

PULMONARY TUBERCULOSIS IN HIV-INFECTED PATIENTS IN ZAIRE

A Controlled Trial of Treatment for Either 6 or 12 Months

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Abstract Background. We studied the efficacy of a short-course regimen of chemotherapy for pulmonary tuberculosis in Kinshasa, Zaire. We also assessed whether, among patients with human immunodeficiency virus (HIV) infection, treatment should be extended from 6 to 12 months.

Methods. HIV-seropositive and HIV-seronegative outpatients with pulmonary tuberculosis were treated with rifampin, isoniazid, pyrazinamide, and ethambutol daily for two months, followed by rifampin plus isoniazid twice weekly for four months. The HIV-positive patients who had no evidence of tuberculosis were then randomly assigned to receive either rifampin plus isoniazid or placebo twice weekly for a further six months. We also followed a comparison group of HIV-seronegative patients who received no further treatment for tuberculosis after six months.

Results. After six months, 260 of 335 HIV-seropositive and 186 of 188 HIV-seronegative participants could be evaluated, and their rates of treatment failure were similar: 3.8 and 2.7 percent, respectively. At 24 months, the HIV-seropositive patients who received extended treatment had a relapse rate of 1.9 percent, as compared with 9 percent among the HIV-seropositive patients who received placebo for the second 6 months ($P < 0.01$). Extended treatment did not improve survival, however. Among the HIV-seronegative patients, 5.3 percent relapsed.

Conclusions. Among HIV-seropositive patients with pulmonary tuberculosis, extending treatment from 6 to 12 months reduces the rate of relapse but does not improve survival. The six-month program of partly intermittent antituberculous treatment may be an acceptable alternative when resources are limited. (N Engl J Med 1995;332:779-84.)

IN 1988, when this study was planned, the recommendation of the Centers for Disease Control and Prevention for the treatment of known or suspected tuberculosis in patients with human immunodeficiency virus (HIV) infection was that at least three drugs (isoniazid, rifampin, and pyrazinamide) should be used during the first two months, with the addition of ethambutol in cases of disseminated disease or suspected resistance to isoniazid. Treatment for nine months was recommended, or for at least six months after conversion to a positive culture, although it was recognized that the optimal duration of therapy was unknown.¹ There was no specific recommendation for the use of intermittent therapy (therapy administered two or three times weekly), which is known to be effective in patients without HIV infection.²⁻⁵

This study was conducted to compare the efficacy of a six-month, partly intermittent regimen for tuberculosis (administered daily during the first two months and then twice weekly) among HIV-infected and HIV-unin-

ected patients with pulmonary tuberculosis and to determine whether an additional six months of antituberculous chemotherapy improves outcomes among HIV-infected patients.

METHODS

Study Design

We conducted a prospective, open-label study of a six-month, partly intermittent regimen of tuberculosis therapy among HIV-seropositive and HIV-seronegative patients with a first episode of smear- and culture-positive pulmonary tuberculosis. At the end of the 6 months, patients without evidence of tuberculosis were followed for relapse over the next 18 months. HIV-seropositive patients entered a randomized, single-blind, placebo-controlled trial of treatment with rifampin plus isoniazid for an additional six months. HIV-seronegative patients were followed as an untreated comparison group.

Setting

In Kinshasa, Zaire, the Centre de Dépistage de la Tuberculose (CDT) is the largest outpatient facility for the diagnosis of tuberculosis. At the center, patients with pulmonary symptoms are screened for tuberculosis by microscopic analysis of sputum. They are then referred for treatment to 1 of 63 primary health care clinics in the greater Kinshasa area. During the study, all patients who had first episodes of pulmonary tuberculosis positive on sputum microscopy were referred to a special clinic to be screened for eligibility for the study and possible follow-up, if they lived in the catchment area of 1 of 21 primary health care clinics collaborating with the study. The clinics were selected on the basis of their size and the quality of their follow-up services, and they treated approximately two thirds of all patients with tuberculosis diagnosed at the CDT during the study.⁶

The seroprevalence of HIV among patients with pulmonary tuberculosis newly diagnosed at the CDT remained about 20 percent during the study, whereas in the general adult population the seroprevalence was between 5 and 7 percent.^{7,8}

Evaluation of Patients

Two hundred consecutive HIV-seropositive patients and the first 200 HIV-seronegative patients, matched to the seropositive patients according to age (within two years on either side of the age of the

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seropositive patients) were eligible for the study if they had a first episode of pulmonary tuberculosis positive by microscopy and culture.

After giving written informed consent, the patients underwent HIV serologic testing as described previously.⁹ Patients who appeared to be eligible on the basis of HIV serologic criteria (i.e., who were presumed to be HIV-seropositive by a rapid assay for anti-HIV antibodies [HIVCHEK, Dupont, Grand Saconnex, Switzerland] or who were presumed to be HIV-seronegative by a rapid test and who also satisfied the criteria for matching) underwent a clinical assessment, sputum microscopy, and culture to verify the diagnosis of pulmonary tuberculosis made at the CDT. Mycobacterial isolates were tested for susceptibility to antimicrobial agents, and the patients were referred to the treatment clinics.

Thereafter, patients were seen in the research clinic every 2 months for 24 months. At each visit a clinical assessment was made that included sputum microscopy and systematic questioning about the occurrence of symptoms reported as side effects. If sputum could not be produced spontaneously, it was induced by asking the patient to inhale 3 percent saline. At 2, 6, 12, 18, and 24 months, sputum cultures were performed, and susceptibility to antituberculous drugs was determined when cultures were positive.

Sputum microscopy was performed as described previously.⁹ Sputum samples were cultured in duplicate on Löwenstein–Jensen medium (BioMérieux, Marcy l'Etoile, France), and isolates were identified by standard methods.¹⁰ Sensitivity to the antimicrobial agents isoniazid, rifampin, ethambutol, and pyrazinamide was assessed on Löwenstein–Jensen medium with antibiotics (BioMérieux) by the proportions method described by Canetti et al.¹¹

Blood was drawn from all the study patients for hematologic analysis and studies of blood chemistry at the start of the study and at two and six months. Another blood sample was obtained at 12 months from the HIV-seropositive patients. Lymphocyte phenotypes were studied by flow cytometry (FACScan, Becton Dickinson, San Jose, Calif.) at entry into the study.

Treatment

The 6-month treatment used in the study consisted of a 2-month (60-day) initial phase and a 4-month (120-day) continuation phase. During the initial phase, treatment was given daily and observed directly, except on Sundays, when the patients administered the treatment to themselves. Each daily dose consisted of combination tablets of rifampin, isoniazid, and pyrazinamide (Rifater, Marion Merrell Dow, Winnersh, United Kingdom; 120 mg of rifampin, 50 mg of isoniazid, and 300 mg of pyrazinamide per tablet; one tablet per 10 kg of body weight) and generic tablets of ethambutol (three 400-mg tablets per day, or two if the body weight was less than 50 kg).

During the continuation phase, treatment was given twice weekly, with one dose given under direct observation and one administered by the patient. Each dose consisted of rifampin (600 mg, or 450 mg if the body weight was less than 50 kg) and isoniazid (15 mg per kilogram), administered as combination tablets of rifampin and isoniazid (Rifinah, Marion Merrell Dow; 300 mg of rifampin and 150 mg of isoniazid, or 150 mg of rifampin and 100 mg of isoniazid), supplemented with generic tablets of 300 mg of isoniazid.

The HIV-seropositive patients receiving extended treatment for an additional six months were given either the same drugs and dosages that they received during the four-month continuation phase or placebo. According to national guidelines in Zaire, patients who had a treatment failure or a relapse were treated again with the same six-month regimen. No patients received antiretroviral drugs at any time during the study.

Outcome Variables

The main outcomes of interest were treatment failure and relapse of tuberculosis. Treatment failure was defined by evidence of tuberculosis at the end of the six-month course. A relapse of tuberculosis was defined by evidence of tuberculosis in a patient who had had no such evidence at the completion of the six-month course. After the six-month course and during subsequent follow-up, tuberculosis was diagnosed when a patient's sputum smears were positive for acid-fast bacilli or a culture from any site was positive for *Mycobacterium tuberculosis* (five or more colonies per slant culture), or when there were

fewer colonies of *M. tuberculosis* on culture and symptoms were suggestive of ongoing active tuberculosis (fever, cough, expectoration, hemoptysis, thoracic pain, dyspnea, or adenopathy).

As in other studies, patients with a clinical response to treatment who had fewer than five colonies of *M. tuberculosis* in specimens obtained late in treatment or after treatment were not considered to have had treatment failures or relapses if subsequent cultures and microscopy were negative and if no clinical deterioration appeared later.¹² This finding is termed an "isolated positive culture" throughout this article.

The secondary outcomes studied were survival, the proportion of patients with negative tests of sputum by microscopy and culture during and at the end of the six-month course, and the incidence of adverse events.

Statistical Analysis

The chi-square test (with Yates' correction in two-by-two tables), Fisher's exact test, the t-test, and the Kruskal–Wallis test were used as appropriate. Survival rates and the incidence of relapse and adverse events were assessed by life-table methods and compared by the log-rank test. P values of less than 0.05 by a two-sided test were considered to indicate statistical significance.

RESULTS

Population of Patients

From March 9, 1989, through September 7, 1991, a total of 568 patients in whom a first episode of pulmonary tuberculosis had been tentatively diagnosed were screened for eligibility for the study. Twenty-six HIV-seropositive and 12 HIV-seronegative patients were excluded for the reasons shown in Table 1, as were 7 patients with indeterminate HIV serologic status. The

Table 1. Base-Line Characteristics of the Study Patients.

CHARACTERISTIC	HIV-POSITIVE	HIV-NEGATIVE
No. screened	361	200
No. excluded*		
Culture negative for mycobacteria	13	5
Missing culture	1	2
Contaminated culture	5	1
Culture grew another pathogen	7†	4‡
No. included with cultures positive for <i>M. tuberculosis</i>	335	188
Male sex — no. (%)	134 (40)	94 (50)
Mean (±SD) age — yr	30.9±7.3	31.0±7.3
CD4+ count — % of patients§		
<200 cells/mm ³	32.9	1.4
200–499 cells/mm ³	37.0	15.8
≥500 cells/mm ³	30.1	82.9
Median CD4+ count — cells/mm ³	316.5	830.5¶
Drug resistance — % total/% partial		
Isoniazid	18.3/1.4	19.1/0
Rifampin	1.4/0.9	0/1.5
Ethambutol	3.2/1.4	2.3/0
Pyrazinamide**	1.6/0.7	1.2/0
Isoniazid and rifampin	0.5/0	0/0

*Seven additional patients were excluded because of indeterminate HIV serologic status.

†Pathogens included *M. terrae*, *M. fortuitum*, *M. duvalii*, and *Nocardia asteroides* (one each), a nontypable mycobacterium (one), and *M. avium* complex (two).

‡Pathogens included *M. terrae*, *M. fortuitum*, *M. gordonae* (with *M. tuberculosis*), and *N. asteroides* (one each).

§Patients for whom data on lymphocyte phenotypes were available (216 HIV-positive and 146 HIV-negative patients) were similar to the other patients with respect to demographic variables, clinical stage of HIV infection, signs and symptoms of tuberculosis, and survival. Because of rounding, not all percentages total 100.

¶P<0.001 for the comparison with the HIV-positive patients.

||Patterns of drug resistance were analyzed in 218 HIV-positive patients and 132 HIV-negative patients.

**A total of 172 isolates from the HIV-positive patients and 92 isolates from the HIV-negative patients were tested.

Table 2. Analysis of the Study Population.*

CHARACTERISTIC	HIV-POSITIVE		HIV-NEGATIVE
	no. of patients		
Included in study	335		188
Discontinued during 6-mo treatment			
Chose to withdraw	14		0
Lost to follow-up	17		2
Died of TB	20		0
Died of other causes	24		0
Completed 6 mo of therapy	260		186
Did not enroll in follow-up on relapse			
Smear-positive treatment failure			
Died later of TB	1		1
Cured with retreatment, died later without TB	1		0
Chronic TB	0		1
Culture-positive treatment failure			
Initially refused randomization, cured with retreatment	1		0
Refused randomization	6		0
Not randomized, by error	4		0
Continued treatment, by error	0		1
	RIFAMPIN + ISONIAZID	PLACEBO	OBSER- VATION
Randomized to 12-mo treatment or enrolled in follow-up on relapse	123	124	183
Excluded, culture-positive treatment failure			
Died of TB	1	0	0
Cured with retreatment	1	4	3
No follow-up data	0	1	0
Included in analysis	121	119	180
Discontinued			
Died, without relapse	19	15	3
Relapsed, cured with retreatment	0	5	8
Relapsed, died of TB	0	3	0
Relapsed, died without TB	0	1	0
Relapsed, chronic TB later	0	0	1
Relapsed, no follow-up	1	0	0
Lost to follow-up	48	36	33

*TB denotes tuberculosis.

remaining 523 patients, 335 HIV-seropositive and 188 HIV-seronegative patients whose diagnoses of pulmonary tuberculosis were confirmed by sputum microscopy and the isolation of *M. tuberculosis* from sputum, were included in the study. The enrollment of the HIV-seronegative patients was completed on May 11, 1990. The enrollment of the HIV-seropositive patients was discontinued on September 7, 1991, because severe and ongoing social unrest made further enrollment impossible. The base-line characteristics of the patients are shown in Table 1.

A total of 260 HIV-seropositive and 186 HIV-seronegative patients completed the six-month course of treatment. After the exclusion of patients who had treatment failures (Table 2), 240 HIV-seropositive patients (121 of them randomly assigned to rifampin plus isoniazid and 119 randomly assigned to placebo) and 180 HIV-seronegative patients were included in the follow-up (Table 3).

Survival

At 12 and 24 months, the probabilities of survival were 77 and 69 percent, respectively, for the HIV-sero-

positive patients and 100 and 98 percent for the HIV-seronegative patients ($P < 0.001$). The 198 HIV-seropositive patients who were enrolled before May 11, 1990, and were followed concurrently with the HIV-seronegative patients had a poorer survival rate than the 137 HIV-seropositive patients enrolled later (73 percent vs. 82 percent after 12 months, and 65 percent vs. 76 percent after 24 months; $P = 0.05$). This was probably due to the differential loss to follow-up of deceased patients after September 1991, when follow-up became more difficult because of the social unrest. Among the HIV-seropositive patients for whom CD4+ lymphocyte counts were obtained at entry into the study, survival worsened with decreasing counts. At 24 months, 33 percent of those with fewer than 200 CD4+ cells per cubic millimeter survived, as compared with 78 percent of those with 200 to 499 CD4+ cells per cubic millimeter ($P < 0.001$) and 92 percent of those with 500 or more CD4+ cells per cubic millimeter ($P < 0.05$ for the comparison of those with ≥ 500 cells per cubic millimeter with those with 200 to 499 cells per cubic millimeter, and $P < 0.001$ for the comparison with those with < 200 cells per cubic millimeter). Within each stratum of the CD4+ count, the groups of HIV-seropositive patients enrolled before and after May 11, 1990, had similar survival rates. The survival rate of HIV-seropositive patients for whom results of lymphocyte typing were available at entry into the study was similar to that of the remaining patients ($P = 0.28$).

Among the HIV-seropositive patients followed for relapse, there was no difference in survival between those assigned to rifampin plus isoniazid and those assigned to placebo ($P = 0.95$). The cumulative survival rates at 12 months were 83 percent and 84 percent, respectively.

Tuberculosis-Related Mortality

Of the 90 deaths among HIV-seropositive patients, 25 (27.8 percent) were considered to be related to tu-

Table 3. Patients Enrolled for Follow-up at the Time of Relapse after Six Months of Treatment for Tuberculosis.

CHARACTERISTIC	HIV-POSITIVE		HIV-NEGATIVE (N = 180)
	RIFAMPIN PLUS ISONIAZID (N = 121)	PLACEBO (N = 119)	
Male sex — no. (%)	52 (43.0)	45 (37.8)	89 (49.4)
Mean (\pm SD) age — yr	31.7 \pm 7.2	29.8 \pm 6.5	31.0 \pm 7.2
Median CD4+ count at start of treatment — cells/mm ³ *	413	338	832
Results of microbiologic analysis at 6 mo — no. of patients			
Microscopy and culture negative	106	107	163
Microscopy negative at 4 and 6 mo, culture contaminated or missing	2	2	3
Isolated positive culture, microscopy negative at 4 and 6 mo	5	2	10
Microscopy and culture missing, microscopy negative at 4 mo	8	8	5

* $P = 0.17$ for the comparison of HIV-positive patients assigned to rifampin plus isoniazid (76 patients with known CD4+ counts) with those assigned to placebo (83 patients); $P < 0.001$ for the comparison of the HIV-positive patients (159 patients) with the HIV-negative patients (139 patients).

berculosis. Tuberculosis was considered a major contributing cause of death for nine patients (four deaths during the six-month treatment period, two deaths from treatment failure, and three deaths after relapses). Sixteen deaths were considered to be related to tuberculosis because they occurred before the response to antituberculous therapy could be assessed. Of the four HIV-seronegative patients who died, one had a treatment failure and died of tuberculosis after the six-month course. The other three patients had negative sputum smears and cultures before their terminal illness.

Negative Sputum Tests and Rates of Treatment Failure

Table 4 shows the proportion of patients with negative sputum tests by microscopy and culture at different times during the six months of treatment. The rates were similar in the HIV-seropositive and the HIV-seronegative patients.

Treatment failed in 10 of the 260 HIV-seropositive patients (3.8 percent) and 5 of the 186 HIV-seronegative patients (2.7 percent) who could be evaluated at the end of the six-month treatment ($P=0.70$). Sixteen patients, seven seropositive and nine seronegative, had isolated positive cultures at the end of the six-month treatment.

Relapse

During follow-up, there were 9 relapses among the 119 HIV-seropositive patients randomly assigned to placebo, 1 relapse among the 121 HIV-seropositive patients randomly assigned to extended treatment, and 9 relapses among the 180 HIV-seronegative patients.

The life-table estimate of the relapse rate 18 months after the completion of the 6-month treatment was 1.9 percent for HIV-seropositive patients randomly assigned to continued treatment with rifampin and isoniazid — lower than the rate of 9 percent in the HIV-seropositive patients assigned to placebo ($P<0.01$) but not significantly lower than the rate of 5.3 percent in the HIV-seronegative patients ($P=0.06$). The relapse rates in the latter two groups of patients did not differ significantly ($P>0.1$). Among the HIV-seropositive patients randomly assigned to placebo, the inci-

dence of relapse was similar in those enrolled before May 11, 1990, and those enrolled after that date ($P=1$).

Two HIV-seropositive patients randomly assigned to treatment with rifampin and isoniazid and 13 HIV-seronegative patients had isolated positive cultures during follow-up; 4 of the HIV-seronegative patients started retreatment.

Treatment Outcomes in Patients with Treatment Failure or Relapse

Follow-up data on patients with treatment failure or relapse were available for 18 HIV-seropositive patients and 14 HIV-seronegative patients and were missing for 2 HIV-seropositive patients. Retreatments were successful in all patients for whom such data were available, except for five HIV-seropositive patients (two who had treatment failure and died of pulmonary tuberculosis, one who relapsed and died of disseminated tuberculosis, and two who relapsed and died of the "wasting" syndrome before a response to retreatment was assessed) and three HIV-seronegative patients (one who had treatment failure and died of pulmonary tuberculosis, and two others, one who had treatment failure and one who relapsed, in whom clinically resistant tuberculosis developed).

Antimicrobial Resistance

The prevalence of primary resistance against antituberculous drugs among *M. tuberculosis* isolates from the HIV-seropositive and HIV-seronegative patients at enrollment was similar (Table 1). All but 1 of the 10 *M. tuberculosis* isolates obtained from patients with treatment failure or relapse that were tested for antimicrobial susceptibility were fully sensitive to antituberculous drugs. The resistant isolate was resistant only to isoniazid and was isolated from an HIV-seronegative patient. That patient was cured with retreatment. Chronic, probably multidrug-resistant, tuberculosis ultimately developed in only two HIV-seronegative patients, whose isolates were not tested for drug susceptibility.

Clinical Evolution

After treatment began, general and pulmonary symptoms became less prevalent in all patients, but at the end of the six-month treatment more HIV-seropositive than HIV-seronegative patients had lost weight since enrollment (13.2 percent vs. 3.2 percent, $P<0.001$), continued to cough (16.7 percent vs. 8.1 percent, $P<0.05$), and continued to produce sputum (21.3 percent vs. 11.3 percent, $P<0.01$).

Treatment-Related Adverse Events

During treatment, a papular pruritic rash developed in 11 percent of the HIV-seropositive and 2 percent of the HIV-seronegative patients ($P<0.001$), but it never interrupted the treatment. There were no cases of hepatitis, but increased levels of alanine aminotrans-

Table 4. Conversion of Sputum Tests to Negative during Six Months of Chemotherapy for Tuberculosis.

SPUTUM TEST	HIV-POSITIVE		HIV-NEGATIVE	
	no. negative/ no. tested	%	no. negative/ no. tested	%
Microscopy				
After 2 mo	248/283	87.6	162/183	88.5
After 4 mo	264/266	99.2	184/186	98.9
After 6 mo	240/242	99.2	179/181	98.9
Culture*				
After 2 mo	259/278	93.2	167/179	93.3
After 6 mo	223/240	92.9	164/178	92.1

*Cultures from which any mycobacteria were grown were counted as positive.

ferase, alkaline phosphatase, and bilirubin, not significantly associated with HIV infection, were occasionally seen. Arthralgia developed in 77.7 percent of the HIV-seropositive and 75.5 percent of the HIV-seronegative patients and was temporally related to the use of pyrazinamide, because 89.8 percent of the cases of arthralgia were detected at the two-month visit. Paresis was reported by 21 percent of the HIV-seropositive and 9 percent of the HIV-seronegative patients ($P < 0.001$).

Overall Efficacy of Treatment

Given the 20 percent seroprevalence of HIV among patients with new cases of pulmonary tuberculosis in Kinshasa, we calculated that 91.1 percent of such patients who presented to the research clinic would be cured if the same six-month treatment were offered to all patients, regardless of HIV serologic status. Indeed, with rates of treatment failure and relapse of 2.7 percent and 5.3 percent, respectively, among 80 HIV-seronegative patients, and of 3.8 percent and 9 percent among 20 HIV-seropositive patients, 8.9 percent of patients with new cases of pulmonary tuberculosis would not be cured. A similar calculation showed that offering extended treatment to HIV-seropositive patients (who had a relapse rate of 1.9 percent) would result in the curing of 92.5 percent of patients with new cases of pulmonary tuberculosis — a gain of 1.4 percent in treatment efficacy.

DISCUSSION

The key variables in the assessment of antituberculous chemotherapy are the rate of treatment failure and the rate of relapse.¹² The treatment-failure rates of 3.8 and 2.7 percent among the HIV-infected and HIV-uninfected patients in our study were similar to those of patients in other studies. Studies of HIV-infected patients that, unlike this one, used treatment with rifampin and isoniazid daily for six to nine months reported rates of treatment failure of 0 to 4 percent.¹³⁻¹⁸ Our 2.6 percent rate of treatment failure among HIV-seronegative patients was also similar to rates found in other studies.^{2-5,19-22}

On the other hand, the 5.3 percent relapse rate for HIV-uninfected patients and the 9 percent rate for HIV-infected patients who discontinued treatment after six months were slightly higher in our study than in previous studies. Relapse rates average 3.6 percent (range, 0 to 4.6 percent) and 3.4 percent (range, 2.8 to 7 percent) among HIV-uninfected patients after intermittent and daily treatment, respectively.^{2,3,5,20-22} Among HIV-seropositive patients receiving treatment daily (and often for periods longer than six months), the relapse rates average 6.3 percent (range, 0 to 15 percent).^{13,16-18,23-25} The higher rates in our study could have several explanations. First, the partly intermittent six-month treatment regimen could be slightly less effective than regimens used in previous studies. Second, our study differed from most other studies of antituber-

culous therapy in that sputum was obtained systematically (by inducing sputum production, if necessary) at each follow-up visit. Third, reinfection with new strains of *M. tuberculosis* is plausible in an area where tuberculosis is endemic, such as Zaire. However, the clustering of essentially all relapses in the first few months after the completion of the six-month treatment argues against reinfection, since with reinfection one would expect recurrences to accrue steadily after the completion of treatment. Finally, compliance with treatment may have been suboptimal, even though drug administration was in large part directly observed during the continuation phase. When drug treatment was stopped after six months, the HIV-seropositive patients tended to relapse more often than the HIV-seronegative patients. This confirms earlier findings about the increased relapse rate among HIV-infected patients treated with standard chemotherapy.^{26,27}

Our finding that extending the period of antituberculous treatment to 12 months reduced the relapse rate among HIV-seropositive patients from 9 percent to 1.9 percent demonstrated that better microbiologic results can be obtained by more intensive — in this case, more extended — therapy. Extended treatment did not improve survival, however.

The implications of our findings for programs of tuberculosis control should take into account fiscal and logistic constraints, as well as epidemiologic settings. In Kinshasa, we consider the introduction of extended treatment for HIV-infected patients unjustified, because offering the same six-month treatment to all patients cures more than 90 percent of patients with new cases of smear-positive tuberculosis. Of course, this decision takes into account the limited resources, the anticipated increase in treatment efficacy of only 1.4 percent, and the lack of improvement in survival among HIV-infected patients with extended treatment. In addition, the effect of a relapse of tuberculosis in Kinshasa, where most of the household contacts of patients with pulmonary tuberculosis have already been infected with *M. tuberculosis*,⁶ was considered small. Moreover, most relapses could be successfully retreated because the selection of multidrug-resistant tuberculosis was very rare. We attributed the latter to the use of combined tablets of rifampin and isoniazid in the continuation phase of treatment. However, where resources are less constrained and the effect of a relapse of tuberculosis might be more serious because patients could have frequent contact with highly susceptible persons not infected with *M. tuberculosis*, one might opt for more intensive chemotherapy for HIV-infected patients, with either more frequent dosing or longer drug administration.

In analyzing our HIV-seropositive patients, we found that among those enrolled in the later part of our study, mortality was underestimated. However, the HIV-seropositive patients enrolled early in the study (before May 11, 1990) had a survival rate similar to that of HIV-seropositive patients in other studies.^{13-18,23-26,28} As

expected, patients with low CD4+ cell counts at entry had poorer survival rates.

Of the 90 deaths of HIV-seropositive patients in our study, 27.8 percent were classified as related to tuberculosis. The proportion of tuberculosis-related deaths among HIV-infected patients varies widely between studies.^{13,14,23,25,28} In our opinion, this reflects the marked differences between industrialized and developing countries and between study teams in the ability to diagnose disseminated tuberculosis and other opportunistic infections.

Finally, our study confirms that antituberculous treatment was well tolerated. The incidence of arthralgia and paresthesia was probably overestimated by the systematic questioning at follow-up visits, but paresthesia was reported significantly more often by HIV-seropositive patients. HIV-infected patients should be considered for vitamin B₆ supplements when they are treated with isoniazid, as is recommended for other patients at risk of polyneuropathy.¹ In contrast with a study in the United States of tuberculosis among patients with advanced immunodeficiency, 10 percent of whom had their treatments altered because of rash,¹³ treatment was never stopped for this reason in our study. This is in agreement with a recent study from Uganda, in which the incidence of rash among HIV-infected patients receiving six months of treatment was 1.6 percent.¹⁴ On the other hand, a papular pruritic rash that has been associated with HIV infection in African patients²⁹ developed in 11 percent of the HIV-seropositive patients in our study. Possibly a different perception of rashes by the American and African investigators and patients explains the differing courses of action taken when rashes occurred.

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