Original Report

Impact of Human Immunodeficiency Virus Infection on Tuberculosis in Kigali, Rwanda: One-Year Study of 377 Consecutive Cases

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ABSTRACT

Objectives: To analyze and compare the clinical, diagnostic, and therapeutic features of tuberculosis (TB) in human immunodeficiency virus (HIV)-seropositive and seronegative patients.

Methods: A 1-year retrospective review of medical records and charts of TB patients admitted to and followed-up at the Department of Internal Medicine of the Centre Hospitalier de Kigali (CHK), Kigali, Rwanda.

Results: Tuberculosis was diagnosed in 510 patients. Complete data, including HIV serologic testing, were available for 377 patients (74%) of whom 227 were male and 150 female, aged 17–70 years (mean, 33 y). Human immunodeficiency virus antibodies were detected in 334 (88.6%) of the 377 evaluable patients. A definite diagnosis of TB was established in similar proportions of HIV-seropositive (66%) and HIV-seronegative (63%) patients. The HIV-infected patients differed from the patients without HIV infection in the following features: proportion of patients in the age group 20–39 years (80% vs. 58%; P = 0.001), extrapulmonary manifestations (56% vs. 40%; P = 0.045), lower/middle lobe infiltrates (18% vs. 6%; P = 0.07), presence of cavities (15% vs. 34%; P = 0.002), pleural disease (23 vs. 12%; P = 0.08), tuberculin anergy (67% vs. 26%; P < 0.001). After 6 months of anti-TB therapy, both HIV-infected and HIV-uninfected patients with smear positive pulmonary TB had their sputum samples cleared of acid-fast organisms. Adverse drug reactions occurred in 16% and 7% of HIV-seropositive and seronegative patients, respectively (P = 0.11).

The 31% mortality rate (57 of 186) among HIV-infected patients who fulfilled the criteria of the World Health Organization (WHO) clinical case definition for acquired immunodeficiency syndrome (AIDS) was significantly higher than the 7% mortality rate (5 of 76) in HIV-infected patients who did not meet these criteria (P = 0.001) and the 12% mortality rate (5 of 43) in those without HIV infection (P = 0.003).

Conclusions: Active TB was strongly associated with HIV infection in urban Rwanda. The clinical and radiographic presentation of TB, described in HIV-seropositive patients hospitalized at the CHK, is most frequently atypical and highly suggestive of advanced HIV disease.

Key words: *HIV infection, Rwanda, tuberculosis*

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Nearly 80% of the 4 million people co-infected with human immunodeficiency virus (HIV) and *Mycobacterium tuberculosis* worldwide are living in Africa.[1] If the 5 to 8% incidence rate of active tuberculosis (TB) is applied to these individuals,[2-5] then 150,000 to 240,000 additional new cases of TB are expected to occur annually in sub-Saharan Africa.

Inferential information on the increasing burden of HIV-associated TB in Rwanda included a 180% increase in reported cases of TB between 1983 and 1989,[6] high HIV seroprevalence rates among TB patients,[6-8] and relative risk of developing active TB of 18 times greater for HIV-infected persons than individuals without HIV infection, according to one report,[5] and 23 times greater, according to another.[2]

In Rwanda, the annual risk of TB infection is estimated at 1.8%, and the prevalence of TB infection exceeds 50%.[9] This high level of TB endemicity coexists with 1.7% and 17.8% prevalence rates of HIV infection in rural and urban areas, respectively.[10] Predictions based on a mathematic model developed by Schulzer and associates,[11] using available data on the epidemiology of TB and HIV infections in Africa, are consistent with 25,000 new cases of TB by the year 2000 for Rwanda. Increased awareness

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of the clinical pattern of HIV-associated TB is therefore of critical importance to lowering the rate of mortality from TB and to reducing the spread of this disease within the community and the hospital. The recommendations issued by the National TB Control Programme for the management of TB cases deal mainly with the diagnosis and the treatment of pulmonary TB, the most hazardous form of the disease.[12] However, extrapulmonary involvement and atypical radiographic abnormalities are frequent manifestations of HIV-associated TB.[13–15] These unusual features can be mistakenly attributed to diseases other than TB, hence increasing the mortality rate through failure to establish an early diagnosis of TB.[16,17]

Most available descriptions of the clinical presentation of TB in HIV-infected patients have focused on patients attending TB treatment centers. Thus, they are strongly biased toward the description of clinical and chest radiographic manifestations of pulmonary TB.[18,19] This report presents the clinical, diagnostic, and therapeutic features from 377 HIV-infected and uninfected TB patients admitted to and followed-up at the Department of Internal Medicine of the Centre Hospitalier de Kigali (CHK), Kigali, Rwanda.

PATIENTS AND METHODS

The CHK is one of the three main referral hospitals of Rwanda. It has a capacity of 500 beds of which 120 belong to the Department of Internal Medicine. At the time of this study, the bed occupation rate exceeded 160% in this department. The prevalence of HIV infection was over 60% in patients admitted to medical wards.[20]

The medical records and charts of all patients newly diagnosed as having TB between January 1 and December 31, 1991, were reviewed and analyzed with regard to demographic data, clinical and chest radiographic features, as well as clinical course and response to therapy. Particular attention was paid to signs and symptoms included in the World Health Organization (WHO) clinical case definition for acquired immunodeficiency syndrome (AIDS).[21] Results of mycobacterial studies and histopathologic examination were extracted from the registries of relevant laboratories.

Patients with proven TB had to meet the following criteria: a positive culture for *M. tuberculosis* from any specimen (sputum, body fluid, or tissue) or detection of acid-fast bacilli (AFB) on smears from any of the above specimens or histopathologic examination demonstrating caseating granulomata with or without the presence of AFB. The diagnosis was likely in patients with respiratory and systemic symptoms suggestive of TB. For pulmonary cases, the symptoms consistent with the diagnosis of TB included cough for more than 15 days, fever, weight loss, chest pain, and pulmonary infiltrate resistant to conventional antibiotics but showing a good response to anti-TB treatment. The diagnosis of pleural and pericardial TB was presumed on the presence of a lymphocytic exudate resorbing under anti-TB chemotherapy.

A tuberculin skin test was performed in the majority of the patients by intradermal injection of 5 tuberculin units (TU) of purified protein derivative (PPD) of tuberculin (equivalent to 2U of PPD RT23). The test was read 48 to 72 hours postinjection and was considered positive in the presence of an induration of 10 mm or more in diameter.

Consenting patients were offered HIV serologic testing. Human immunodeficiency virus antibodies were detected using an enzymatic immunoassay (EIA, Vironostika Organon Tekhnika, Boxtel, The Netherlands). Sera reactive to EIA were further confirmed by an indirect immunofluorescent assay (IFA, Serofluor, Virion, Zürich, Switzerland). Discordant results between EIA and IFA were examined by Western blot (Biotech, Dupont de Nemours, Wilmington, DE). A positive test was defined by the presence of at least one reactive band to HIV core protein and one reactive band to HIV envelope protein.

Most patients received a standard short-course chemotherapy regimen of 6 months of daily isoniazid and rifampin with daily pyrazinamide and ethambutol for the first 2 months of therapy. This was followed by rifampin and isoniazid twice weekly for the 4-month continuation phase. As the Rwandan National TB/Leprosy Control Programme was being integrated into the health care system, a few patients were inadvertently prescribed the former, long, standard chemotherapy regimen consisting of 12 months of daily isoniazid and ethambutol with daily streptomycin for the first 2 months of treatment.

Differences in proportions were compared by chi-square and Fischer's exact tests and comparison of means by Student's t-test for normally distributed values. The Mann-Whitney test was used for the comparison of means from abnormally distributed values ($P < 0.05$ was considered to indicate significance).

RESULTS

Demographic Data, Clinical and Chest Radiographic Findings

Of the 510 patients admitted to the Department of Internal Medicine during the study period, 377 (74%) consented to HIV serologic testing and form the basis of this retrospective review. Of these, 334 (88.6%) were HIV-seropositive. Median ages of HIV-infected and uninfected patients were similar (33.1 and 33.6 y). Table 1 shows the distribution by HIV serostatus, sex, and age group of the study population. Sixty percent of the patients were male. There was no difference in HIV seropositivity rate between male and female patients (91% and 87%, respectively). Patients

Table 1. Distribution of the Study Population by Sex and Age Group

Characteristic	HIV-Seropositive Patients n = 334 (%)	HIV-Seronegative Patients n = 43 (%)	P Value
Gender			
Male	197 (59)	30 (70)	0.2
Female	137 (41)	13 (30)	
Age group (y)			
< 20	4 (1)	5 (12)	0.001
20–39	266 (80)	25 (58)	0.0015
40–59	60 (17)	12 (27)	0.11
> 60	4 (1)	1 (2)	

of the 20 to 39 year age group predominated among the HIV-seropositive group (P = 0.001), whereas the HIV-seronegative group contained a larger proportion of patients aged 20 years or less (P = 0.001).

Evaluation of the WHO clinical case definition was carried out in 349 patients. Of the 323 HIV-infected patients, 240 (74%) met the criteria of that definition, as did 8 (31%) of 26 patients without HIV infection (P < 0.001).

Table 2 lists the clinical manifestations and chest radiographic abnormalities in patients with or without HIV infection. The symptoms and signs more significantly common in HIV-seropositive than in HIV-seronegative patients included fever, weight loss of greater than 10% of body weight, peripheral lymph node, persistent diarrhea, oral candidiasis, and active or past history of herpes zoster. Other symptoms such as cough, hemoptysis, and chest pain were reported at equal frequency.

On chest radiographic examination (Table 3), HIV-seropositive patients were less likely than patients without HIV infection to present with cavitary lesions (P = 0.002). Middle/lower (P = 0.07) and pleural disease (P = 0.08) tended to be more prevalent in HIV-seropositive patients. Upper lobe and bilateral involvement and miliary infiltrates and intrathoracic adenopathies were similarly distributed among the two groups.

Results of tuberculin skin tests were available for 274 HIV-infected and 33 HIV-uninfected patients. Seventy-one HIV-seropositive patients (26%) had a positive skin test compared with 22 patients without HIV infection (66%) (P < 0.001). Within the HIV-seropositive group, only 17% (33 of 200) of HIV-infected patients who fulfilled the criteria of the WHO clinical definition for AIDS were able to mount a positive reaction, as were 53% (36 of 67) of HIV-infected patients who did not meet these criteria (P < 0.001). There was no difference in the prevalence rate of tuberculin reactivity between the patients who were included in the study and those who were not.

Table 2. Clinical and Chest Radiographic Findings in 334 HIV-Seropositive and 43 HIV-Seronegative Patients with Tuberculosis

Findings	HIV-Seropositive n (%)	HIV-Seronegative n (%)	P Value
Clinical			
Fever	281 (84)	30 (65)	0.01
Weight loss			
>10% body weight	270 (80)	29 (67)	0.04
Cough >15 days	328 (98)	41 (95)	
Chest pain	50 (15)	7 (14)	
Hemoptysis	10 (3)	2 (5)	
Peripheral lymph node	62 (18)	3 (7)	0.06
Diarrhea >1 month	56 (17)	2 (5)	0.03
Oral candidiasis	51 (15)	2 (5)	0.05
Itchy rash	36 (11)	1 (2)	
Herpes zoster (active or scar)	34 (10)	—	0.02
Meeting WHO CDA*	240/328 (74)	8/26 (31)	< 0.0007
Positive tuberculin skin test	71/274 (26)	22/33 (67)	< 0.0001
Radiographic			
Cavities	53 (15)	15 (34)	0.002
Lower/middle lobe infiltrates	59 (18)	3 (6)	0.07
Upper lobe infiltrates	31 (9)	3 (6)	
Bilateral infiltrates	55 (16)	7 (16)	
Pleural effusion	77 (23)	5 (12)	0.08
Mediastinal/hilar adenopathy	42 (12)	4 (9)	
Miliary infiltrates	25 (7)	2 (5)	

*WHO CDA: World Health Organization clinical definition for AIDS.

Diagnosis of Tuberculosis

The procedures used for the diagnosis of TB are shown in Table 3. Tuberculosis was bacteriologically and histologically proven in 247 (66%) of the 377 cases. The proportion of HIV-seropositive patients (65%) with a definite diagnosis of TB did not differ from that of HIV-seronegative patients (63%). Absence of cavities was strongly associated with a low yield of microbiologic examination. Of the 68 patients with a cavitary disease, 55 (80%) had a positive sputum smear for AFB or culture of sputum positive for *M. tuberculosis* compared with only 124 (40%) of the remaining 309 patients who were not found to have cavitary lesions (P < 0.001). The rates of positive sputum smear and cultures for *M. tuberculosis* were similar in HIV-seropositive (84%) and in HIV-seronegative (73%) patients with cavitary disease. However, a smear negativity rate of 28% (42 of 152) was noted among positive sputum cultures from HIV-seropositive patients

Table 3. Results of Histologic and Microbiologic Studies in 334 HIV-Seropositive and 43 Seronegative Patients with Tuberculosis

Specimen	HIV-Seropositive	HIV-Seronegative	P Value
Sputum	n = 221	n = 33	
Smear positive; culture positive	110	19	
Smear negative; culture positive	42	1	0.07
Smear positive; culture negative	6	1	
Other*	n = 3	n = 1	
Culture positive	3	0	
Pleural	n = 77	n = 5	
Culture of fluid positive	11	1	0.08
Biopsy culture and/or history positive	48	4	
Pericardial	n = 15	n = 3	
Culture of fluid positive	0	0	
Lymph node	n = 14	n = 2	
Biopsy culture or history positive	14	2	

*Urine (n = 2); cerebrospinal fluid (n = 2).

compared to 6% (1 of 17) among positive cultures from HIV-seronegative patients (P = 0.07). Overall, TB was bacteriologically diagnosed in 158 (71%) of the 221 HIV-infected patients and in 21 (64%) of the 33 HIV-seronegative patients, who had a pulmonary infiltrate.

Site of Tuberculosis

Table 4 shows the relation between HIV status and sites of TB. Although the lungs were the most frequent sites of the disease, 186 (56%) of the 334 HIV-infected patients presented with extrapulmonary involvement. This rate compares to 17 (40%) of the 43 patients without HIV infection (P = 0.045). At individual sites, pleural TB was found to be the only extrapulmonary site significantly associated with HIV infection (P = 0.08). Pericardial disease, peripheral TB lymphadenitis, miliary TB, and intrathoracic lymph node involvement occurred at equal frequency in the two groups.

Treatment and Outcome

Of the 377 patients, 361 (96%) received the 6-month short-course regimen of chemotherapy, and the remaining 16 were treated with the long, 12-month course. Sputum conversion on smears occurred after 2 months of therapy in 84% (86 of 92) and 87% (14 of 16) of HIV-seropositive and seronegative patients, respectively. After 6 months, clearance of AFB from sputum was achieved in both HIV-infected and uninfected patients with smear-positive pulmonary TB. However, cultures for mycobacteria were not performed. Three HIV-seronegative patients (7%) and 54 HIV-seropositive patients (16%) developed adverse drug effects, but not severe enough to dictate the modification of the treatment. The signs and symptoms of drug-related toxicity in HIV-infected patients included rashes (7% of cases), neuritis (5%), arthralgias (4%), and jaundice (1%) without significant increase in liver enzymes.

During the period of treatment, 6 HIV-seronegative (14%) and 21 HIV-seropositive (5%) patients were transferred to other treatment centers. Five HIV-seronegative patients (12%) were lost to follow-up as were 63 (19%) HIV-seropositive patients. A higher mortality rate was noted in HIV-seropositive patients; 19% (62 of 334) died compared to 12% (5 of 43) without HIV infection. This difference was not statistically significant. Within the HIV-seropositive group, 31% (57 of 186 patients) who fulfilled the criteria of the WHO clinical definition for AIDS died. This compares with 7% (5 of 76) of HIV-infected patients who did not meet these criteria (P = 0.001) and 12% (5 of 43) of patients without HIV infection (P = 0.003). All deaths occurred within the 6 months of therapy. However, the cause of death could not be accurately determined because of the retrospective design of the study.

Table 4. Forms and Sites of Tuberculosis according to HIV Serostatus

	HIV-Positive n = 334 (%)	*HIV-Negative n = 43 (%)*	*P Value*
Overall			
Pulmonary	148 (44)	26 (60)	0.045
Extrapulmonary	113 (33)	10 (23)	
Both	73 (21)	7 (16)	
Extrapulmonary sites affected			
Pleural	77 (23)	5 (12)	0.08
Intrathoracic lymph node	43 (13)	4 (9)	
Miliary	27 (8)	2 (5)	
Pericarditis	18 (5)	1 (2)	
Peripheral adenitis	14 (4)	2 (5)	
Abdominal	3	1	
Meninges	1	1	
Skeletal	1	1	
Genitourinary tract	2	—	

DISCUSSION

During the study period, TB accounted for 12% (510 of 4718) of adult medical admissions to the Department of Internal Medicine. This proportion is twice as high as the proportion of TB patients who were admitted to medical wards in Kenya before the HIV epidemic.[22]

From 1983 through 1991, a substantial gradual increase at first, with a sharp rise thereafter has been noted in the yearly number of smear or culture positive pulmonary TB at the Centre Hospitalier de Kigali (CHK) (Figure 1). This increase may result from a better case-finding rate or the availability of short-course chemotherapy regimen through the National TB/Leprosy Control Programme. Beginning in January 1990, this program was progressively integrated into the health care services and may have attracted a substantial number of patients, particularly noticeable around the year 1990. Although not definitely proven, HIV infection appears to have been an important contributing factor for this nearly 10-fold increase in TB cases between 1983 and 1991. During the same period, the number of cases of HIV-associated cryptococcal meningitis increased dramatically from one case per year in 1983 to two cases per week in 1991.[23] Moreover, 80% of the HIV-seropositive patients belong to the 20- to 39-year-old age group, known to be at the highest risk of HIV infection in urban Rwanda.[10]

The 88.6% HIV prevalence rate is one of the highest rates ever reported in TB patients from sub-Saharan Africa[14] and exceeds the 73% recently found by Elliott and associates in a cohort of TB patients in Lusaka, Zambia.[24] Because the HIV status was not determined in 133 patients (26%), the study population could have been biased in favor of HIV-seropositive patients. However, the fact that both included and non-included patients had a similar rate of tuberculin reactivity (26% and 29%, respectively), is highly suggestive of the same level of immunodeficiency, probably induced by HIV infection, in the two groups of patients. One factor that might explain this

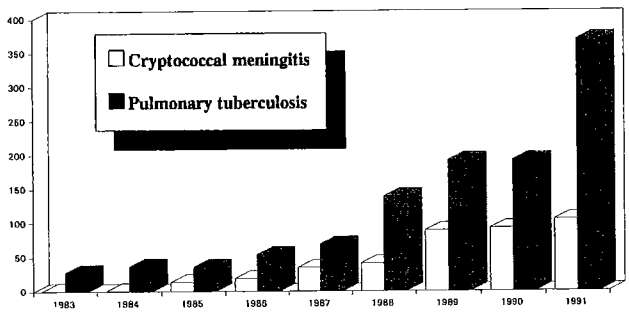

Figure 1. Yearly number of new cases of smear, culture positive pulmonary tuberculosis, or both, and new cases of cryptococcal meningitis diagnosed in the Department of Internal Medicine, Centre Hospitalier de Kigali (CHK), Rwanda, 1983–1991.

high prevalence of HIV infection is the 30% baseline HIV prevalence rate among young urban dwellers in Rwanda.[10] In keeping with this is the large predominance of the 29- to 39-year-old age group among the HIV-seropositive patients.

The association between HIV infection and extrapulmonary TB proved significant, yet the exclusion of 133 patients may have resulted in a bias toward extrapulmonary forms. An extrapulmonary site of TB was documented in 56% of the 334 HIV-infected patients. This figure is similar to that reported by Elliott and colleagues,[24] in Lusaka, Zambia, and by Gilks and associates,[25] in Nairobi, Kenya, among TB patients admitted to medical wards of general hospitals.

Human immunodeficiency virus-seropositive and -seronegative patients did not differ in extrapulmonary site of disease except for pleural involvement. This is explained by the high proportion (39%) of HIV-seronegative patients with extrapulmonary involvement, which far exceeds the usual 15% that would be expected to occur in otherwise immunocompetent patients.[26] The high frequency of extrapulmonary TB among the HIV-seronegative patients reflects the fact that the Department of Internal Medicine is a tertiary referral service to which most pulmonary and TB cases with diagnostic problems are referred. Chest radiographic abnormalities, such as intrathoracic adenopathy, miliary infiltrate, or pleural effusion, could be the manifestations of primary TB in HIV-seronegative patients.[27,28] Frequent referrals of patients with such radiographic features for additional investigations may have resulted in bias for extrapulmonary disease in the HIV-seronegative group.

Despite the availability of valuable diagnostic facilities (i.e., laboratory services), a definite diagnosis of TB was not obtained in 34% of cases, which is not significantly different from the 26% in Zambian patients reported by Elliott and co-workers.[24] Both the infrequency of cavitary disease and the predominance of extrapulmonary forms accounted for this low proportion of proven cases.[24,29] The diagnosis of TB was bacteriologically confirmed in similar proportions in both HIV-infected and uninfected patients. However, direct microscopy proved to be less sensitive in HIV-seropositive than HIV-seronegative patients, a finding consistent with previous reports.[24,29]

Thoracocentesis and pleural biopsy previously have been shown to be of critical importance for the diagnosis of pleural TB.[30] Histologic and microbiologic examination of pleural tissues provided a definite diagnosis of pleural TB in 48 (62%) of the 77 HIV-seropositive patients and in four (80%) of the five patients without HIV infection.

Reports by Voetberg and Lucas in rural Zambia on the utility of peripheral lymph node biopsy for the diagnosis of TB lymphadenitis indicate that histologic microbiologic examination of lymph node aspirate and biopsy specimens yielded a definite diagnosis in 100% of cases.[31]

The confirmation of pericardial TB was possible in only five cases through examination and culture of tissues and fluid sampled from other accessible sites: pleura in two cases and lymph node in three cases.

In this study, nearly 95% of patients were treated with a 6-month course of chemotherapy. Drug-related adverse reactions occurred more frequently in HIV-infected patients than in patients without HIV infection. This observation agrees with previous reports on the particular susceptibility of HIV-infected patients to anti-TB drug-related toxicity.[32] Patients who were HIV-seropositive experienced a higher mortality rate than HIV-seronegative patients, although the difference was not statistically significant. However, the difference in mortality rate proved significant between HIV-infected patients who fulfilled the criteria of the WHO clinical definition for AIDS (31%), HIV-infected patients who were found not to meet these criteria (7%) ($P = 0.001$), and patients without HIV infection (12%) ($P = 0.003$). This observation suggests an association between the severity of immunodeficiency and adverse outcome in patients with HIV-associated tuberculosis.[33]

In summary, this retrospective analysis of 377 TB patients hospitalized at the CHK found infection with HIV in 334 (88.6%), of whom 266 (80%) were 20 to 39 years of age. In the HIV-seropositive group, the clinical and radiographic presentation was strongly suggestive of a disease complicating the late stage of HIV infection. Selective referrals to a specialized department such as this one explain the unusually large proportion of HIV-seronegative patients with extrapulmonary tuberculosis. The high frequency of extrapulmonary forms of TB and the infrequency of cavitary lesions were the major determinants of the failure to establish a definite diagnosis of TB. The 19% mortality rate experienced by the HIV-seropositive patients probably represents a low estimate. Indeed, recent autopsy surveys carried out in the Ivory Coast and Zaire found TB to be the primary cause of death in 41% and 54% of patients who died of AIDS, respectively.[34,35] Half of these infections were not even clinically suspected before death. These autopsy findings emphasize the importance of making an early diagnosis

of TB, followed by a prompt initiation of treatment for patients presenting with clinical features suggestive of TB in areas where both HIV and *M. tuberculosis* infections are known to be prevalent.

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