-prevalent settings[1]. WHO recommendations for standard TB retreatment, on the other hand, do not depend on HIV status[1], likely because although poor standard retreatment outcomes have been attributed to high HIV-prevalence[4], there are limited data on retreatment outcomes in HIV-infected individuals[1,5].

It is uncertain whether HIV-infected patients with access to ART have adequate success rates with standard TB retreatment. Therefore, we conducted a study to determine outcomes of HIV-infected patients treated for recurrent TB with 2HRZES/1HRZE/5HRE in Haiti.

METHODS

Study Setting

Haiti has the highest incidence of TB in the Western Hemisphere: 238 cases per 100,000 population in 2009. The rate of multi-drug resistance is 3%[6]. We conducted the study at the Groupe Haitien d'Etude du Sarcome de Kaposi et des Infections Opportunistes (GHESKIO) in Port-au-Prince.

HIV-1 infected patients at GHESKIO with new TB are treated with the WHO recommended directly observed regimen of isoniazid (H), rifampin (R), ethambutol (E), and pyrazinamide (Z) for two months and HR daily for four months. Patients with recurrent TB receive the standard retreatment regimen: 2 months of HRZE and streptomycin (S), 1 month of HRZE, and 5 months of HRE[1].

Study Population

The study population was a subset of patients with recurrent TB among a large cohort of 1,318 HIV-1 infected adults enrolled in a longitudinal study of patients initiating antiretroviral therapy according to WHO guidelines[7,8,9,10]. Patients in this cohort all had access to highly active antiretroviral therapy; were well characterized with standardized demographic, clinical, and laboratory data; and had excellent long-term follow-up after completion of the TB retreatment regimen. The study was approved by the institutional review boards of GHESKIO and Weill Cornell Medical College.

We analyzed treatment outcomes for all patients from this cohort who were ≥ 13 years old and who were diagnosed with recurrent TB and treated with 2HRZES/1HRZE/5HRE between 1 March 2003 and 31 December 2008. We defined a recurrent TB case as a patient who had successfully completed TB treatment in the past and who was subsequently diagnosed with a second epidsode of TB at GHESKIO. Cases met the American Thoracic Society definition of confirmed, probable or clinically-diagnosed pulmonary TB, which has been used previously in GHESKIO reports[3,11,12].

Study Outcomes

We examined treatment outcomes on 2HRZES/1HRZE/5HRE, categorized according to WHO criteria as cure, treatment completed, treatment failure, died, and default[1]. We also examined outcomes after the completion of TB retreatment, including death, lost to follow-up, and a second recurrence (third occurrence) of TB. The expected follow-up period ranged from 12 to 80 months from the initiation of TB retreatment, depending on when the participant was enrolled. Patients who were lost or who were still alive at the end of the study were censored. The short-term retreatment outcomes of the HIV-infected cohort were compared to the outcomes of the 97 HIV-uninfected patients who were treated for recurrent TB at GHESKIO during the study period. The HIV-negative cohort was not followed after completion of recurrent TB therapy.

Statistical Analysis

Data were analyzed with STATA, version 11.0. Proportions were compared by the chi-squared test or, for expected cell values of less than five, by Fisher's exact test. Medians were compared with the Wilcoxon rank-sum test. Kaplan-Meier survival analysis was used to estimate the time from the initiation of TB retreatment to death. For patients who did not reach the endpoint, the data were censored at the date of the last visit. Cox multivariate analysis was performed to identify predictors of mortality among the characteristics measured: age, weight, hemoglobin, and CD4 count at the start of TB retreatment. Time-varying cox regression was performed on ART exposure and CD4 count, which changed during the retreatment period.

RESULTS

Patient Characteristics

Of 1,318 HIV-infected adult patients, fifty-six (4%) were diagnosed with recurrent TB and treated with the standard retreatment regimen, 2HRZES/1HRZE/5HRE. The characteristics of the 56 patients at the time of diagnosis are described in Table 1. The median age was 37 years (Interquartile Range [IQR] 32–44 years), the median weight was 121 pounds (IQR 109–133 pounds) for men and 100 pounds (93–113 pounds) for women, and the median CD4 T-cell count was 183 cells per mm^3 (IQR 92–298 cells per mm^3).

Of the 56 patients, 28 (50%) were diagnosed and treated for recurrent TB at least one month after initiating antiretroviral therapy, with a median of 9 months (IQR 4–11) between starting antiretroviral therapy and TB retreatment. Fourteen patients (25%) started ART and TB retreatment at the same time (+/− 1 month). Fourteen patients (25%) started TB retreatment and deferred the initiation of ART for a median of 7 months (IQR 2–17).

Twenty patients (36%) had recurrent TB confirmed by either positive sputum smear or culture. Of these, three patients (15%) had negative smear and positive culture. Thirty-six patients (64%) were diagnosed with recurrent TB based on clinical findings, chest radiograph consistent with TB, and response to empirical TB therapy (Table 1).

During the same study period, 97 HIV-uninfected patients were treated at GHESKIO for recurrent TB. The median age of the HIV-uninfected patients was 30 years (IQR 24–39). Forty-five percent were female, and 80% had microbiologically-confirmed TB.

TB Retreatment Outcomes

The TB retreatment outcomes of the 56 HIV-infected patients and 97 HIV-uninfected patients are listed in Table 2. In the HIV-infected cohort, 41 patients (73%) had good retreatment outcomes (cure, treatment completed), 10 patients (18%) died, 3 patients (5%)

defaulted, and 2 patients (4%) failed. All ten patients who died during retreatment were women (relative risk 2.3, p = 0.001, Fisher's Exact Test). Both patients who failed standard retreatment subsequently received therapy for multi-drug resistant TB but died. In the HIV-uninfected control group, 79 patients (81%) had good retreatment outcomes (cure, treatment completed), 4 patients (4%) died, 10 patients (10%) defaulted, and 4 patients (4%) failed. Half of the patients who died were women. The relative risk of death during TB retreatment between HIV-infected and HIV-uninfected patients was 2.3 (p = 0.01, Fisher's Exact Test), Table 2.

Survival

The 41 HIV-infected patients (73%) who successfully completed TB retreatment were followed for a period between 12 and 80 months from the initiation of TB retreatment (median 54 months, IQR 29–70 months). Eight patients (20%) died during post-treatment follow-up, 5 patients (12%) were lost, and 5 patients (12%) had a second recurrence (third occurrence) of TB a median of 17 months after completion of 2HRZES/1HRZE/5HRE. Kaplan Meier analysis estimated that the survival of the 56 HIV-infected patients during retreatment and follow-up was 78% at 12 months, 70% at 24 months, and 67% at 36 months. Only 26 (46%) of the 56 HIV-infected patients successfully completed 2HRZES/1HRZE/5HRE and remained alive, in-care, and TB-recurrence-free at the end of the study.

Cox proportional hazards model of baseline patient characteristics (age, weight, hemoglobin, and CD4 count) stratified by gender found a decrease in mortality with increasing weight (HR 0.7 for 5 pound increase, 95%CI 0.6–0.9, p = 0.001) and hemoglobin (HR 0.5 for 1 gram/deciliter increase, 95%CI 0.4–0.8, p < 0.001), Table 3. Cox regression with time-dependent analysis of ART exposure and CD4 count during retreatment found that a 50 cell per mm^3 increase in CD4 count was associated with a 30% decrease in mortality (95%CI 10% to 40%, p = 0.004).

DISCUSSION

HIV-infected patients retreated for recurrent TB with the WHO recommended standard regimen, 2HRZES/1HRZE/5HRE, had poor retreatment outcomes, with only 73% of patients successfully completing therapy. Moreover, these patients had high mortality during three years of follow-up. Only 46% of HIV-infected patients were alive, in care, and tuberculosis-free after a median of 36 months of care.

The 73% success rate of TB retreatment in our HIV-infected cohort compares favourably to the 72% global success rate in 2008 for all TB retreatment cases worldwide, including HIV-uninfected patients and patients who received empiric MDR-TB regimens or individualized regimens based on DST[7]. The 4% failure rate in our HIV-infected cohort is lower than the global average of 10%, and the 5% default rate is half the global average of 10%. However, the percentage of patients in our HIV-infected cohort who died during retreatment (18%) is more than double the global average for all patients, 7%[7]. In addition, 44% of the patients in our cohort who successfully completed retreatment subsequently died, relapsed, or were lost during an average of 3-years of follow-up.

Our data show that HIV-infected patients have a high mortality during standard TB retreatment. While the rate of successful retreatment for HIV-infected patients initially is, based on WHO treatment outcome categories, on par with the global average for all TB retreatment patients, follow-up for a median of 36 months reveals high subsequent mortality and relapse (third occurance) rates[1,7]. Data on prior TB treatment were not available for the majority of patients in the study; therefore, it is not possible to analyze retreatment outcomes by primary treatment outcome category[4].

In our study, HIV-infected patients had a lower rate of successful TB retreatment (73%) compared to HIV-uninfected patients (81%), although the difference in the retreatment success rate between the two groups was not statistically significant. HIV-infected patients are, however, more than twice as likely than uninfected patients to die during standard TB retreatment. Retreatment success rates amoung HIV-infected and HIV-uninfected patients in Haiti were similar to those observed by Jones-Lopez et al (2011) in Uganda, a country which also has a relatively low MDR-TB rate, in which 74% of HIV-infected patients and 80% of HIV-uninfected patients had good standard TB retreatment outcomes[5]. These authors found increased mortality during retreatment among HIV-infected patients and increased mortality during post-treatment follow-up among patients with CD4 count < 200 cells/mm^3 who were not on ART[5]. All of the patients in our study had access to ART. Despite this, there was high mortality during treatment and high mortality and relapse rate during post-treatment follow-up.

Two thirds of the cases in our study were smear negative. This makes our results particularly relevant to TB treatment in resource-poor settings with high HIV prevalence, but it also makes identification of a second recurrence (third occurrence) of TB in our cohort difficult.

It is more difficult to confirm TB diagnosis in HIV-infected patients than in HIV-uninfected patients because the former are more likely to be smear negative[3]. Among HIV-infected patients on standard treatment for new TB, smear negative cases are generally more immunosuppressed than smear positive cases and, therefore, have higher mortality[1,3,13]. If the same holds for HIV-infected patients on standard retreatment, then cohorts that include only smear positive cases would underestimate mortality[5]; unfortunately, our sample size was not large enough to compare outcomes between smear positive and smear negative cases.

Due to the high proportion of smear negative cases, our study may actually underestimate the already significant proportion (12%) of patients who had a second recurrence (third occurrence) of TB. This, coupled with the significant proportion of patients (20%) who died during post-treatment follow-up, should make clinicians in resource-poor settings uneasy about apparently successful standard retreatment of TB in HIV-infected patients.

We found that lower weight and hemoglobin for gender were associated with increased mortality. In the short term, these data can help clinicians and HIV/TB program managers in resource-poor settings with limited DST determine which patients are the highest priority candidates for potentially scarce second-line TB drugs and/or DST. About half of the HIV-infected patients had initial CD4 counts below 200 cells/mm^3. Low initial CD4 count and delayed ART initiation were not associated with increased mortality, though failure to observe an increase in mortality in patients with very low CD4 (<50 cells/mm^3), as was found in Uganda[5], and in those with delayed ART initiation may be due to small sample size. Notably, in time-varying Cox Regression, mortality decreased with increasing CD4 count while patients were on ART.

Since DST was not available in Haiti at the time of the study, it is not possible to determine whether the poor long-term survival is due, for example, to undiagnosed MDR-TB that does not respond to a streptomycin-based regimen. Increasing access to DST and MDR-TB therapy in low-income countries, even those with low MDR prevalence such as Haiti, is a high priority, especially given that all patients with MDR-TB in Uganda who underwent standard TB retreatment had unsuccessful outcomes[5].

TB recurrence rates are high among HIV-infected patients[2]. It is likely that hundreds of thousands of HIV-infected patients in Africa, the Carribean and other resource-poor settings receive the standard retreatment regimen. Further study of this regimen in HIV-infected

patients might identify a subset of patients likely to respond well to standard TB retreatment, and the addition of familiar measures, such as nutritional support[14] and post-treatment isoniazid prophylaxis[2], might lead to some improvement in short- and long-term standard TB retreatment outcomes; however, given the high mortality and recurrence rates, despite access to ART and low country-wide MDR-TB prevelance, it is probably time to abandon the standard TB retreatment regimen in HIV-infected patients altogether. Second line anti-TB drugs and DST should be made available to HIV-infected patients with recurrent TB.

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Table 1

Characteristics of 56 patients with AIDS and recurrent pulmonary TB

Characteristics at TB retreatment	
Male/Female	26/30
Age, median years (IQR)	37 (32–44)
Weight, median pounds (IQR)	
Male patients	121 (109–133)
Female patients	100 (93–113)
CD4 count, median cells/mm^3(IQR)	183 (92–298)
Hemoglobin, median grams/deciliter (IQR)	
Male patients	11.1 (9.9–12.1)
Female patients	9.3 (8.9–10.5)
Symptoms at TB retreatment	
Fever — no. (%)	33 (59)
Cough — no. (%)	51 (91)
Weight loss — no. (%)	27 (48)
Microbiologic confirmation (smear or culture) — no. (%)	20 (36)
Time between ART initiation and TB retreatment	
ART before TB retreatment — no. (%), median months between ART and TB retreatment (IQR)	28 (50%), 9 (4–11)
ART and TB retreatment at the same time — no. (%)	14 (25%)
ART after TB retreatment (months) — no. (%), median months between ART and TB retreatment (IQR)	14 (25%), 7 (2 – 17)

Table 2

TB retreatment outcomes in 56 HIV-infected and 97 non-HIV-infected patients

TB retreatment outcome	HIV+	HIV−	p-value
Cure/ Treatment Completed — no. (%)	41 (73)	79 (81)	0.23
Default — no. (%)	3 (5)	10 (10)	0.38
Failure — no. (%)	2 (4)	4 (4)	1.00
Died — no. (%)	10 (18)	4 (4)	0.01
Total	56 (37)	97 (63)	

Table 3

Predictors of mortality by Cox proportional hazards regression. 1) Patient characteristics at retreatment initiation, stratified by gender. 2) Time-Dependent analysis of ART exposure and CD4 count during retreatment.

Factor	Hazard Ratio (95% CI)	p-value
Characteristics at Retreatment Initiation		
Age (5 year increment)	1.1 (0.9–1.3)	0.54
Weight (5 pound increment)	0.7 (0.6–0.9)	0.001
Hemoglobin (1 gram/deciliter increment)	0.5 (0.4–0.8)	<0.001
Initial CD4 Count (50 cell/mm increment)	1.0 (1.0–1.1)	0.35
ART Exposure and CD4 Count During Retreatment		
ART Exposure	0.6 (0.1–2.7)	0.48
CD4 Count (50 cell/mm increment)	0.7 (0.6–0.9)	0.004