MAJOR ARTICLE

The Effect of HIV-Related Immunosuppression on the Risk of Tuberculosis Transmission to Household Contacts

Chuan-Chin Huang,[1] Eric Tchetgen Tchetgen,[1] Mercedes C. Becerra,[2] Ted Cohen,[1] Katherine C. Hughes,[1] Zibiao Zhang,[3] Roger Calderon,[4] Rosa Yataco,[4] Carmen Contreras,[4] Jerome Galea,[5] Leonid Lecca,[4] and Megan Murray[2]

[1]Department of Epidemiology, Harvard School of Public Health, [2]Department of Global Health and Social Medicine, Harvard Medical School, and [3]Brigham and Women's Hospital, Boston, Massachusetts; [4]Socios en Salud, Lima, Peru; and [5]Partners in Health, Boston, Massachusetts, USA

Background. Coinfection with human immunodeficiency virus (HIV) may modify the risk of transmitting tuberculosis. Some previous investigations suggest that patients coinfected with HIV and tuberculosis are less likely to transmit infection, whereas others do not support this conclusion. Here, we estimated the relative risk of tuberculosis transmission from coinfected patients compared to HIV-negative patients with tuberculosis.

Methods. Between September 2009 and August 2012, we identified and enrolled 4841 household contacts of 1608 patients with drug-sensitive tuberculosis in Lima, Peru. We assessed the HIV status and CD4 counts of index patients, as well as other risk factors for infection specific to the index patient, the household, and the exposed individuals. Contacts underwent tuberculin skin testing to determine tuberculosis infection status.

Results. After adjusting for covariates, we found that household contacts of HIV-infected tuberculosis patients with a CD4 count ≤250 cells/μL were less likely to be infected with tuberculosis (risk ratio = 0.49 [95% confidence interval, .24–.96]) than the contacts of HIV-negative tuberculosis patients. No children younger than 15 years who were exposed to HIV-positive patients with a CD4 count ≤250 cells/μL were infected with tuberculosis, compared to 22% of those exposed to non-HIV-infected patients. There was no significant difference in the risk of infection between contacts of HIV-infected index patients with CD4 counts >250 cells/μL and contacts of index patients who were not HIV-infected.

Conclusions. We found a reduced risk of tuberculosis infection among the household contacts of patients with active tuberculosis who had advanced HIV-related immunosuppression, suggesting reduced transmission from these index patients.

Keywords. HIV; tuberculosis infection; CD4; infectiousness; contacts.

Although multiple studies have shown that human immunodeficiency virus (HIV) drives tuberculosis epidemics at the population level [1], the impact of HIV on the spread of tuberculosis at the individual and household levels remains unclear. Because coinfected patients are often sputum smear negative, have relatively few cavitary lesions, and have a reduced period of infectiousness, they may be less likely than non-HIV-infected patients to transmit tuberculosis to their contacts [2–4]. Previous studies that have compared the relative infectiousness of HIV-infected and non-HIV-infected tuberculosis patients have been inconsistent; a meta-analysis found similar rates of infection as measured by the tuberculin skin test (TST) between the household contacts of HIV-positive and -negative tuberculosis index patients [5], but noted marked heterogeneity across the studies [6]. Another group found that although the HIV status of a tuberculosis index patient did not modify the prevalence of TST positivity among

Received 6 September 2013; accepted 14 December 2013; electronically published 23 December 2013.

Correspondence: Megan Murray, MD, Department of Global Health and Social Medicine, Harvard Medical School, 641 Huntington Ave, 4th Floor, Rm 4A07, Boston, MA 02115 (mmurray@hsph.harvard.edu).

Clinical Infectious Diseases 2014;58(6):765–74

DOI: 10.1093/cid/cit948

household contacts (HHCs), there was a lower TST conversion rate among uninfected HHCs exposed to HIV-positive index tuberculosis patients [7]. Consistent with this, 2 other studies suggested that contacts of HIV-positive patients with tuberculosis were less likely to be TST positive [8] and had a decreased risk of tuberculosis disease [9, 10] compared to contacts of HIV-negative patients.

A possible source of heterogeneity in these results may be the degree of HIV-induced immunosuppression among the coinfected index patients. Few of the studies cited above report results stratified by CD4 count or other indicators of HIV-related immunosuppression, and thus important differences in the transmissibility of tuberculosis related to the different clinical manifestations of HIV/tuberculosis coinfection may have been aggregated. Here, we evaluate the risk of tuberculosis infection among household contacts of index patients with and without HIV, stratifying by CD4 count.

METHODS

Data Collection and Categorizations

Index Patients

Between September 2009 and August 2012, we identified newly diagnosed adult patients with culture-positive pulmonary tuberculosis from 106 participating health centers located in a catchment area of Lima, Peru. The study area contains approximately 3.3 million residents. The tuberculosis case notification rate in this area was 96.1 per 100 000 person-years in 2009 [11].

We excluded index patients with drug-resistant tuberculosis to avoid potential heterogeneity in transmission due to the drug resistance phenotype. We also excluded index patients who lived outside the catchment area, resided in a nursing home, or were younger than 15 years of age. At enrollment, we recorded the index patient's age, sex, sputum smear status, time between the onset of tuberculosis symptoms and diagnosis, presence of cavitary disease as confirmed by chest radiography, HIV infection status (negative or positive) and, if HIV positive, HIV treatment history from the medical record. From September 2009 to August 2011, HIV infection status was determined using a lab-based enzyme immunoassay (EIA), and nonnegative samples were confirmed using an immunofluorescence assay (IFA). After August 2011, a new HIV testing algorithm was employed [12]; we first performed a rapid screening test and followed those with nonnegative tests with an EIA and a confirmatory IFA. HIV disease status was further categorized based on CD4 count <250 or ≥250 cells/μL. We obtained the CD4 count from the patients' medical records using the value obtained at the time that was closest to the patient's tuberculosis diagnosis date. When there was no CD4 count measurement within a 180-day window (±90 days) of the tuberculosis diagnosis, the degree of immunosuppression was determined using the criteria shown in Table 1. The time to treatment was measured as the number of days the patient reported coughing prior to diagnosis.

Table 1. Algorithms for Categorizing Tuberculosis Patients Who Did Not Have at Least 1 CD4 Measurement Within 180-Day Window (±90 Days) of the Time of Diagnosis

CD4 Measurement Time	HIV Treatment	Observed CD4, Cells/μL	Defined CD4, Cells/μL	Assumption
Had 1 measurement between −180 and −90 d of T_0[a] and 1 between 90 and 180 d of T_0[b]	Yes	>250	>250	. . .
		≤250	≤250	. . .
	No	>250	>250	. . .
		≤250	≤250	. . .
Only had measurements before −180 d of T_0[c]	Yes	>250	>250	CD4 counts will not decrease with HIV treatment
		≤250	Missing	. . .
	No	>250	Missing	. . .
		≤250	≤250	CD4 counts will not increase without HIV treatment
Only had measurements after 180 d of T_0[c]	Yes	>250	Missing	. . .
		≤250	Missing	. . .
	No	>250	>250	CD4 counts will not increase without HIV treatment
		≤250	Missing	

Abbreviation: HIV, human immunodeficiency virus.

[a] T_0: Time of tuberculosis diagnosis.

[b] Mean of CD4 counts of the 2 observations was used.

[c] Measurement closest to the T_0 was used.

Household Contacts

Within a month following the index patient's diagnosis, a nurse visited the index patient's household and invited HHCs to participate in a baseline assessment to identify those infected with tuberculosis by using TST. We classified people as tuberculosis infected if their TST was ≥10 mm or ≥5 mm if they were HIV positive. HHCs who reported a previous diagnosis of active tuberculosis or a positive TST were excluded. At the baseline visit, we collected the following information for each participating HHC: age, sex, height, weight, tobacco use, alcohol intake, number of BCG vaccination scars, and relation to the index patient. We categorized participants according to their alcohol intake as nondrinkers (no alcoholic drinks consumed per day), light drinkers (<40 g or <3 alcoholic drinks consumed per day), and heavy drinkers (≥40 g or ≥3 alcoholic drinks consumed per day) [13]. A large proportion of smokers reported smoking an average of only a single cigarette per day. Consequently, we categorized smoking use as nonsmokers (no cigarettes per day), light smokers (1 cigarette per day), and moderate or heavy smokers (>1 cigarette per day). The World Health Organization body mass index (BMI) *z* score tables were used to define nutritional status [14]. We assigned HHCs with BMI *z* scores <2 as underweight, and those with *z* scores >2 as overweight.

Household Characteristics

We assessed the relationship between the following household characteristics and the risk of tuberculosis infection among contacts: number of people per room, secondhand tobacco exposure, and the type of housing. Housing was considered substandard if participants resided in any of the following: hut, shack, makeshift housing, or space not intended for human habitation.

Data Analysis

We estimated prevalence ratios with a modified Poisson generalized estimating equation to account for correlation among participants within a household [15]. We specified an exchangeable working correlation structure for observations within the same household. For inference, we obtained empirical standard error estimates that were used to construct Wald-type 95% confidence intervals. We first performed age-adjusted univariate analyses for covariates that were expected to modify tuberculosis infection based on a priori background knowledge. Subsequently, we included all covariates in the multivariate model, with the exception of sputum smear status, length of symptomatic period, and presence of cavitary disease, as we hypothesized that these risk factors may mediate the effects of the index patient's HIV disease progression on the contact's risk of tuberculosis infection. We also aimed to quantify the direct effect of HIV on risk of tuberculosis transmission, which was not mediated by smear status, duration of symptomatic disease, or cavitation. We evaluated the direct effect by adding the mediators to the regression model, assuming that upon adjusting for the observed covariates, no unobserved confounding prevailed for the joint effects of the degree of the index patient's immunosuppression and these 3 mediators on the HHC's risk of tuberculosis infection.

The above analytic approach implicitly assumes that all infected HHCs acquired infection from the index patient. However, it is clear that some HHCs will have acquired infection from other tuberculosis patients either within the home or from other sources in the community in the past; this would lead to nondifferential misclassification and would be expected to attenuate our results toward the null. Another potential bias could arise if there were other index patient–related or household characteristics associated with the degree of the index patient's immunosuppression and tuberculosis transmission in the past. We performed 2 sensitivity analyses to address the direction and magnitude of these potential biases. First, we repeated the analysis excluding households that reported any tuberculosis cases occurring earlier than the index patient's diagnosis. Second, we restricted our analysis to HHCs' children <15 years of age, because of the low likelihood that these children were infected before an index patient's diagnosis and much more limited risk of being infected in the community.

RESULTS

Baseline Characteristics

We identified 1608 index patients with incident drug-sensitive pulmonary tuberculosis and 4841 exposed HHCs who had not had a previous diagnosis of active tuberculosis or previous positive TST. TST results were available for 4253 (87.85%) of the HHCs. Table 2 shows the baseline characteristics of HHCs, stratified by HIV status of the index patient. The prevalence of tuberculosis infection in HHCs was 44.99% in adults and 22.07% in children. The prevalence of HIV in tuberculosis cases was 3.00%.

Age-Adjusted Univariate Analyses

After adjusting for age, we found that HHCs were more likely to be TST positive at enrollment if they had ≥3 BCG vaccination scars, were related to the index patient, lived in an apartment or substandard housing, or had been exposed to an index patient who had a smear-positive sputum test or had delayed diagnosis from the onset of symptoms (Table 3).

Multivariate Analysis

We used the 3925 (92.29%) observations with complete data in a multivariate analysis. The prevalence of tuberculosis infection was similar to those who were excluded from this analysis because of missing data (35.72% vs 36.44% for adults and

Table 2. Baseline Characteristics of Household Contacts, Stratified by Index Patient HIV Status

Variables	Persons, No. (%)		
	HIV-Negative (n = 4106; 97.65%)	HIV-Positive (n = 99; 2.35%)	Total (N = 4205)
Sex			
Female	2322 (57)	58 (59)	2380 (56)
Male	1784 (43)	41 (41)	1825 (43)
Age, y			
0–15	1541 (38)	33 (33)	1574 (37)
16–30	1117 (27)	32 (32)	1149 (27)
31–45	675 (16)	17 (17)	692 (16)
46–60	510 (12)	10 (10)	520 (12)
>60	263 (7)	7 (7)	270 (6)
BCG scars			
0	556 (14)	16 (16)	572 (14)
1	2686 (65)	58 (59)	2744 (65)
2	694 (17)	20 (20)	714 (17)
≥3	168 (4)	5 (5)	173 (4)
Missing data	2 (0)	0 (0)	2 (0)
Smoking			
Never	3829 (93)	86 (87)	3915 (93)
Yes	251 (6)	12 (12)	263 (6)
Missing	26 (1)	1 (1)	27 (1)
Alcohol consumption			
Never	30743 (74)	69 (70)	3121 (74)
Light	812 (20)	20 (20)	832 (20)
Heavy	200 (5)	4 (6)	204 (5)
Missing	51 (1)	6 (6)	57 (1)
Relation to tuberculosis case			
Child	745 (18)	20 (20)	765 (18)
Parent	598 (15)	10 (10)	608 (14)
Sibling	862 (21)	28 (28)	890 (21)
Spouse	302 (7)	5 (5)	307 (7)
Other relationship[a]	1574 (38)	35 (35)	1609 (38)
Missing	25 (1)	1 (1)	26 (1)
Nutritional status[b]			
Normal weight	3658 (89)	89 (90)	3747 (89)
Underweight	55 (1)	1 (1)	56 (1)
Overweight	393 (10)	9 (9)	402 (10)
Characteristics of household environment			
Household smoke exposure			
No	3561 (87)	91 (92)	3652 (87)
Yes	535 (13)	7 (7)	542 (13)
Missing	10 (0)	1 (1)	11 (0)
Type of housing			
House	2992 (73)	74 (75)	3066 (73)
Apartment	671 (16)	16 (16)	687 (16)
Substandard housing	412 (10)	9 (9)	421 (10)
Missing	31 (1)	0 (0)	31 (1)
Median density, people/room	2.67	3.33	2.67
Characteristics of tuberculosis-infected household case			
Sex			
Female	1766 (43)	34 (34)	1800 (43)
Male	2340 (57)	65 (66)	2405 (57)
Age, y			
15–30	2502 (61)	57 (58)	2559 (61)
31–45	797 (19)	34 (34)	831 (20)
46–60	393 (10)	8 (8)	401 (10)
>60	414 (10)	0 (0)	414 (10)
Smear sputum status			
Negative	1037 (25)	14 (14)	1051 (25)
+	1128 (27)	34 (34)	1162 (28)
++	687 (17)	18 (18)	705 (17)
+++	1254 (31)	33 (33)	1287 (31)
Treatment delay, d			
0	312 (8)	8 (8)	320 (8)
1–14	297 (7)	7 (7)	304 (7)
15–28	1208 (29)	35 (35)	1243 (30)
>28	2243 (55)	43 (43)	2286 (54)
Missing	46 (1)	6 (6)	52 (1)
Cavitary disease			
No	3266 (80)	87 (88)	3353 (80)
Yes	780 (19)	9 (9)	789 (19)
Missing	60 (1)	3 (3)	63 (1)

Table 2 continued.

Abbreviations: BCG, Bacillus Calmette-Guerin; HIV, human immunodeficiency virus.

[a] Includes nonrelatives and relatives other than child, parents, sibling, and spouse.

[b] Defined by body mass index *z* score from World Health Organization; *z* score <2 was defined as underweight; >2 was defined as overweight.

21.95% vs 22.07% for children). The risk of TST positivity was higher among HHCs who had 3 BCG vaccination scars, relative to those with 1 BCG vaccination scar (risk ratio [RR] = 1.25; 95% confidence interval [CI], 1.08–1.44) and HHCs who were close relatives of the index patient (RR = 1.47 [95% CI, 1.28–1.70] for a child, 1.25 [95% CI, 1.08–1.43] for a parent, 1.17 [95% CI, 1.01–1.32] for a sibling, and 1.38 [95% CI, 1.18–1.56] for a spouse). HHCs exposed to an HIV-positive patient who had a CD4 count <250 cells/μL were less likely to be infected than those exposed to HIV-negative tuberculosis patients (RR = 0.49 [95% CI, .24–.96]; Tables 3 and 4).

Direct Effect

The observed direct effect of HIV-induced immunosuppression on the risk of an HHC's tuberculosis infection that was not

Table 3. Age-Adjusted Univariate and Multivariate Analyses in Household Contacts for Characteristics Associated With Baseline Tuberculin Skin Test Positivity

	Univariate (n = 4253[a])		Multivariate (n = 3925)		
Variables	No. (%)	RR (95% CI)	No. (%)	Final[b] RR (95% CI)	Direct Effect Model[c] RR (95% CI)
Characteristic of household contacts					
Sex					
Female	2405 (57)	1.00 (referent)	2248 (57)	1.00 (referent)	1.00 (referent)
Male	1848 (43)	0.97 (.91–1.04)	1677 (43)	0.96 (.88–1.03)	0.95 (.88–1.03)
BCG scars					
0	576 (14)	0.97 (.86–1.09)	535 (14)	0.98 (.86–1.11)	0.97 (.86–1.10)
1	2774 (65)	1.00 (referent)	2582 (66)	1.00 (referent)	1.00 (referent)
2	725 (17)	1.07 (.98–1.17)	649 (17)	1.07 (.97–1.18)	1.07 (.97–1.18)
≥3	176 (4)	1.28 (1.12–1.46)	159 (4)	1.25 (1.08–1.44)	1.25 (1.08–1.45)
Smoking					
None	3961 (94)	1.00 (referent)	3695 (94)	1.00 (referent)	1.00 (referent)
Light	156 (4)	1.14 (.97–1.33)	137 (3)	1.15 (.96–1.36)	1.16 (.97–1.38)
Moderate or heavy	109 (3)	1.08 (.91–1.28)	93 (2)	1.03 (.85–1.25)	1.03 (.85–1.25)
Alcohol consumption					
None	3145 (75)	1.00 (referent)	2965 (76)	1.00 (referent)	1.00 (referent)
Light	845 (20)	0.98 (.90–1.06)	772 (20)	0.98 (.89–1.07)	0.98 (.89–1.07)
Heavy	205 (5)	1.04 (.89–1.21)	188 (5)	1.01 (.84–1.20)	1 (.84–1.19)
Relation to index patient					
Child	773 (18)	1.42 (1.25–1.62)	717 (18)	1.47 (1.28–1.70)	1.47 (1.28–1.70)
Parent	615 (14)	1.20 (1.05–1.38)	569 (15)	1.25 (1.08–1.43)	1.26 (1.10–1.45)
Sibling	902 (210	1.16 (1.03–1.30)	837 (21)	1.17 (1.01–1.32)	1.17 (1.03–1.33)
Spouse	313 (7)	1.39 (1.22–1.58)	286 (7)	1.38 (1.18–1.56)	1.39 (1.21–1.59)
Other relationship[d]	1623 (39)	1.00 (referent)	1516 (39)	1.00 (referent)	1.00 (referent)
Nutritional status[e]					
Normal	3791 (89)	1.00 (referent)	3487 (89)	1.00 (referent)	1.00 (referent)
Underweight	57 (1)	0.85 (.57–1.26)	50 (1)	0.84 (.53–1.33)	0.84 (.53–1.32)
Overweight	405 (10)	1.18 (.99–1.40)	388 (10)	1.18 (.99–1.41)	1.19 (.99–1.42)
Characteristics of household environment					
Household smoke exposure					
No	3732 (87)	1.00 (referent)	3419 (87)	1.00 (referent)	1.00 (referent)
Yes	573 (13)	1.14 (1.01–1.28)	506 (13)	1.17 (1.02–1.33)	1.14 (1.00–1.30)
Type of housing					
House	3089 (73)	1.00 (referent)	2885 (74)	1.00 (referent)	1.00 (referent)
Apartment	701 (17)	1.15 (1.02–1.30)	648 (17)	1.12 (.99–1.28)	1.11 (.98–1.26)
Substandard housing	430 (10)	1.25 (1.09–1.44)	392 (10)	1.25 (1.09–1.45)	1.25 (1.09–1.44)
Density, people/room					
Continuous	. . .	1.01 (.99–1.03)	. . .	1.01 (.99–1.04)	1.01 (.99–1.03)
Characteristics of tuberculosis-infected household case					
Sex					
Female	1814 (43)	1.00 (referent)	1656 (42)	1.00 (referent)	1.00 (referent)
Male	2439 (57)	1.00 (.91–1.10)	2269 (58)	1.02 (.92–1.13)	1.02 (.92–1.13)
HIV status					
Negative	4106 (98)	1.00 (referent)	3859 (98)	1.00 (referent)	1.00 (referent)
Positive	99 (2)	0.96 (.73–1.27)	79 (2)	0.96 (.86–1.08)[f]	0.98 (.87–1.09)[f]
CD4 level of HIV, cells/μL					
Negative	4106 (98)	1.00 (referent)	3859 (98)	1.00 (referent)	1.00 (referent)
≥250	58 (1)	0.90 (.61–1.34)	50 (1)	0.90 (.55–1.47)	0.89 (.53–1.49)

Table 3 continued.

Variables	Univariate (n = 4253[a])		Multivariate (n = 3925)		
	No. (%)	RR (95% CI)	No. (%)	Final[b] RR (95% CI)	Direct Effect Model[c] RR (95% CI)
<250	22 (1)	0.607 (.35–1.05)	16 (0)	0.49 (.24–.96)	0.5 (.29–.88)
Sputum smear status					
Negative	1055 (25)	1.00 (referent)	993 (25)	. . .	1.00 (referent)
+	1172 (28)	1.15 (1.00–1.31)	1096 (28)	. . .	1.12 (.97–1.29)
++	713 (17)	1.28 (1.09–1.49)	648 (17)	. . .	1.22 (1.04–1.43)
+++	1313 (31)	1.26 (1.10–1.45)	1188 (30)	. . .	1.21 (1.05–1.40)
Treatment delay, d					
0	320 (8)	1.00 (referent)	297 (8)	. . .	1.00 (referent)
1–14	308 (7)	1.27 (.96–1.68)	291 (7)	. . .	1.24 (.93–1.66)
14–28	1259 (30)	1.24 (.99–1.57)	1178 (30)	. . .	1.18 (.93–1.50)
>28	2314 (55)	1.39 (1.11–1.73)	2159 (55)	. . .	1.33 (1.06–1.68)
Cavitary disease					
No	3387 (81)	1.00 (referent)	3164 (81)	. . .	1.00 (referent)
Yes	801 (19)	1.01 (.90–1.14)	761 (19)	. . .	1.02 (.90–1.15)

Abbreviations: BCG, Bacillus Calmette-Guerin; CI, confidence interval; HIV, human immunodeficiency virus; RR, risk ratio.

[a] Sample size varies across covariates due to missing value.

[b] Model with age of household contacts (HHCs) and tuberculosis index patient, smoking status, alcohol intake, nutritional status, number of BCG scars, and relation to index patient of HHCs; household cigarette smoke exposure, type of housing, and density of household; sex and CD4 counts of index patient.

[c] In addition to the covariates included in final model, sputum smear status, treatment delay, and cavitary disease were included in direct effect model.

[d] Includes nonrelatives and relatives other than child, parents, sibling, and spouse.

[e] Defined by body mass index *z* score from World Health Organization; *z* score <2 was defined as underweight; >2 was defined as overweight.

[f] Replaced CD4 counts of index patient in final model and direct effect model with HIV status of index patient.

mediated by sputum smear status, treatment delay, and cavitary disease (RR = 0.50 [95% CI, .29–.88]) was slightly larger than the observed marginal effect (RR = 0.49) when the potential mediators were removed from the model (Table 3).

Sensitivity Analysis

When we excluded households with a previous case of active tuberculosis, the RR of infection in HHCs exposed to an HIV-positive index patient with CD4 <250 cells/μL compared to those exposed to an HIV-negative index patient was reduced from 0.50 to 0.43. Among children <15 years of age, none of the 6 exposed to HIV-positive patients with a CD4 count <250 cells/μL was infected with tuberculosis, compared to 22% of those exposed to non-HIV-infected patients (Table 4).

DISCUSSION

We found that HHCs exposed to HIV-positive tuberculosis patients whose CD4 counts were <250 cells/μL had half the risk of tuberculosis infection compared to HHCs exposed to HIV-negative index patients. The estimated effect was unaltered by further adjusting for potential mediators, suggesting that the observed association is only partially mediated by sputum smear status, treatment delay, and cavitary disease. None of the children <15 years of age exposed to HIV-positive patients with a CD4 count <250 were infected with tuberculosis. We also showed that there was no significant difference in risk between those exposed to HIV-infected index patients with mild or moderate immunosuppression (CD4 counts ≥250 cells/μL) and those exposed to HIV-negative cases.

Whereas some previous studies reported that the HIV status of tuberculosis cases is associated with the prevalence of TST positivity among their HHCs [8] or is associated with risk of TST conversion [7], other studies reported that the HIV status of tuberculosis cases does not modify the risk of tuberculosis infection [5, 16]. Two observations may help explain these inconsistent results. First, the wide confidence intervals in several studies [8, 16] suggest that the sample sizes may have been too small to reliably detect an effect. Second, HIV may not modify the infectiousness of tuberculosis patients until the HIV-induced immunosuppression becomes more advanced. If these studies included a large proportion of HIV patients with mild or moderate immunosuppression, our results suggest that an effect would likely not have been observed. The 2 previous studies examining the impact of the degree of HIV-induced immunosuppression on the infectiousness of tuberculosis have

Table 4. Age-Adjusted Univariate and Multivariate Analysis in Child Contacts for Characteristics Associated With Baseline Tuberculin Skin Test Positivity

	Univariate (n = 1586[a])		Multivariate (n = 1494)[b]	
Variables	No. (%)	RR (95% CI)	No. (%)	RR (95% CI)
Characteristics of household contacts				
Sex				
Female	779 (49)	1.00 (referent)	742 (50)	1.00 (referent)
Male	807 (51)	1.00 (.86–1.17)	752 (50)	0.96 (.81–1.12)
BCG scars				
0	305 (19)	1.00 (referent)	286 (19)	1.00 (referent)
1	1237 (78)	1.01 (.82–1.24)	1173 (79)	1.04 (.83–1.29)
2	40 (3)	1.26 (.81–1.96)	35 (2)	1.39 (.91–2.12)
Relation to index				
Child	506 (32)	1.68 (1.30–2.19)	483 (32)	1.73 (1.30–2.32)
Sibling	301 (19)	1.30 (.97–1.74)	288 (19)	1.37 (1.00–1.85)
Other relationship[c]	766 (49)	1.00 (referent)	723 (48)	1.00 (referent)
Nutritional status[d]				
Normal	1154 (73)	1.00 (referent)	1083 (72)	1.00 (referent)
Underweight	50 (3)	0.82 (.49–1.36)	46 (3)	0.90 (.53–1.53)
Overweight	382 (24)	1.34 (1.12–1.61)	365 (24)	1.37 (1.13–1.67)
Characteristics of household environment				
Household smoke exposure				
No	1397 (88)	1.00 (referent)	1397 (88)	1.00 (referent)
Yes	182 (12)	1.06 (.75–1.48)	182 (12)	1.16 (.81–1.68)
Type of housing				
House	1151 (73)	1.00 (referent)	1086 (73)	1.00 (referent)
Apartment	254 (16)	1.12 (.84–1.49)	244 (16)	1.04 (.77–1.40)
Substandard housing	172 (11)	1.24 (.89–1.73)	164 (11)	1.18 (.82–1.68)
Density, people/room				
Continuous	. . .	1.02 (.98–1.07)	. . .	1.03 (.98–1.08)
Characteristics of tuberculosis-infected household case				
Sex				
Female	750 (47)	1.00 (referent)	692 (46)	1.00 (referent)
Male	836 (53)	0.83 (.66–1.03)	802 (54)	0.89 (.71–1.12)
HIV status				
Negative	1541 (98)	1.00 (referent)	1470 (98)	1.00 (referent)
Positive	33 (2)	0.43 (.12–1.58)	24 (2)	0.31 (.04–2.65)[e]
CD4 counts, cells/μL				
Negative	1541 (98)	1.00 (referent)	1469 (98)	1.00 (referent)
≥250	20 (1)	0.38 (.06–2.28)	19 (1)	0.50 (.09–2.94)
<250	6 (0)	NA-	6 (0)	NA
Sputum smear status[e]				
Negative	391 (25)	1.00 (referent)	372 (25)	. . .
+	427 (27)	1.60 (1.09–2.34)	400 (27)	. . .
++	271 (17)	2.08 (1.41–3.06)	251 (17)	. . .
+++	497 (31)	2.21 (1.54–3.17)	471 (31)	. . .
Treatment delay, d				
0	106 (7)	1.00 (referent)	99 (7)	. . .
1–14	114 (7)	3.22 (.96–1.68)	109 (7)	. . .
14–28	505 (32)	2.28 (.98–5.30)	482 (32)	. . .
>28	846 (54)	3.62 (1.58–8.25)	804 (54)	. . .

Table 4 continued.

Variables	Univariate (n = 1586[a])		Multivariate (n = 1494)[b]	
	No. (%)	RR (95% CI)	No. (%)	RR (95% CI)
Cavitary disease				
No	1274 (82)	1.00 (referent)	1218 (82)	. . .
Yes	286 (18)	1.30 (1.01–1.67)	276 (18)	. . .

Abbreviations: BCG, Bacillus Calmette-Guerin; CI, confidence interval; HIV, human immunodeficiency virus; RR, risk ratio.

[a] Sample size varies across covariates due to missing values.

[b] Model with age of household contacts (HHCs) and tuberculosis index patient; nutritional status, number of BCG scars, and relation to index patient of HHCs; household cigarette smoke exposure, type of housing, and density of household; sex and CD4 counts of index patient.

[c] Includes nonrelatives and relatives other than child, parents, sibling, and spouse.

[d] Defined by body mass index *z* score from World Health Organization; *z* score <2 was defined as underweight; >2 was defined as overweight.

[e] Replaced CD4 counts of index patient in final model with HIV status of index patient.

yielded inconsistent results. Carvalho et al reported that CD4 counts were not associated with tuberculosis infection among contacts [7], whereas Kenyon et al found fewer instances of tuberculosis infection among child contacts of HIV-positive tuberculosis patients with CD4 levels <200 cells/μL than in those exposed to an HIV-positive index patient with CD4 levels ≥200 cells/μL (odds ratio = 0.08 [95% CI, .01–.50]) [17]. Our result is consistent with this finding and provides additional evidence that HIV modifies the infectiousness of tuberculosis, but only in patients with advanced HIV-related immunosuppression.

Several possible mechanisms may explain the reduced infectiousness of tuberculosis patients with advanced HIV-induced immunosuppression. First, they may be infectious for less time than those without immunosuppression, as immunosuppressed tuberculosis patients typically progress to diagnosis or death more quickly than others [2]. Second, tuberculosis patients with advanced HIV infections are more likely to be sputum smear negative and therefore less infectious [18, 19]. Third, compared to those without immunosuppression, tuberculosis patients with lower CD4 counts may have less lung tissue damage and cavitary tuberculosis, factors that have been associated with infectiousness in humans [20]. Such tissue destruction results, in part, from the expression of host metalloproteinases (MMPs), a cluster of fibroblast collagenases that break down the extracellular matrix of lung [21, 22]. Previous studies show that CD4 counts of HIV-positive tuberculosis patients are inversely associated with the extent of lung tissue damage or cavitation [23] and that tuberculosis patients with CD4 counts <200 cells/μL had lower levels of MMP-1, -2, -8, and -9 in induced sputum samples [24]. Another study demonstrated that tissue inhibitors of MMPs were higher in tuberculosis infection in HIV-positive compared to HIV-negative mice [25]. These data raise the possibility that tuberculosis patients with advanced immunosuppression are less infectious because of lower levels of MMPs leading to less lung tissue damage and cavitation.

We found that the direct effect of HIV-induced immunosuppression of an index patient on his/her HHCs remained strong after adjusting for sputum bacilli load and for diagnostic delay, suggesting the possible existence of other factors leading to a lower transmissibility for these patients. As these 3 proxies of disease severity and delays to treatment for the index patients are relatively imprecise indicators, there may be some measurement error in quantifying disease severity and treatment delays, and the observed direct effect may be overestimated. Against our expectation, our data also suggested that there is only a slight indirect effect. Because the cross-sectional data do not allow us to distinguish the order of exposure, mediator, and outcome, an indirect effect of these mediators might have been attenuated in our analysis. We also assumed that there is no confounding of the exposure-outcome, exposure-mediator, and mediator-outcome relations, and a potential violation of this assumption may also have led to the attenuation of a true indirect effect.

We also found that HHCs who had ≥3 BCG scars had increased risk of TST positivity at baseline compared to those who had 1 BCG scar. This suggests that repeated BCG vaccination increases the rate of false-positive TSTs [26] or, less probably, that multiple BCG vaccinations increase the risk of tuberculosis infection.

We found a higher proportion of index patients who were male than female, which reflects the distribution of tuberculosis incidence in Lima, Peru [11]. The estimated prevalence of tuberculosis infection in Lima varies widely from 1% among incoming health science students to 77% among the workers in the informal public transport sector [27–30]. In our cohort, the prevalence of tuberculosis infection in HHCs is 38%. The prevalence of HIV in tuberculosis cases in our study (3.00%) is 2 times higher than the general population in Peru (1.5%) [11].

A possible explanation is that the reported tuberculosis incidence rate is high in Lima.

The major limitation of our study is the potential nondifferential misclassification that could have arisen from 2 sources. First, we used the CD4 levels closest to the time of tuberculosis patients' diagnosis to represent the degree of their HIV-induced immunosuppression. Because the actual CD4 counts at the time of tuberculosis infection may have changed, our results may be biased toward the null because of this potential nondifferential misclassification of exposure. Second, some HHCs will have acquired tuberculosis infection prior to their exposure to the index patient. Although this would also be expected to lead to nondifferential misclassification and attenuation of the effect of HIV coinfection toward the null, it is also possible that other index patient or household characteristics may have affected tuberculosis transmission to HHCs in the past. When we conducted a sensitivity analysis to explore this possibility by restricting our analysis to the HHCs who reported that they had not been previously exposed to a household tuberculosis patient, we observed an increase in the magnitude of the effect of being exposed to an HIV-infected index patient with a CD4 count <250 cells/μL, suggesting that nondifferential misclassification is more likely than confounding of the effect of immunosuppression by some other unmeasured variables. When we restricted the analysis to children who were less likely to have been infected prior to the current exposure, we found that none of the children exposed to an index patient with CD4 count <250 cells/μL had baseline positive TST results. Based on these results, we infer that the true effect of HIV disease progression on HHCs' tuberculosis infection is even larger than what we observed. Another limitation of our study is the possibility of false-positive TSTs induced by BCG vaccination. To minimize their effect on our results, we selected a conservative cutoff (10 mm induration) [31] and included the reported number of BCG scars in the regression model to adjust for the misclassification of outcome. The distribution of the number of BCG scars in HIV-negative index patients is similar to that in HIV-positive index patients (Table 2). This suggests that false-positive TSTs due to BCG vaccination would also be expected to lead to nondifferential misclassification that would drive the results toward null.

CONCLUSIONS

Our results suggest that HIV–induced immunosuppression reduces the risk of tuberculosis transmission from HIV-coinfected index patients within households. Possible biological explanations are that immunosuppressed patients are infectious for shorter periods of time and that the reduced tuberculosis bacillary load and tissue destruction typical of late-stage HIV reduced the likelihood of spread.

Notes

Acknowledgments. We thank the patients and their families who gave their time and energy to contribute to this study, the National Strategy for TB Control at the Peruvian Ministry of Health, and the healthcare personnel at the 90 participating health centers in 2 regions of Lima: Lima Ciudad Health District (Rímac, San Martin de Porres, Los Olivos, Lima, and Tupac Amaru networks) and Lima Este Health District (Lima Metropolitana network).

Financial support. This work was supported by the National Institutes of Health (grant number U19 AI-076217), the National Institute of Allergy and Infectious Diseases (U01 AI057786), and the Rose Traveling Fellowship Program in Chronic Disease Epidemiology and Biostatistics, Harvard School of Public Health.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Bekker LG, Wood R. The changing natural history of tuberculosis and HIV coinfection in an urban area of hyperendemicity. Clin Infect Dis **2010**; 50(suppl 3):S208–14.
2. Dye C, Williams BG. The population dynamics and control of tuberculosis. Science **2010**; 328:856–61.
3. Rodrigo T, Cayla JA, Garcia de Olalla P, et al. Characteristics of tuberculosis patients who generate secondary cases. Int J Tuberc Lung Dis **1997**; 1:352–7.
4. Tornee S, Kaewkungwal J, Fungladda W, Silachamroon U, Akarasewi P, Sunakorn P. Risk factors for tuberculosis infection among household contacts in Bangkok, Thailand. Southeast Asian J Trop Med Public Health **2004**; 35:375–83.
5. Cruciani M, Malena M, Bosco O, Gatti G, Serpelloni G. The impact of human immunodeficiency virus type 1 on infectiousness of tuberculosis: a meta-analysis. Clin Infect Dis **2001**; 33:1922–30.
6. Pai M, McCulloch M, Colford JM Jr. Meta-analysis of the impact of HIV on the infectiousness of tuberculosis: methodological concerns. Clin Infect Dis **2002**; 34:1285–7.
7. Carvalho AC, DeRiemer K, Nunes ZB, et al. Transmission of *Mycobacterium tuberculosis* to contacts of HIV-infected tuberculosis patients. Am J Respir Crit Care Med **2001**; 164:2166–71.
8. Mohammad Z, Naing NN, Salleh R, Ahmad N, Hamzah WM, Mahmud R. A preliminary study of the influence of HIV infection in the transmission of tuberculosis. Southeast Asian J Trop Med Public Health **2002**; 33:92–8.
9. Crampin AC, Floyd S, Ngwira BM, et al. Assessment and evaluation of contact as a risk factor for tuberculosis in rural Africa. Int J Tuberc Lung Dis **2008**; 12:612–8.
10. Crampin AC, Glynn JR, Traore H, et al. Tuberculosis transmission attributable to close contacts and HIV status, Malawi. Emerg Infect Dis **2006**; 12:729–35.
11. Plan Estratégico Multisectorial de la Respuesta Nacional a la Tuberculosis en el Perú, 2009–2018. Available at: ftp://ftp2.minsa.gob.pe/descargas/dgsp/ESN-tuberculosis/Material de Difusion/Notas de Prensa/PEM_TB_06marzo_2009.pdf. Accessed 9 July 2012.
12. Galea JT, Contreras C, Lecca L, et al. Rapid home-based human immunodeficiency virus testing to reduce costs in a large tuberculosis cohort study. Public Health Action **2013**; 3:172–74.
13. Rehm J, Samokhvalov AV, Neuman MG, et al. The association between alcohol use, alcohol use disorders and tuberculosis (TB). A systematic review. BMC Public Health **2009**; 9:450.
14. World Health Organization. Child growth standards. Available at: http://www.who.int/childgrowth/standards/bmi_for_age/en/index.html. Accessed 22 January 2013.

15. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. Biometrics **1986**; 42:121–30.
16. Kifai EJ, Bakari M. Mantoux skin test reactivity among household contacts of HIV-infected and HIV un-infected patients with sputum smear positive TB in Dar es Salaam, Tanzania. East Afr J Public Health **2009**; 6:211–8.
17. Kenyon TA, Creek T, Laserson K, et al. Risk factors for transmission of *Mycobacterium tuberculosis* from HIV-infected tuberculosis patients, Botswana. Int J Tuberc Lung Dis **2002**; 6:843–50.
18. Samb B, Sow PS, Kony S, et al. Risk factors for negative sputum acid-fast bacilli smears in pulmonary tuberculosis: results from Dakar, Senegal, a city with low HIV seroprevalence. Int J Tuberc Lung Dis **1999**; 3:330–6.
19. Tostmann A, Kik SV, Kalisvaart NA, et al. Tuberculosis transmission by patients with smear-negative pulmonary tuberculosis in a large cohort in the Netherlands. Clin Infect Dis **2008**; 47:1135–42.
20. Reichler MR, Reves R, Bur S, et al. Evaluation of investigations conducted to detect and prevent transmission of tuberculosis. JAMA **2002**; 287:991–5.
21. Elkington PT, Ugarte-Gil CA, Friedland JS. Matrix metalloproteinases in tuberculosis. Eur Respir J **2011**; 38:456–64.
22. Sheen P, O'Kane CM, Chaudhary K, et al. High MMP-9 activity characterises pleural tuberculosis correlating with granuloma formation. Eur Respir J **2009**; 33:134–41.
23. Chamie G, Luetkemeyer A, Walusimbi-Nanteza M, et al. Significant variation in presentation of pulmonary tuberculosis across a high resolution of CD4 strata. Int J Tuberc Lung Dis **2002**; 14:1295–302.
24. Walker NF, Clark SO, Oni T, et al. Doxycycline and HIV infection suppress tuberculosis-induced matrix metalloproteinases. Am J Respir Crit Care Med **2012**; 185:989–97.
25. Elkington P, Shiomi T, Breen R, et al. MMP-1 drives immunopathology in human tuberculosis and transgenic mice. J Clin Invest **2011**; 121:1827–33.
26. Saito M, Bautista CT, Gilman RH, et al. The value of counting BCG scars for interpretation of tuberculin skin tests in a tuberculosis hyperendemic shanty-town, Peru. Int J Tuberc Lung Dis **2004**; 8:842–7.
27. Perez-Lu JE, Carcamo CP, Garcia PJ, et al. Tuberculin skin test conversion among health sciences students: a retrospective cohort study. Tuberculosis **2013**; 93:257–62.
28. Pelly TF, Santillan CF, Gilman RH, et al. Tuberculosis skin testing, anergy and protein malnutrition in Peru. Int J Tuberc Lung Dis **2005**; 9:977–84.
29. Horna-Campos OJ, Consiqlio E, Sanchez-Perez HJ, et al. Pulmonary tuberculosis infection among workers in the informal public transport sector in Lima, Peru. Occup Environ Med **2011**; 68:163–5.
30. Hohmuth BA, Yamanija JC, Dayal AS, et al. Latent tuberculosis infection: risks to health care students at a hospital in Lima, Peru. Int J Tuberc Lung Dis **2006**; 10:1146–51.
31. Bugiani M, Borraccino A, Migliore E, et al. Tuberculin reactivity in adult BCG-vaccinated subjects: a cross-sectional study. Int J Tuberc Lung Dis **2003**; 7:320–6.