

Infectiousness of *Mycobacterium tuberculosis* in HIV-1-infected patients with tuberculosis: a prospective study

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Summary

Background Previous studies concerning the relative infectiousness of HIV-1-positive individuals with pulmonary tuberculosis have produced conflicting results. Thus, we assessed the effect of HIV-1 on the infectiousness of *Mycobacterium tuberculosis* in a prospective study.

Methods We organised in Santo Domingo, Dominican Republic, a cohort study of household contacts of HIV-1-positive and HIV-1-negative individuals with newly diagnosed pulmonary tuberculosis. Household contacts were assessed at their houses at baseline and followed up for 14 months for evidence of *M tuberculosis* infection and tuberculosis with a multi-step tuberculin skin test, anergy skin test, physical examinations, chest radiographs, and sputum smears.

Findings Tuberculin induration of 5 mm or greater was seen in 153 (61%) of 252 household contacts of HIV-1-positive index cases and in 418 (76%) of 551 household contacts of HIV-1-negative index cases (odds ratio 0.49 [95% CI 0.35–0.67], $p=0.00001$). In multivariate logistic-regression analysis after allowance for between-household variation in tuberculin response, HIV-1 infection of the index case remained inversely associated with the tuberculin response of the household contacts (0.52 [0.29–0.93], $p=0.02$). When the analysis was restricted to household contacts aged between 2 years and 15 years the adjusted association remained significant (0.37 [0.14–0.98], $p=0.04$). Among household contacts who had a negative tuberculin skin test at baseline, conversion to tuberculin skin test positivity was less frequent among household contacts of HIV-1-positive index cases (cut-off ≥ 5 mm: 32/131 [24%] vs 71/204 [35%], $p=0.05$; cut-off ≥ 10 mm: 23/153 [15%] vs 55/245 [22%], $p=0.07$).

Interpretation These data suggest that HIV-1-positive individuals with tuberculosis are less likely than HIV-1-negative individuals with tuberculosis to transmit *M tuberculosis* to their close contacts. No changes in the current policy regarding tuberculosis contact tracing are needed in the presence of HIV-1.

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Introduction

In 1991, WHO outlined research priorities in the area of HIV-1 infection and tuberculosis, including the assessment of the effect of coexisting HIV-1 infection on the infectiousness of patients with tuberculosis.¹ Since that time, several studies of this question have produced conflicting results. Some studies suggest that HIV-1-positive individuals with tuberculosis are more likely to spread *Mycobacterium tuberculosis* to their close contacts than are HIV-1-negative individuals, perhaps because HIV-1-induced immunosuppression allows more extensive replication of *M tuberculosis* in the lungs.^{2–5} Other studies have found no difference in the relative infectiousness of tuberculous patients with and without HIV-1 infection, and some studies have suggested that HIV-1-positive individuals with tuberculosis are less infectious than HIV-1-negative individuals with tuberculosis.^{6–10}

Several factors may have contributed to these inconsistent results. First, because most of the studies were cross-sectional, they could not ascertain when the household contacts examined become infected relative to when the index patient showed symptoms. Second, most of these studies did not assess the HIV-1 infection status of the household contacts or do anergy testing, making it difficult to know whether household contacts with a negative tuberculin skin test were truly uninfected or simply unable to respond to the skin-test antigen. To shed further light on this subject, we did a prospective cohort study of household contacts of HIV-1-positive and HIV-1-negative individuals with newly diagnosed pulmonary tuberculosis in the Dominican Republic.

Methods

Index patients

All consenting patients older than 15 years with newly diagnosed active tuberculosis diagnosed at any of five medical institutions (Padre Billini Hospital, Moscoso Puello Hospital, Dispensario Anti-tuberculosis, Salvador Gautier Hospital, and Rodolfo de la Cruz Lora Hospital) and living in Santo Domingo or its surroundings were potentially eligible for enrolment in the study and were asked to give written informed consent. An individual of appropriate age and area of residence was eligible for enrolment if he or she had: no previous diagnosis of tuberculosis, systemic signs and symptoms (fever, cough, weight loss, sweating, anorexia), and *M tuberculosis* infection as shown by recovery of *M tuberculosis* from a clinical specimen; characteristic acid-fast bacilli shown by the Ziehl-Neelsen stain on a smear of respiratory tract secretions together with material aspirated from an enlarged lymph node, a tissue biopsy specimen, or other appropriate clinical specimens; or chest radiograph compatible with tuberculosis, previous exposure to tuberculosis (contact with a person with tuberculosis or who was tuberculin positive), and clinical response to antituberculosis therapy. Cultures of *M tuberculosis* were prepared by the Lowenstein-Jensen medium followed by drug-susceptibility testing by the proportion method.¹¹

After tuberculosis was diagnosed, study participants were tested for HIV-1 antibodies by ELISA (Genelavia Mixt, Sanofi Diagnostics, Institut Pasteur, Paris, France), with pretest and

post-test counselling. HIV-1 testing followed WHO recommendations for the selection and use of HIV-1 antibody tests.¹² These guidelines suggest a three-test approach for countries where the prevalence of HIV-1 infection is estimated to be 10% or less. All serum samples found positive on initial ELISA testing were tested again by ELISA, and all repeatedly positive samples were confirmed by the indirect immunofluorescence assay. Each patient was interviewed to collect demographic data, indicators of socioeconomic status, risk factors for HIV-1 infection, and history of previous vaccination with BCG. In addition, clinical data concerning signs, symptoms, findings on physical examination, and results of laboratory tests pertinent to a possible diagnosis of AIDS according to WHO criteria were recorded by the examining physician on a specially designed clinical data form. Each HIV-1-positive index patient with tuberculosis was matched with two HIV-1-negative index patients with tuberculosis on age (± 5 years), sex, and the results of acid-fast bacilli sputum smears.

Household visits and assessment of contacts

At baseline every household was visited as soon as possible after HIV-1 test results of the index patients were available and the matching procedure was completed (7–15 days). The study was explained at each household and written consent obtained individually from each adult and, for children, from a parent or household-head. Household contacts who gave their consent were interviewed about a history of tuberculosis, current symptoms, socioeconomic and demographic status, health, and relationship to the index patient (spouse/child *vs* other). Whether the contact shared the same bed as the index case, the same bedroom but not the same bed or slept in a different bedroom was used as a measure to the closeness of the index case and the household contact. We also recorded how many people were living in the house, number of rooms, bedrooms, and beds, and the availability of basic services (electricity, toilet, and indoor piped water). Crowding was estimated by dividing the number of people living in the house by the number of rooms. Each household contact was examined for a BCG scar and for signs of tuberculosis. Serum samples from household contacts of HIV-1-positive index patients were obtained for HIV-1-antibody testing, and pretest and post-test counselling was provided.

To test for *M tuberculosis* infection and anergy, household contacts were injected intradermally on the volar surface of the left forearm with 0.1 mL of Tubersol (purified protein derivative, 5 tuberculin units; Connaught Laboratories, Toronto, Canada) and on the volar surface of the right forearm with 0.1 mL of fluid tetanus toxoid (1 in 5 dilution; Connaught Laboratories) and Candidine (*Candida albicans* antigen, undiluted; Allermid Laboratories, San Diego, California, USA). A separate syringe was used for each antigen. The largest transverse diameter of palpable induration at each site was measured 48–72 h later. A positive response was defined as 5 mm or more of induration in response to purified protein derivative and 3 mm or more of induration in response to the other antigens. Household contacts with less than 3 mm of induration in response to all of the three antigens were regarded as anergic. All skin tests were done and read by a team of two trained individuals who were not aware of the HIV-1 status of the index patient and of the household contact.

Household contacts not reacting to tuberculin test at the baseline visit were tested again with purified protein derivative, candida, and tetanus toxoid during follow-up visits at 2 months and 8 months after the baseline visit to detect tuberculin conversion. At the household visits at 2 months and 8 months, as well as at the final visit at 14 months, household contacts were also asked about symptoms of tuberculosis and were examined. At each visit, household contacts with signs or symptoms suggestive of active tuberculosis were referred to one of the participating hospitals, where a study physician was available to conduct an evaluation (chest radiography, smear microscopy, and detailed physical examination) and provide standard treatment (short-course chemotherapy with isoniazid, rifampicin, pyrazinamide, and streptomycin or ethambutol). Chest radiographs were read

and physical exams done without the physician being aware of the HIV-1 status of either the household contact or the index patient. Household contacts were compensated for the cost of travel to and from the hospital. At the baseline visit to the household, the addresses of a close friend and a close relative were collected to help locate individuals who did not appear for follow-up visits. Each patient was also asked to notify the study team of any change of address.

The study was approved by the research ethics committees of the participating hospitals and of the University of California at Berkeley.

Statistical analysis

All data collection forms were checked twice for completeness and consistency and all errors or discrepancies were corrected. Data were double-entered and checked for data-entry errors. Univariate analyses included Student's *t* test for the comparison of the means of continuous variables; χ^2 test with continuity correction factor and χ^2 for trends for the comparison of categorical variables.

Because *M tuberculosis* infection tends to aggregate within households, analyses that treat each household contact as an independent observation will give spuriously precise results. Therefore, the relation between the tuberculin response of the household contact (induration ≥ 5 mm and ≥ 10 mm were explored) and the HIV-1 infection of the index patient, as well as with other variables related to the index patients, the household setting, and the household contact, were examined with logistic-binomial regression with random effects for distinguishable data, with household contacts as matched sets (EGRET, Version 1.02.10, Statistics and Epidemiology Research Corporation, Seattle, WA, USA). This method superimposes a random household effect upon the fixed effects representing the measured covariates, allowing for the possible effects of between-household variations in tuberculin response. Odds ratios obtained by this method are the antilogs of the regression coefficients from the fitted logistic-binomial model. Variables found biologically and statistically significant in univariate analysis were explored in multivariate modelling with logistic-binomial regression with random effects for distinguishable data. Different models were explored by means of the χ^2 likelihood-ratio statistic to identify the models that best fitted the data. Adjusted odds ratios and 95% CIs were calculated.

Results

Index patients and tuberculosis

755 of 816 patients with newly diagnosed tuberculosis consented to participate in the study between January, 1994, and July, 1995. Of these consenting individuals, 69 (9.1% [95% CI 7.2–11.3]) were HIV-1 positive. There were no differences between HIV-1-positive and HIV-1-negative individuals in regard to age, sex, education, or other demographic characteristics. Of the 69 HIV-1-positive individuals, 11 could not participate in the household visit (three died before the visit could be arranged, three did not have household contacts, and five decided to drop out after they had given consent). Of the 686 consenting HIV-1-negative individuals with tuberculosis, 86 were not eligible for the matching procedure (seven died, 41 did not have household contacts, and 38 dropped out after they had given consent). Of the remaining 600 eligible HIV-1-negative individuals with tuberculosis, 116 were selected by the matching criteria described above. Thus, 174 index patients with tuberculosis (58 HIV-1-positive and 116 matched HIV-1-negative individuals) were visited at their place of residence to assess their household contacts for *M tuberculosis* infection and tuberculosis. All individuals with tuberculosis who were not included in the household visit received appropriate treatment for tuberculosis.

	HIV-positive index case	HIV-negative index case
Tuberculin skin-test reactions		
Prevalent (tuberculin-positive at baseline)	121/252 (48%)	347/551 (63%)
Incident (tuberculin skin-test conversions)	32/131 (24%) [†]	71/204 (35%) [†]
Total (combined)	153/252 (61%)	418/551 (76%)
Tuberculin skin-test conversions by visit		
First follow-up visit (2 months)	25/131 (19%) [†]	60/204 (29%) [†]
Second follow-up visit (8 months)	7/106 (7%) [†]	11/144 (8%) [†]

* ≥ 5 mm induration. [†]% of those tuberculin-negative at the time of the previous visit.

Table 1: Results of tuberculin skin tests at baseline and thereafter among household contacts of index patients with tuberculosis

Household contacts

896 household contacts were reported, of whom 275 were contacts of HIV-1-positive index cases (mean 4.7 per patient) and 621 were contacts of HIV-1-negative index cases (5.4 per patient). Of these household contacts, 252 (91.6%) of HIV-1-positive index patients and 551 (88.7%) of HIV-1-negative index patients participated in the study. Of the 211 household contacts of HIV-1-positive index patients who agreed to have an HIV-1 test, 12 (5.7%) were HIV-1 positive. There were no differences with regard to demographic and other characteristics of the household contacts by HIV-1 status of the index patient (data available from the investigators).

Risk of infection among household contacts

After baseline and follow-up visits tuberculin induration of 5 mm or more was seen in 153 (61%) household contacts of HIV-1-positive index patients and in 418 (76%) household contacts of HIV-1-negative index cases (odds ratio 0.49 [95% CI 0.35–0.67], $p=0.00001$, table 1). After allowance for between-household variation in tuberculin response, the difference was still significant (0.51 [0.33–0.80], $p=0.003$). Of the 12 HIV-1-positive household contacts, ten (83%) were tuberculin-positive, and exclusion of these individuals from the analysis had no impact on the results. Of the variables related to the household contacts—age, education, presence of BCG scar, and the relationship of the household contact with the index patient—all were significantly associated with the tuberculin response (≥ 5 mm) after allowance for between-household variation in the tuberculin response (table 2). In contrast, household contacts who were anergic at any time during follow-up were much less likely to have a positive response to purified protein derivative (0.04 [0.02–0.08], $p<0.001$). When household contacts who were anergic were excluded from analysis, the relation between the tuberculin response in the household contacts and the HIV-1 status of the index cases was still significant (0.51 [0.38–0.79], $p=0.002$). Of the variables relating to the index patient and the household, being a household contact of an index patient with a higher-grade sputum smear or a positive culture for *M tuberculosis* was associated with a greater likelihood of having a positive tuberculin skin test (table 3). In multivariate logistic-regression analysis with random effects HIV-1 infection status of the index case and presence of anergy in the household contacts were inversely associated with a positive tuberculin skin test. The sputum smear grade of the index patient, the household contact's age, presence of a BCG scar, and relationship with the index patient were all significantly related to having a positive tuberculin skin test (table 4). When only these variables were included in the model, the effect of the HIV-1 status of the index patient

on skin test positivity was almost the same (0.52 [0.29–0.93], $p=0.02$).

In an analysis restricted to household contacts aged 2–15 years, the relation between HIV-1-infection status of the index patient and the tuberculin response of the household contact was similar to that seen when all household contacts were included after allowance for between-household variation in tuberculin response (0.45 [0.20–1.02], $p=0.05$). In multivariate logistic-regression analysis with random effects, the adjusted odds ratio for the HIV-1-infection status of the index patient and the tuberculin response of the household contact was 0.40 (0.15–1.01, $p=0.06$). The presence of anergy in the household contacts was also inversely associated with having a positive tuberculin skin test. In contrast, the household contact's age and relationship with the index patient, as well as the grade of sputum smear of the index patient, were associated with having a positive tuberculin skin test. When the closeness of the household contact to the index patient and crowding in the household were added to the previous model, the odds ratio for the HIV-1-infection status of the index patient and tuberculin induration of 5 mm or more of the household contact declined slightly to 0.37 (0.14–0.98, $p=0.04$, table 5).

When the analyses were repeated with a cut-off of 10 mm or more of tuberculin induration, no important differences in the results were seen (data not shown). We also examined predictors of tuberculin skin test conversion among those household contacts who initially had a negative tuberculin skin test. Household contacts of HIV-1-positive index patients were less likely to convert to a positive test than were household contacts of HIV-1-negative index patients (cut-off ≥ 5 mm 32/131 [24%] vs 71/204 [35%], $p=0.05$; cut-off ≥ 10 mm 23/153 [15%] vs 55/245 [22%], $p=0.07$). Increasing age was associated with a higher likelihood of a tuberculin conversion whereas

	Proportion of household contacts tuberculin-positive*	Odds ratio		P [†]
		Crude	Random-effects model	
Age (years)				
0–4	65/133 (49%)	1.00	1.00	0.001 [‡]
5–14	136/224 (61%)	1.52	1.80	
15–25	118/146 (81%)	4.71	6.55	
>25	247/290 (85%)	8.50	8.74	
Sex				
Female	320/455 (70%)	1.00	1.00	0.6
Male	251/348 (72%)	1.09	1.11	
Education (years)				
0	121/210 (58%)	1.00	1.00	0.001 [‡]
1–8	332/444 (75%)	2.18	2.64	
9–12	96/126 (76%)	3.71	3.06	
>12	22/23 (96%)	12.1	28.2	
Relationship to index patient				
Other	399/579 (69%)	1.00	1.00	0.02
Spouse/child	172/224 (77%)	1.49	1.33	
BCG scar present				
No	205/311 (66%)	1.00	1.00	0.004
Yes	366/492 (74%)	1.50	1.71	
Anergy§				
No	557/720 (77%)	1.00	1.00	<0.001
Yes	14/83 (17%)	0.05	0.04	
Closeness to index patient				
Share a bed	79/109 (73%)	1.00	1.00	0.9
Share bedroom	123/165 (75%)	1.11	1.02	
Different bedroom	369/529 (70%)	0.87	0.93	

* ≥ 5 mm induration. [†]p value for odds ratio allows for random effect. [‡] χ^2 test for trend. [§]Anergy was defined as induration <3 mm to all of the three antigens.

Table 2: Relation between tuberculin skin-test response and variables related to household contact

	Proportion of household contacts tuberculin-positive*	Odds ratio		p†
		Crude	Random-effects model	
Age (years)				
<25	149/211 (71%)	1.00	1.00	0.9‡
25–34	227/322 (71%)	0.99	0.99	
35–44	155/209 (74%)	1.19	1.25	
≥45	40/61 (66%)	0.79	0.72	
Sex				
Female	203/273 (74%)	1.00	1.00	0.3
Male	368/530 (69%)	0.78	0.77	
Education (years)				
0–8	349/488 (72%)	1.00	1.00	0.9‡
9–12	173/245 (71%)	0.95	0.99	
>12	49/70 (70%)	0.92	1.00	
Calvitiation on chest radiograph§				
Absent	208/296 (70%)	1.00	1.00	0.9
Present	302/424 (71%)	1.06	0.98	
Sputum smear grade (number of bacilli/field)				
0	37/57 (65%)	1.00	1.00	0.01‡
1–10	428/605 (71%)	1.30	1.67	
>10	76/93 (82%)	2.41	3.11	
Culture status§				
Negative	111/171 (65%)	1.00	1.00	0.02
Positive	392/525 (75%)	1.59	1.84	
Drug susceptibility 				
Susceptible	176/239 (74%)	1.00	1.00	0.8
Resistant	158/209 (76%)	1.10	0.94	
Duration of cough (days)§				
<30	119/185 (64%)	1.00	1.00	0.09
≥30	449/615 (73%)	1.51	1.54	
Working status§				
No	412/589 (70%)	1.00	1.00	0.8
Yes	151/201 (75%)	1.21	1.31	
Crowding (persons/room)				
≤2.0	162/218 (74%)	1.00	1.00	0.01‡
2.1–3.0	238/323 (74%)	1.01	0.98	
3.1–4.0	81/121 (67%)	0.70	0.72	
>4.0	90/141 (64%)	0.63	0.66	
Basic services¶				
All	189/261 (72%)	1.00	1.00	0.9‡
Two	150/219 (69%)	0.82	0.91	
One	222/308 (72%)	1.02	1.04	
None	10/15 (67%)	0.73	0.73	

*≥5 mm induration. †p value for odds ratio allowing for random effects. ‡χ² test for trend. §Numbers do not add up to total because of missing values. ||Only patients from whom *Mycobacterium tuberculosis* was isolated.

Table 3: Relation between tuberculin skin-test response (induration ≥5 mm) and variables related to the index patient and the household setting

previous vaccination with BCG did not change the likelihood of converting to a positive tuberculin skin test.

Cases of tuberculosis among household contacts

Over the course of 14 months of follow-up, active tuberculosis was diagnosed in 46 (6%) household contacts, including 33 (6%) contacts of HIV-1-negative index patients and 13 (5%) contacts of HIV-1-positive index patients ($p>0.2$). 50% of the cases of tuberculosis in household contacts were confirmed by smear microscopy or culture. Of the household contacts who were diagnosed with tuberculosis, 80% had a tuberculin induration of 10 mm or more and 94% were not anergic. None of the cases of tuberculosis among household contacts of HIV-1-positive index patients were HIV-1-positive. The likelihood of tuberculosis decreased significantly with increasing age of the household contact (χ^2 for trend 10.4, $p<0.001$), being more common in household contacts aged less than 15 years (54%). Development of tuberculosis was more common among household contacts who were closely related to the index patient (spouse/child;

	Adjusted odds ratio (95% CI)	p
Household contact		
Age (years)		
0–4	1.00	<0.001
5–14	1.44 (0.61–3.35)	
15–25	5.68 (2.03–15.9)	
>25	6.52 (2.69–15.7)	
Education (years)		
0	1.00	0.1
1–8	1.37 (0.65–2.85)	
9–12	0.87 (0.35–2.19)	
>12	6.88 (0.67–70.1)	
Relationship with index patient		
Other	1.00	<0.001
Spouse/child	2.97 (1.61–5.49)	
BCG scar present		
No	1.00	0.04
Yes	1.58 (1.01–2.48)	
Anergy on skin testing*		
No	1.00	<0.001
Yes	0.03 (0.02–0.07)	
Closeness to index patient		
Share a bed	1.00	0.1
Share bedroom	1.86 (0.81–4.26)	
Different bedroom	1.27 (0.60–2.70)	
Index patient		
HIV status		
Negative	1.00	0.02
Positive	0.52 (0.29–0.93)	
Sputum smear grade (bacilli/field)		
0	1.00	0.02
1–10	1.98 (0.75–5.23)	
>10	5.88 (1.60–21.3)	
Culture status		
Negative	1.00	0.9
Positive	1.02 (0.51–2.05)	
Duration of cough (days)		
<30	1.00	0.4
≥30	1.24 (0.66–2.34)	
Household		
Crowding (persons/room)		
≤2.0	1.00	0.7
2.1–3.0	1.07 (0.54–2.10)	
3.1–4.0	0.94 (0.40–2.22)	
>4.0	0.67 (0.29–1.55)	

*Anergy was defined as induration <3 mm to all of the three antigens.

Table 4: Multivariate analysis of the relation between the tuberculin response (induration >5 mm) and variables related to the household contact, index case, and the household

odds ratio 3.0 [95% CI 1.6–5.5], $p<0.001$). However, the likelihood of tuberculosis developing among household contacts was not related to the sex or BCG-scar status of the household contact, degree of household crowding, the grade of sputum smear, the culture status, or the presence of cavitory disease in the index patient.

Discussion

Clarifying the relative infectiousness of HIV-1-positive patients with tuberculosis is of public health interest, because some researchers have proposed that if HIV-1-positive patients with tuberculosis are more infectious, active rather than passive contact investigation may be necessary in developing countries.⁸ The evidence so far is conflicting, small sample sizes and examination of household contacts only at the time of diagnosis of the index patient, or both, make interpretation difficult. For instance, in Spain, 18 (8%) of 225 household contacts of HIV-1-positive index patients with smear-positive tuberculosis were found to have active tuberculosis, compared with seven (3%) of 216 household contacts of HIV-1-negative index cases with smear-positive tuberculosis. Similar results were reported from studies done in Italy and Burundi.^{3–5} Conversely, studies from Zaire, Uganda, and Kenya did not find any difference in

Variable value	Adjusted odds ratio (95% CI)	p
Household contact		
Age (years)		
0-4	1.00	
5-14	2.36 (1.04-5.34)	0.03
Relationship with index patient		
Other	1.00	
Spouse/child	5.84 (2.17-15.6)	<0.001
Anergy on skin testing*		
No	1.0	
Yes	0.01 (0.003-0.08)	<0.001
Closeness to index patient		
Share a bed	1.00	
Share bedroom	3.78 (0.83-16.1)	0.1
Different bedroom	1.73 (0.46-6.52)	
Index patient		
HIV status		
Negative	1.00	
Positive	0.37 (0.14-0.98)	0.04
Sputum smear grade (bacilli/field)		
0	1.00	
1-10	2.24 (0.51-8.96)	0.04
>10	8.41 (1.27-66.7)	
Culture status		
Negative	1.00	
Positive	0.81 (0.25-2.59)	0.8
Duration of cough (days)		
<30	1.00	
≥30	1.99 (0.70-5.65)	0.1
Household		
Crowding (persons/room)		
≤2.0	1.00	0.8
2.1-3.0	0.43 (0.19-1.65)	
3.1-4.0	0.70 (0.16-2.98)	
>4.0	0.61 (0.21-3.08)	

*Anergy was defined as induration <3 mm to all of the three antigens.

Table 5: **Multivariate analysis of the relation between the tuberculin response (induration ≥5 mm) and variables related to the household contact, index case, and the household, among household contacts 2-15 years of age**

the prevalence of *M tuberculosis* infection among household contacts of HIV-1-positive and HIV-1-negative index patients.⁶⁻⁸ Studies in Zambia and the USA have suggested that the infectiousness of HIV-1-positive individuals with tuberculosis is lower than that of HIV-1-negative individuals with tuberculosis.^{9,10} All of these studies may have underestimated the extent of transmission of *M tuberculosis* to household contacts of HIV-1-positive and HIV-1-negative index patients because they did not test again those who initially had a negative tuberculin skin test, and the tuberculin reaction may take several weeks to become positive after infection with *M tuberculosis*. Indeed, in our study, a significant proportion of positive skin tests occurred after 2 months and 8 months (24% and 35% of household contacts of HIV-1-positive and HIV-1-negative index cases, respectively).

Our results show that HIV-1-positive patients with tuberculosis are less rather than more likely to transmit *M tuberculosis* to others. A lower proportion of tuberculin induration among household contacts of HIV-1-positive index patients was observed at cut-offs of 5 mm or more (61% vs 76%) and 10 mm or more (54% vs 70%). This effect persisted when the analysis was restricted to household contacts aged between 2 years and 15 years, in whom skin test positivity is usually attributed to contact with an older household member.¹³ Furthermore, the proportion of initially skin-test-negative household contacts of HIV-1-positive index patients who converted their tuberculin response was lower at both cut-offs than was that of household contacts of HIV-1-negative index cases, and the proportion who developed active tuberculosis did not differ between the two groups.

This investigation also assessed household contacts for evidence of anergy, which can be induced by HIV-1 infection and other infectious diseases, and can lead to a lower sensitivity of the tuberculin skin test.¹⁴ Not surprisingly, we found that anergic household contacts were less likely to develop a positive tuberculin response. After exclusion of HIV-1-positive household contacts, the proportion of household contacts of HIV-1-positive index patients who were anergic remained higher than that of household contacts of HIV-1-negative index cases. Because the individuals reading the skin-test results were unaware of the HIV-1 status of the index patients, differential misclassification is an unlikely explanation for this finding. It is possible that HIV-1 infection went undetected among some household contacts of HIV-1-positive index patients, if they were in the window period of HIV-1 infection. Also, only 83% of the eligible household contacts of HIV-1-positive index patients consented to be tested for HIV-1 antibodies. Nevertheless, when we excluded from the analysis those household contacts who were anergic, the proportion of household contacts of HIV-1-positive index patients who had a positive tuberculin skin test response was still significantly lower than that among household contacts of HIV-1-negative index patients.

Several factors known to be associated with the likelihood of transmission of *M tuberculosis* were confirmed in our study, including the age and relationship of household contacts with the index patient, as well as the sputum-smear grade in the index patient.^{15,16} We defined a close relationship as being the index patient's spouse or child, because these individuals were likely to spend most time with the index patient. This variable was also strongly associated with the risk of active tuberculosis among household contacts. Not surprisingly, increasing age was associated with a higher likelihood of tuberculin-positivity, suggesting that the tuberculin reactivity is attributable to infection with *M tuberculosis* rather than BCG immunisation. This effect, which has been documented before, was seen among household contacts who had been vaccinated with BCG and those who had not.^{8,9} Similarly, an association between the grade of the sputum smear in the index patient and the likelihood of a positive skin test in a household contact was seen. The higher the bacillary load, the better the efficiency of transmission.¹⁷ After the grade of the sputum smear had been taken into account, other factors such as duration of cough, degree of cavitation, and culture status of the index patient were not significant predictors of infection in a household contact. Even after allowance for grade of sputum smear in the multivariate analysis, the inverse association between HIV-1-infection status of the index patient and the tuberculin response of the household contact remained significant. What led to this effect is beyond the scope of our investigation, but one possible explanation is that a high degree of illness in HIV-1-infected patients resulted in weakened cough and, perhaps, in less effective dissemination of *M tuberculosis* into their surroundings.

Several limitations of our study need to be acknowledged. We did not test for HIV-1 infection in the household contacts of the HIV-1-negative index patients because of limited resources. We believe the prevalence of HIV-1 infection among contacts of HIV-1-negative tuberculosis cases in Santo Domingo is likely to be very low. In our study, the prevalence of HIV-1 infection among index patients with tuberculosis was only 9%,

much lower than in Africa. Nunn and colleagues found that while 37% of tuberculosis patients in Kenya were HIV-1 positive, only two household contacts of HIV-1-negative index patients were HIV-1 positive.⁸ Serosurveys of pregnant women and of children with tuberculosis suggest that the prevalence of HIV-1-infection in Santo Domingo is much lower than that seen in Africa.^{18,19} Furthermore, the main problem with any undetected HIV-1 infection in these household contacts would be that HIV-1-induced anergy would have prevented us from detecting tuberculosis infection in these individuals. Because we tested all household contacts for anergy, this problem should have been obviated.

We were not able to evaluate the boosting effect of multistep tuberculin testing. In immunocompetent individuals infected with *M tuberculosis*, the response to tuberculin may gradually wane over time. Reactivity may be restored by repeating tuberculin testing as soon as 1 week after the first test.²⁰ We retested with purified protein derivative those household contacts who were initially negative, 2 months and 8 months later. Boosting is likely to overestimate the true rate of *M tuberculosis* infection. However, the size of this effect should not have differed between household contacts of HIV-1-positive and HIV-1-negative index patients, unless the proportions with anergy or BCG vaccination differed between the two groups. After exclusion of household contacts who were anergic and vaccinated with BCG, the proportion of household contacts of HIV-1-positive index patients who converted their tuberculin skin test was still lower than that among household contacts of HIV-1-negative index patients (22% vs 29%), although not significantly lower. The lack of significance may well reflect the small sample size available for stratified analysis. Nevertheless, there is no reason to believe that our results can be explained by a boosting effect.

Although we cannot rule out unknown confounding factors, the data presented show that HIV-1-positive individuals with tuberculosis are less likely to spread *M tuberculosis* to their close contacts than HIV-1-negative individuals with tuberculosis. In light of these findings, we believe that the current policy in respect of tuberculosis-contact tracing for developing countries does not need to be revised based on the prevalence of HIV-1 infection. As previously suggested, adoption of active contact tracing in developing countries would not be cost-effective in view of the slight increase in the detection rate for tuberculosis cases that would result from this strategy.²¹ Our study does not support the adoption of such a policy.

Contributors

Marcos Espinal was involved in the grant preparation, study design, execution, data analysis, and writing of the paper. Eddy Pérez and Jannette Baéz participated in design and execution, and organised the data management. Luis Hénriquez organised and supervised the fieldwork. Karina Fernández, Pedro Olivo, and Maria Lopez did the epidemiological and clinical investigations and participated in the execution of the project. Arthur Reingold was involved in the grant preparation, study design, and writing of this work. All investigators contributed critical revisions for the final version of the paper.

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