Mycobacterium tuberculosis in Household Contacts of Human Immunodeficiency Virus Type 1–Seropositive Patients with Active Pulmonary Tuberculosis in Kinshasa, Zaire

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Rates of infection with *Mycobacterium tuberculosis* were compared in Kinshasa, Zaire, in 521 household contacts of 74 human immunodeficiency virus type 1 (HIV-1)–seropositive index patients and in 692 household contacts of 95 HIV-1–seropositive index patients with sputum smear–positive pulmonary tuberculosis: No difference was noted between contacts of HIV-1–seropositive and –seronegative patients. The increasing prevalence of *M. tuberculosis* infection with increasing age was similar in household contacts of seropositive and seronegative patients; by age 16 years, 75% were purified protein derivative–positive. The similarly low rates of *M. tuberculosis* infection in household contacts of HIV-1–seropositive and –seronegative index patients with sputum smear–positive pulmonary tuberculosis indicates that HIV-1–seropositive patients with pulmonary tuberculosis are not more infectious than HIV-1–seronegative patients with pulmonary tuberculosis.

In developing countries, more than 2.6 million persons die each year from tuberculosis (TB), making it the world's leading infectious cause of death [1–3]. Infection with *Mycobacterium tuberculosis* is endemic in Africa. In Kinshasa, >70% of healthy adults have a positive purified protein derivative (PPD) skin test, indicating latent infection with *M. tuberculosis* [4, 5]. Before the onset of the human immunodeficiency virus type 1 (HIV-1) epidemic, most patients acquired *M. tuberculosis* infection early in life; the infection usually remained latent for the duration of their lives. Clinically apparent tuberculosis developed in ~10% of infected patients, either soon after primary infection or years later (reactivation tuberculosis) [6].

Since 1985, the incidence of TB has increased dramatically throughout sub-Saharan Africa [7–9]. At present, an estimated 0.2% of the population acquire TB annually [10]. Most of this increase appears to be the result of HIV-1–induced immunodepression and subsequent reactivation of latent *M. tuberculosis* infection [11–13]. For several reasons, this large increase in Africa in the number of HIV-1–seropositive patients with active TB may have created a secondary wave of *M. tuberculosis* infection in their close contacts (both HIV-1–seropositive and –seronegative): the reservoir of persons with active TB has increased substantially; only one-third to one-half of smear-positive persons who transmit infection are routinely diagnosed; the present standard antituberculosis chemotherapeutic regimens have success rates of <50% (largely due to noncompliance) [14]; newly acquired *M. tuberculosis* infection can spread rapidly in HIV-infected persons; and most families in sub-Saharan Africa live in crowded, extremely poor conditions conducive to the spread of *M. tuberculosis* infection.

To evaluate the potential role of increased infectiousness of *M. tuberculosis* in HIV-1–seropositive patients with pulmonary TB in promoting secondary cases of *M. tuberculosis* infection, we carried out a cross-sectional study in 1989–1990 of 521 household contacts of 74 HIV-1–seropositive and 692 household contacts of 95 HIV-1–seronegative patients with sputum smears positive for acid-fast bacilli.

Methods

Study population. Recruitment into the study occurred from April 1989 through February 1990. During this period, all patients (index patients) presenting to the Centre de Dépistage de la Tuberculose (CDT) in Kinshasa with suspected TB and residing in the catchment zones of 21 of the 63 CDT satellite clinics

Received 10 August 1992; revised 18 February 1993.
This study was approved by the National AIDS Ethical Committee of the Government of Zaire. Patients gave informed consent for HIV-1 screening.
Grant support: World Health Organization Global Programme on AIDS (IR/RES/GPA/421/FX/88.310).
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The Journal of Infectious Diseases 1993;168:106–11

0022–1899/93/6801–0016$01.00

located throughout the city were screened for TB and for HIV-1 infection. These clinics, selected on the basis of size (large clinics were preferentially selected) and efficient operation, accounted for 67% of all referrals to the CDT. The CDT is the principal center for TB diagnosis and treatment in western Zaire; services are provided at no cost.

Upon presentation, all patients residing in one of the selected catchment areas were asked to submit three early-morning sputum samples collected on separate days. Patients with a sputum smear positive for acid-fast bacilli, a clinical history suggestive of TB, radiologic evidence of active pulmonary TB, and at least one household contact ≤10 years of age were invited to participate in the study. We were particularly interested in examining children ≤10 years of age because this age group has the greatest risk of acquiring TB infection through casual contact.

Only index patients with recently diagnosed TB were included to eliminate the potential confounding effects of partially treated or resistant cases of TB. All eligible index patients were then asked permission for the study team to contact all of their eligible household contacts. Household contacts were defined as housemates of an index patient who were >1 year of age and who had been living in the same house as the index patient for at least the 4 previous weeks. All household contacts were provided transportation to the CDT, where they were evaluated for evidence of *M. tuberculosis* infection with an interview, physical examination, chest radiograph, and Mantoux tuberculin test.

Tuberculin testing was carried out with PPD manufactured by the Statens Seruminstitut (Copenhagen). Five tuberculin units (0.1 cm^3) of tuberculin was placed intradermally on each person's forearm by a trained technician. A positive PPD skin test was defined as induration ≥10 mm (or ≥5 mm in HIV-1–seropositive persons) when examined 48–72 h after placement. All index patients and household contacts had the tuberculin test placed and subsequent induration measured by the same trained technician.

Sputum smears for acid-fast bacilli and samples for culture for *M. tuberculosis* were obtained from all household contacts with signs and symptoms suggestive of pulmonary TB or a positive chest radiograph or, if ≤15 years of age, with a positive tuberculin test.

Clinical and laboratory examinations. All index patients and household contacts were interviewed and examined by study physicians at a special clinic at the CDT. Throughout the study, physicians and nurses in the research team remained unaware of the HIV-1 serostatus of index patients.

A chest radiograph was considered suggestive of active pulmonary TB if it had at least one of the following characteristics: pulmonary cavitation, patchy infiltrates, or hilar or mediastinal adenopathy. All radiographs were interpreted independently by two physicians (J.C.W. and J.P.) with long-standing experience in interpreting chest radiographs of patients in Africa suspected of having TB. Differences in interpretation were resolved through consensus.

Patients requiring sputum to be collected but unable to produce a satisfactory sample were assisted by a nebulizer. Fresh sputum samples were first decontaminated and homogenized with SDS and NaOH. After 30 min of incubation, the reaction was neutralized with phosphoric acid. The samples were then centrifuged at 4000 rpm for 30 min. The pellet was stained for acid-fast bacilli using Ziehl-Neelsen stain and cultured on Löwenstein-Jensen medium [15]. A trained laboratory technician prepared and examined sputum cultures for growth each week for 8 weeks or until positive, whichever occurred first. Positive and negative control cultures for isolating mycobacteria were concurrently done. When growth was macroscopically evident, an acid-fast stain was done. Tests for determining the production of niacin (Difco, Detroit) and nitrate reduction were done to confirm the isolation of *M. tuberculosis* [16]. All *M. tuberculosis* isolates were referred to the Mycobacterium Reference Laboratory, Institute of Tropical Medicine, Antwerp, for confirmation and complete identification.

Sera from all index patients were tested for IgG antibodies to HIV-1 with an EIA (Vironostika; Organon Teknika, Rockville, MD). Repeatedly reactive specimens on EIA were confirmed by HIV-1 Western blot (HTLV-III Western blot; Du Pont, Geneva). If at least two of the bands corresponding to p24, gp41, or gp120/gp160 were visualized, the Western blot was considered positive [17].

Measures of infection and disease. Infection with *M. tuberculosis* was defined as being PPD-positive. TB was defined as the presence of a positive sputum culture for *M. tuberculosis*. The World Health Organization clinical case definition was used to define AIDS in HIV-1–seropositive patients [18].

Statistical analysis. χ^2 with Yates's correction, Fisher's exact test, and Student's *t* test were used to compare parametric and nonparametric variables between groups. Multivariate analyses were conducted using a logistic regression model with SAS software to determine multivariate adjusted odds ratios and their 95% confidence intervals [19]. All *P* values reported are two-tailed.

Results

Index cases. During the 10-month enrollment period, 19,009 patients were examined at the CDT. Figure 1 demonstrates the origin of the 169 index patients (74 HIV-1–seropositive and 95 HIV-1–seronegative). (As part of a separate, concurrently running study, 767 of the 825 patients consecutively presenting to the CDT from 16 of the 21 selected satellite clinics in the catchment area were tested for HIV-1 and 170 [22%] were HIV-1–seropositive.) In the present study, 21 (28%) of the 74 HIV-1–seropositive index patients had AIDS. HIV-1–seropositive index patients were less likely than HIV-1–seronegative index patients to have received bacille Calmette-Guérin (BCG) vaccination (69% vs. 86%; $P < .01$). Ninety-seven percent of all index patients had sputum cultures positive for *M. tuberculosis*. All positive mycobacterial cultures grew only *M. tuberculosis*. Eleven (61%) of 18 HIV-1–seropositive index patients with AIDS were PPD-positive compared with 35 (71%) of 49 HIV-1–seropositive index patients without AIDS and 87 (96%) of 91 seronegative index patients ($P < .01$, χ^2 for trend). Twenty-six (35%) of 74 HIV-1–seropositive index patients were male compared with 40 (42%) of 95 seronegative index patients. The mean ages of HIV-1–seropositive and –seronegative index patients were

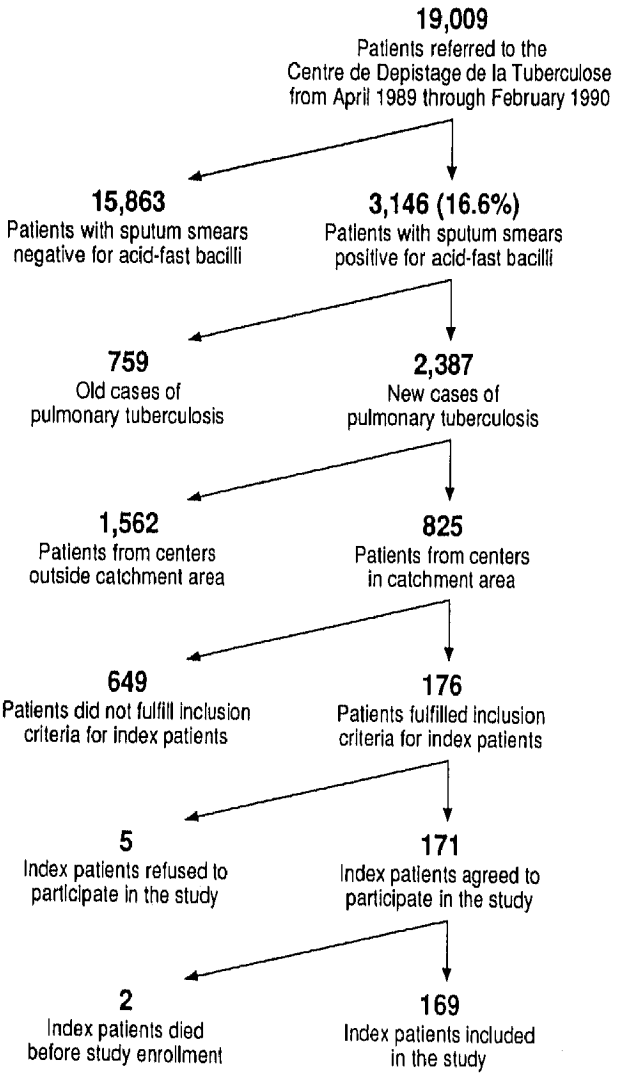

Figure 1. Selection scheme for index patients included in *M. tuberculosis* household transmission study.

32.3 and 31.4 years, respectively. HIV-1–seropositive index patients were more likely than seronegative index patients to have had a nontraumatic genital ulcer in the previous 5 years (19% vs. 5%; $P < .01$), to have had a greater number of sex partners in the past 5 years (mean, 1.4 vs. 1.2; $P < .01$), and to be unmarried (59% vs. 43%; $P < .05$).

Household contacts. A total of 1283 household contacts were identified. Twenty-five refused to participate in the study, and data collection was incomplete on another 45, leaving 1213 (95%) available for analysis. Of these, 521 (52% male; mean age, 17.7 ± 14.9 years; range, 1–81) were contacts of HIV-1–seropositive index patients and 692 (44% male; mean age, 17.2 ± 15.1 years; range, 1–85) of HIV-1–seronegative index patients. Contacts of HIV-1–seropositive index patients were more likely than contacts of HIV-1–seronegative index patients to be male (Student's *t* test, $P < .01$). No difference was observed in the mean number of household contacts per index patient (7.2; range, 1–27) between households with an HIV-1–seropositive or HIV-1–seronegative index patient.

Table 1 demonstrates the prevalence of PPD and sputum culture positivity for *M. tuberculosis* in household contacts according to their age and the index patient's HIV-1 serostatus. In household contacts of both kinds of index patients, PPD positivity increased significantly with increasing age. Within each age group, no difference existed in the prevalence of PPD or sputum culture positivity.

BCG vaccination rates were similarly high in household contacts of HIV-1–seropositive and –seronegative index patients; within each age group of contacts, no significant differences or trends existed in vaccination rates. The reported BCG vaccination rate for household contacts ≤5 years of age was 99% (79% had BCG vaccination scars); 6–10 years of age, 99% (82% had BCG vaccination scars); and 11–15 years of age, 97% (81% had BCG vaccination scars). For contacts ≥16 years of age, 72% had BCG vaccination scars.

Table 2 demonstrates the PPD prevalence in 1213 household contacts according to their age, length of stay with the index patient, known exposure to contacts with TB other than the index patient, radiographic evidence of cavitary pulmonary lesions in the index patient, and HIV-1 serostatus of the index patient. When multivariate analyses were used to determine the odds ratio and 95% confidence intervals in a logistic regression model adjusting for these five risk factors, there was no evidence of increased rate of PPD positivity according to the HIV-1 serostatus of the index patient. Traditional risk factors such as age, exposure to contacts with TB other than the index patient, and presence of cavitary lesions in the index patient were highly statistically significant. The length of stay with the index patient was not a statistically significant risk factor.

Table 1. Prevalence of purified protein derivative (PPD) reactivity and *M. tuberculosis* sputum culture positivity in household contacts according to HIV-1 serostatus of index patient and age of household contacts.

Age of household contact (years)	HIV-1–positive index patient		HIV-1–negative index patient	
	PPD+	Sputum culture+	PPD+	Sputum culture+
1–5	108 (43)	108 (2)	160 (48)	160 (3)
6–10	99 (53)	99 (8)	135 (51)	135 (3)
11–15	79 (53)	79 (5)	109 (62)	109 (9)
≥16	235 (74)	235 (5)	288 (78)	288 (2)
Total	521 (60)	521 (5)	692 (63)	692 (4)

NOTE. Data are total no. tested (% positive). Trend for increasing prevalence of PPD positivity with increasing age, $P < .01$ (χ^2). No significant differences were seen in prevalence of PPD or culture positivity between contacts of HIV-1–seropositive or –seronegative patients in any age group.

Table 2. Purified protein derivative (PPD) status of 1213 household contacts of 169 index patients with active pulmonary tuberculosis (TB).

Risk factor*	No. tested (% PPD+)	Odds ratio (95% CI)†	χ^2 (*P*)
Age of household contact (years)			
≥16	523 (76)		
≤15	690 (51)	2.62 (1.96–3.50)	42.7 (<.0001)
Length of stay with index patient (years)			
>4	591 (64)		
≤4	622 (61)	1.27 (0.96–1.69)	2.7 (NS)
Exposure to TB contacts other than index patient			
≥1 exposure	380 (73)		
No exposure	833 (57)	1.64 (1.20–2.23)	9.8 (<.002)
Radiographic evidence of cavitary pulmonary lesions in index patient			
≥1 lesion	549 (67)		
No lesions	384 (55)	1.71 (1.29–2.28)	13.7 (<.001)
HIV-1 serostatus of index patient			
Positive	521 (60)		
Negative	692 (63)	1.05 (0.79–1.41)	0.1 (NS)

NOTE. NS, not significant.
* Odds ratios were adjusted for listed factors.
† Determined by multivariate analysis using logistic regression model. CI, confidence interval.

Complete radiographic data were available on 80% of the index patients. There were no statistically significant differences ($P > .05$) in chest radiographic findings between HIV-1–seropositive and –seronegative index patients (93% vs. 95% with pulmonary infiltrates, 52% vs. 67% with cavitary lesions, 23% vs. 22% with evidence of pleural disease, and 27% vs. 15% with hilar or mediastinal lymphadenopathy).

Discussion

Perhaps the most sinister aspect of infection with *M. tuberculosis* in sub-Saharan Africa is that it is a family disease. Africa has the highest sputum smear–positive pulmonary TB rate in the world, and smear-positive TB is the most infectious type [20, 21]. Because the major determinants of infectivity are the intensity and duration of exposure to droplet nuclei containing *M. tuberculosis* organisms exhaled by a person with sputum-positive TB (such as from coughing or sneezing), their family members with close, repeated contact are at greatest risk of being infected [22]. Consequently, children are most often infected by their parents or relatives. The crowded, suboptimally hygienic living conditions and poor nutritional status of many individuals living in urban sub-Saharan Africa and the long-standing high rates of infection with *M. tuberculosis* in this region have created a situation in which acquiring *M. tuberculosis* infection has become a part of growing up. In Zaire, ~70% of the population have been infected with *M. tuberculosis* by adulthood [5]. Skin test surveys of children in sub-Saharan Africa have shown *M. tuberculosis* infection rates of 1%–3% per year of life [9].

The concordance in sub-Saharan Africa of the highest global rate of sputum-positive TB and the highest global prevalence of HIV-1 infection is markedly changing the clinical, epidemiologic, and therapeutic aspects of TB in Africa. That HIV-1 infection has become such a major determinant of the incidence and prevalence of TB in Africa raises several new questions about TB. Are HIV-1–seropositive individuals with active TB more or less infectious to their close contacts? Will there be a resultant large and growing number of secondary cases of *M. tuberculosis* infection in seronegative close contacts of HIV-1–seropositive persons with active TB? Secondary transmission of TB is widely known to occur, and attack rates have been reported to be as high as 8.2/1000 person-years in households of sputum-positive index patients [23]. The finding that 50% of the staff members of a housing facility for HIV-infected persons in the United States became infected with *M. tuberculosis* during an outbreak of TB suggests that HIV-infected patients with TB may be particularly infectious [24]. Although two small studies in Burundi found rates of active TB in household contacts of HIV-1–seropositive index patients with pulmonary TB to be 18% and 13% compared with none in household contacts of HIV-1–seronegative index patients with pulmonary TB, no large-scale studies examining *M. tuberculosis* transmission in association with HIV-1 infection have been carried out in Africa [25, 26].

We were unable to demonstrate any difference in infectivity to close household contacts between HIV-1–seropositive and –seronegative index patients with sputum-positive pulmonary TB. The prevalence of *M. tuberculosis* infection in household contacts documented in the present study was similar to those reported in a large study carried out between 1930 and 1960 in Tennessee, in which rates in poor rural and urban African-Americans were between 52% and 91% in age groups similar to those in the present study [23]. The 2%–9% rates of active TB in household contacts found in the present study are similar to the 5%–10% rates found in household contacts in the Tennessee study [23]. Our findings of an increase in rate of PPD positivity with increasing age and of the lowest PPD positivity rate in the youngest age group suggest that a large proportion of this tuberculin reactivity can be attributed to naturally acquired *M. tuberculosis* infection rather than to BCG immunization.

The similarity in risk factors for PPD positivity between household contacts of HIV-1–seropositive and HIV-1–seronegative index patients in the present study and those documented in household contacts of HIV-1–seronegative individuals in the study in Tennessee suggest that HIV-1 infection does not alter an index patient's infectivity to his or her household contacts [23]. This similarity and the established cost-effectiveness associated with chemotherapy for pulmonary TB in Africa highlights the importance of continuing aggressively to treat sputum-positive patients with TB regardless of their HIV-1 serology [3]. Our study suggests that although the HIV epidemic in Africa has increased the reservoir of patients with TB, it has not changed their infectivity. The lack of association between length of stay with the index patient and PPD positivity may indicate that in our study, length of stay was not an adequate surrogate measure for duration of exposure to the index patient when the time of infectivity is unknown.

The rates of PPD positivity in HIV-1–seropositive index patients in our study was consistent with other studies of patients with HIV-1 infection, which also demonstrated increasing anergy with increasing immunosuppression [27]. However, our study had a higher rate of PPD positivity in patients with AIDS (61%) than has been observed in AIDS patients in the United States (25%) [28]. The reason(s) for this difference is not clear.

The HIV-1 seroprevalence rate (43.8%) among index patients presenting to the CDT and meeting the inclusion criteria for this study was similar to that of other HIV-1 seroprevalence studies in TB patients in Zaire and in other sub-Saharan African countries [29–33]. Underlining the importance of heterosexual transmission in the epidemiology of HIV-1 infection in Africa, the identifiable risk factors for HIV-1 seropositivity in the male and female index patients in the present study were a history of a nontraumatic genital ulcer, being single or unmarried, and having multiple sex partners.

This study has certain limitations that may have biased our results and conclusions. First, we estimated secondary transmission rates in this cross-sectional study. The time of *M. tuberculosis* infection of household contacts relative to the index patient was unknown. Second, both HIV-1–seropositive and –seronegative patients with only extrapulmonary TB were excluded. Extrapulmonary TB occurs in >70% of patients with TB and preexisting AIDS or AIDS diagnosed soon after the diagnosis of TB but in only 24%–45% of patients with TB and less advanced HIV-1 infection [34–38]. Thus, extrapulmonary TB appears to be more common in patients with more severe HIV-induced immunosuppression. Patients with severe HIV-induced immunosuppression may be more effective transmitters of *M. tuberculosis*. We previously reported, however, that we could find no difference between transmitters and nontransmitters based on level of immunosuppression [39].

Third, we included index patients who were most infectious for *M. tuberculosis* to their household contacts. We included only sputum smear–positive individuals as index patients. Acid-fast smears of sputum are positive in only 31%–82% of patients with HIV-1 infection who have pulmonary TB [40–42]. This ascertainment bias probably led to our underestimating the number of HIV-1–seropositive index patients who were infectious to their household contacts. However, this bias is unlikely to have affected our estimation of different rates of secondary transmission in the households. Finally, it is possible that the high rate of BCG vaccination and prior exposure to *M. tuberculosis* (based on PPD positivity) greatly limited the number of susceptible household contacts. However, the protective efficacy of BCG for anything other than tuberculous meningitis has never been well documented [43]. Even though >97% of children ≤15 years of age reported receipt of BCG vaccination, the relatively low rate of PPD positivity in this group (~50%) suggests that this vaccination had not induced durable immunity.

Our study also has particular strengths. First, a large number of HIV-1–seropositive and –seronegative index patients were included. Second, 95% of the eligible household contacts were included. Finally, this study was carried out in an urban region with very high background prevalence rates for both of these chronic infectious diseases. The extreme conditions of poverty, crowding, and poor hygiene that characterized the living conditions of our study cohort should have maximized the likelihood of our detecting increased secondary transmission.

In conclusion, the index patients included in this study were representative of the Kinshasa population at large: young to middle-aged, slightly more likely to be female, living in an average household with about seven other close and extended family members, and generally middle-class by Zairian standards. For this reason, we believe that our study demonstrates that in Kinshasa, household contacts of HIV-1–seropositive persons with sputum-positive pulmonary TB are not at increased risk of acquiring *M. tuberculosis* compared with household contacts of a seronegative individual with sputum-positive TB. This finding should be of some comfort for the currently overextended TB control programs in sub-Saharan Africa in which household contacts of patients with TB are routinely tested for evidence of secondary *M. tuberculosis* infection. While the number of patients with active TB and HIV infection will undoubtedly increase, our study suggests that this increase will not be accompanied by an increase in the number of cases of secondary *M. tuberculosis* infection induced by each primary case.

Acknowledgments

We acknowledge the assistance of Paul Pauwels, Jacques Jeugmans, Frieda Behets, Veronique Batter, Ephrem Mpozayo, Alvara McBean, Claire Klausner, William Heyward, David Heymann, Helene Gayle, Robert Holzman, and Gilbert Ngandu-Kabeya, Minister of Health, Republic of Zaire.

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