Quantitative Impact of Human Immunodeficiency Virus Infection on Tuberculosis Dynamics

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Rationale: Human immunodeficiency virus (HIV) infection has a major but unquantified impact on the risk of tuberculosis.

Objectives: To quantify the impact of HIV infection on the number of tuberculosis cases in San Francisco.

Methods: We studied all patients reported with tuberculosis in San Francisco from 1991 to 2002. The initial isolates of *Mycobacterium tuberculosis* were genotyped using IS6110 restriction fragment-length polymorphism genotyping as the primary method, and clustered cases (identical genotype patterns) were identified.

Measurements and Main Results: We determined the case number, case rate, and the fraction of tuberculosis attributable to HIV infection. Of 2,991 reported tuberculosis cases, 2,193 (73.3%) had a genotype pattern of *M. tuberculosis* available. Genotypic clusters with at least one HIV-positive person were larger, lasted longer, and had a shorter time between successive cases relative to clusters with only HIV-uninfected persons ($P < 0.00005$, $P = 0.0009$, $P = 0.018$, respectively). Overall, 13.7% of the tuberculosis cases were attributable to HIV infection and an estimated 405 excess tuberculosis cases occurred.

Conclusions: During a period encompassing the resurgence and decline of tuberculosis in San Francisco, a substantial number of the tuberculosis cases were attributable to HIV infection. Coinfection with HIV amplified the local tuberculosis epidemic.

Keywords: tuberculosis; HIV infection; transmission; genotyping

Infection with the human immunodeficiency virus (HIV) has an enormous impact on the epidemiologic and clinical features of tuberculosis worldwide, particularly in resource-poor countries (1–5). Advanced HIV infection alters the clinical manifestations of tuberculosis: it increases the risk of reactivation of latent tuberculosis infection and exogenous reinfection (6–9), the infection progresses more rapidly to active disease (10), pulmonary cavitation is less likely to occur (11), and death rates are higher (12, 13). Although an increased number of HIV-coinfected tuberculosis cases might increase tuberculosis case rates overall, a higher death rate among HIV-positive patients with tuberculosis could reduce the sources of infection with *Mycobacterium tuberculosis* within the community. The overall impact of HIV on tuberculosis may ultimately depend on the interplay of multiple, complex factors (5).

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AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Human immunodeficiency virus (HIV) infection has a major but unquantified impact on the risk of tuberculosis.

What This Study Adds to the Field

Genotypic clusters of tuberculosis with at least one HIV-positive person were larger, lasted longer, and had a shorter time between successive cases relative to clusters with only HIV-uninfected persons. Coinfection with HIV amplified the local tuberculosis epidemic in San Francisco from 1991 to 2002, as 13.7% of tuberculosis cases were attributed to HIV infection.

We sought to quantify the extent to which HIV infection affects a local tuberculosis epidemic over a relatively long period of time. We used data from a prospective, 12-year, population-based, molecular epidemiologic study of tuberculosis to determine the tuberculosis case rates in HIV-positive compared with HIV-uninfected patients, to estimate the magnitude of transmission from HIV-positive patients to HIV-uninfected individuals; and to estimate the fraction of tuberculosis cases attributable to HIV infection. Because highly active antiretroviral therapy (HAART) became widely available in San Francisco during late 1996, we also assessed its impact on tuberculosis case numbers and rates.

The study was conducted in San Francisco, a city that has been severely affected by the HIV and AIDS epidemics. In 2004, San Francisco had the third largest number of persons living with AIDS in the United States (14). In 2003, an estimated 18,000 to 19,000 people were living with HIV and AIDS out of 719,600 San Francisco residents, for an overall HIV prevalence of 2.5%. The AIDS epidemic in San Francisco has mainly affected homosexual men and a smaller proportion of heterosexuals, injection drug users (IDUs), and nonwhites (14). During the 1990s, the estimated HIV prevalence levels were 29% among homosexual men (15), 24% among homeless males (16), and 31% among IDUs (15) in San Francisco, similar to HIV prevalence levels in sub-Saharan Africa (17). The preliminary results of this study were previously reported as an abstract (18).

METHODS

Study Population

All patients with tuberculosis reported in San Francisco from January 1, 1991, through December 31, 2002, were enrolled as part of a prospective study of the molecular epidemiology of tuberculosis (19). The routine microbiologic evaluation included microscopy for acid-fast bacilli, mycobacterial culture, and drug susceptibility tests if the culture was positive. All patients, regardless of HIV serostatus, were treated with

a regimen consisting of isoniazid, rifampin, ethambutol, and pyrazinamide for 2 months followed by isoniazid and rifampin for 4 months unless modifications were made because of drug intolerance, underlying drug resistance, or to avoid drug interactions. The Committee on Human Research of the University of California, San Francisco, approved the study protocol.

Genotyping

The initial isolates of *M. tuberculosis* were analyzed by standardized IS6110 restriction fragment-length polymorphism (RFLP) genotyping (20) and were compared using computer software (BioImage Whole Band Analyzer, version 3.0; Millipore, Ann Arbor, MI) (21). We defined a genotypic cluster as a group of two or more patients whose isolates had at least six bands in identical IS6110 RFLP patterns and were collected within 12 months of each other (19, 20, 22). We further analyzed isolates with fewer than six bands in their IS6110 RFLP pattern using a probe for the polymorphic guanine-cytosine-rich sequence and compared the patterns visually (23). Patients whose isolate had fewer than six bands were clustered if their IS6110 RFLP patterns were identical; if the number, relative intensity, and molecular weights of polymorphic guanine-cytosine-rich sequence bands were identical; and if the isolates were collected within 12 months of each other (19, 20).

We chronologically ordered the tuberculosis cases in each genotypic cluster by the date that the first culture-positive specimen was obtained for each patient. We initially assumed that the first case of pulmonary tuberculosis in a cluster resulted from the reactivation of a latent tuberculosis infection and was the source case patient. Subsequent pulmonary and/or extrapulmonary cases in the same genotypic cluster likely resulted from recent transmission and rapid progression to disease, and were defined as secondary cases if they occurred within 12 months of the source case or each other. Because of temporal variation in the time to diagnosis and the possibility that case finding and diagnosis were more rapid among HIV-infected persons, it is likely that the first case of pulmonary tuberculosis was not the source case in every single cluster. Therefore, we performed a sensitivity analysis by assuming that the second, then the third, case of pulmonary tuberculosis to be diagnosed was the source case. Finally, we assumed that patients whose initial isolate had a unique genotype pattern resulted from reactivation of a latent tuberculosis infection (19, 20).

Statistical Analysis

We used California state estimates of the population of San Francisco (24, 25) to calculate case rates and used the incidence rate data test or the χ^2 test for trends. For the analysis, persons who were HIV negative and persons who did not have a test result were grouped as HIV uninfected. We calculated the tuberculosis case rate among persons coinfected with HIV using the estimated number of HIV-positive persons in San Francisco as the denominator (San Francisco Department of Public Health, unpublished data). Similarly, we calculated the tuberculosis case rate among HIV-uninfected patients using the estimated number of persons in San Francisco not known to be HIV positive as the denominator. The treatment success ratio was estimated as the percentage of patients with tuberculosis who were cured, defined by either bacteriologic confirmation, or completion of their drug treatment regimen with no clinical or radiographic evidence of active tuberculosis. The case fatality ratio (CFR) was estimated as the percentage of tuberculosis cases who died during treatment.

We used estimates of the number of HIV-positive persons in San Francisco during each year of the study to calculate the population attributable fraction (PAF), the attributable fraction of tuberculosis among the HIV-positive population (AFE), and the number of excess patients coinfected with *M. tuberculosis* and HIV that did occur but could have been prevented if HIV infection were absent. We calculated the PAF of tuberculosis cases due to the direct effect of HIV as follows:

$$\text{PAF} = P_{\text{cases}}(\text{RR} - 1) / \text{RR}$$

where P_{cases} is the prevalence of HIV among tuberculosis cases and RR is the rate ratio of tuberculosis among HIV-positive versus HIV-uninfected persons. We estimated the AFE using the following equation:

$$\text{AFE} = (\text{RR} - 1) / \text{RR}$$

where RR is the rate ratio of tuberculosis among HIV-positive versus HIV-uninfected persons.

We performed univariate and multivariate logistic regression modeling to identify the patient characteristics associated with secondary tuberculosis cases and to estimate the odds ratios (ORs) or rate ratios (RRs) for associations with HIV infection, and their 95% confidence interval (CI).

RESULTS

A total of 2,991 tuberculosis cases were reported to the Tuberculosis Section of the San Francisco Department of Public Health during the 12-year study period. We excluded 25 cases that met predefined criteria for laboratory cross-contamination (26), 11 cases of *Mycobacterium bovis*, and 2 patients who had been treated with *M. bovis* bacille Calmette-Guérin for bladder cancer that resulted in extrapulmonary disease, and analyzed the remaining 2,953 cases (Figure 1). The annual number of cases was greatest in 1992 (364 cases; case rate, 49.8 per 100,000 population) and progressively decreased thereafter ($P < 0.000005$) (Table E1 of the online supplement).

An HIV test result was available for 44.1% of all patients with tuberculosis and 61.6% of patients aged between 18 and 55 years. Patients who did not have HIV counseling and testing were more likely to have characteristics of low-HIV risk groups in San Francisco: for example, being female, foreign born, or of Asian race; younger than 25 years or older than 44 years; and with no report of substance abuse or homelessness (Table E2). In a multivariate model, being a young adult (25–44 yr) was the patient characteristic most strongly associated with having an HIV test result (OR, 3.8; 95% CI, 3.2–4.4; $P < 0.0001$). Patients were more likely to have an HIV test result during 1997–2002, when antiretroviral therapy for HIV disease was widely available, than during 1991–1996 ($P < 0.0005$). By age, 70.9% of patients with tuberculosis 18–55 years old who were reported during 1997–2002 had an HIV test result versus 56.9% of those reported during 1991–1996 ($P < 0.0001$).

Tuberculosis case rates in San Francisco were nearly eight times higher among persons infected with HIV than among persons who were not infected with HIV (RR, 7.7; 95% CI, 6.9–8.5). During the 12-year period, the tuberculosis case rate decreased significantly among HIV-positive patients by 56.6% ($P < 0.00006$), and it decreased, but not significantly, among HIV-uninfected patients by 54.4% ($P = 0.086$) (Figures 2A and 2B, and Table E1).

Genotyping

Approximately 85% of the 2,953 tuberculosis cases had a positive culture for *M. tuberculosis*. A genotyping result was available among 87.7% of the culture-positive cases (Figure 1). Culture-positive patients who lacked a genotype result were more likely to be Asian/Pacific Islanders, younger than 25 years old or at least 45 years old, or foreign born; to have extrapulmonary tuberculosis only; and to have no reported substance abuse (injecting drugs, non-injecting drugs, and/or excessive alcohol) or homelessness during the 12 months before their diagnosis ($P < 0.005$ for each comparison).

There were 1,593 tuberculosis cases whose isolate had a unique fingerprint pattern (72.6%) and 600 cases (27.4%) whose isolate had a fingerprint pattern that was clustered. A putative source case could not be identified for two clusters of two persons each with only extrapulmonary tuberculosis, and all four patients were excluded from further analyses of genotyping. We analyzed the remaining 2,189 patients, including 596 patients in 158 clusters. Among HIV-infected persons, 59.0% (230/390) of the culture-positive genotyped tuberculosis cases

Figure 1. Derivation of the study population for genotypic cluster analysis, San Francisco, 1991–2002. Boxes to the right indicate exclusions leading to a study population of 2,193 patients with genotyped isolates. We excluded 25 patients whose isolates were laboratory contaminants, 11 cases of *Mycobacterium bovis*, and 2 patients who were treated with bacille Calmette-Guérin (BCG). RFLP = restriction fragment-length polymorphism.

were due to reactivation of latent tuberculosis infection and 41.3% (161/390) were due to recent transmission that generated HIV-positive secondary cases. Among HIV-uninfected persons, 84.5% (1,521/1,799) of the culture-positive genotyped cases were likely due to reactivation of a latent tuberculosis infection and 15.5% (278/1,799) were secondary cases due to recent tuberculosis transmission ($P < 0.0005$). Approximately 11% (230/2,189) of all culture-positive genotyped tuberculosis cases were due to reactivation of a latent tuberculosis infection in an HIV-positive person and 7.4% (161/2,189) were due to recent transmission that generated an HIV-positive secondary case.

Of the 596 clustered cases, 438 were secondary cases, and 36.6% of the secondary cases were HIV-positive persons. The strongest independent risk factors associated with being a secondary case of tuberculosis in a genotypic cluster were as follows: if the source case was sputum smear positive (adjusted OR [AOR], 1.8; 95% CI, 1.2–2.5; $P < 0.0005$), reported noninjecting drug use (AOR, 3.7; 95% CI, 1.4–9.4; $P = 0.007$), and reported substance abuse (AOR, 13.5; 95% CI, 5.3–34.1; $P < 0.0005$); and if the secondary case individual was of Asian race (AOR, 14.5; 95% CI, 4.4–47.4; $P < 0.0005$) or African-American race (AOR, 4.0; 95% CI, 1.6–9.4; $P = 0.003$), born in the United

States (AOR, 31.8; 95% CI, 10.7–93.9; $P < 0.0005$), or HIV positive (AOR, 6.1; 95% CI, 3.0–12.7; $P < 0.0005$) (Table 1). There is confounding in the multivariate model by place of birth, substance abuse, increasing age, and race.

Of 158 genotypic clusters, 8 (5.1%) had only HIV-positive patients, 66 (41.8%) had a mixture of HIV-positive and HIV-uninfected patients, and 85 (53.8%) had only HIV-uninfected patients (Table 2). However, 63.6% of the 596 clustered patients were in genotypic clusters with a mixture of both HIV-positive and HIV-uninfected patients. We combined all of the genotypic clusters that had at least one HIV-positive patient and compared them with the genotypic clusters of only HIV-uninfected patients. Genotypic clusters that had at least one HIV-positive patient were significantly larger than genotypic clusters with only HIV-uninfected patients ($P < 0.00005$) (Table 2).

The median time from the first to the last tuberculosis cases of the genotypic clusters was 178.0 days, and the longest time that a strain was prevalent in the 12-year period was 2,346 days or 6.6 years (Table 2). The median duration of genotypic clusters with at least one HIV-positive person was significantly greater (243 d) than that of genotypic clusters with only HIV-uninfected patients (96 d) ($P = 0.009$). In addition, the median

Figure 2. Tuberculosis case rates as the number of tuberculosis cases per 100,000 population, by HIV test result. (A) Rates of HIV-positive tuberculosis cases due to reactivation of latent tuberculosis infection (solid line) versus secondary cases caused by recent transmission and rapid progression to disease (dashed line). We calculated the tuberculosis case rate among persons coinfecting with HIV and *Mycobacterium tuberculosis* using the estimated number of HIV-positive persons in San Francisco as the denominator (San Francisco Department of Public Health, unpublished data). (B) Rates of HIV-uninfected tuberculosis cases due to reactivation of latent tuberculosis infection (solid line) versus secondary cases caused by recent transmission and rapid progression to disease (dashed line). We calculated the tuberculosis case rate among HIV-uninfected patients using the estimated number of persons living in San Francisco minus the estimated number of HIV-positive persons in San Francisco as the denominator. TB = tuberculosis.

time between successive cases in the 158 genotypic clusters was 62.0 days, but was significantly shorter in clusters with at least one HIV-positive patient (57 d) compared with genotypic clusters with only HIV-uninfected patients (78.5 d) ($P = 0.018$).

We further examined the 438 secondary cases in genotypic clusters. Assuming that the first pulmonary case diagnosed in the cluster was the source case, 80 (18.3%) HIV-positive individuals and 90 (20.5%) HIV-uninfected individuals were in clusters with an HIV-positive source case. Seventy-eight (17.8%) HIV-positive individuals and 190 (43.4%) HIV-uninfected individuals were in clusters with an HIV-uninfected source case. Overall, 61.2% of the secondary tuberculosis cases had the same HIV serostatus as their respective source case. By sensitivity analysis, the percentages of HIV-positive and HIV-uninfected source cases and secondary cases changed little (<3% in each category) (Table E3).

The tuberculosis case rate decreased between 1991 and 2002 by 58.7% ($P = 0.00081$) among tuberculosis cases due to reactivation of a latent tuberculosis infection, and by 62.4% ($P = 0.00002$) among the secondary cases due to recent transmission. During 1991–1996, the tuberculosis case rate due to reactivation

of a latent tuberculosis infection and secondary cases decreased (13.7 and 47.8%, respectively), but not significantly ($P = 0.277$ and $P = 0.052$, respectively). However, during 1997–2002, after the introduction of HAART, the tuberculosis case rate due to reactivation of a latent tuberculosis infection decreased significantly by 44.9% ($P = 0.017$) and tuberculosis case rates due to recent transmission declined by 34.4%, but this decline was not significant ($P = 0.154$).

Attributable Fraction of Tuberculosis Cases Caused by HIV Coinfection

The average prevalence of HIV coinfection among patients with tuberculosis in San Francisco during 1991–2002 was 15.7%, ranging from 21.6% in 1991 to a low of 7.4% in 1997 (Table 3). The PAF for HIV infection over the entire study period was 13.7%, but it declined by 30.6% from 19.2% in 1991 to 14.7% in 2002 and was lowest in 1997 (5.4%). Among tuberculosis cases caused by reactivation of latent infection, the PAF for HIV infection was 11.1%, ranging from 16.4% in 1991 to 5.3% in 1999. Among secondary cases in genotypic clusters, who had

TABLE 1. FACTORS ASSOCIATED WITH BEING A SECONDARY CASE OF TUBERCULOSIS, SAN FRANCISCO, 1991–2002

	Unadjusted OR	95% CI	P Value	Adjusted OR	95% CI	P Value
Characteristics of the Source Cases						
Male	2.7	2.0–3.6	<0.00005			
Age < 45 yr	1.5	1.0–2.2	0.0418			
Race						
Asian	Ref			0.1	0.0–0.2	<0.0005
White	1.0	0.7–1.6	0.9574			
African American	2.6	1.5–4.5	0.0002	0.2	0.1–0.6	0.002
Latino	0.1	0.1–0.2	<0.00005			
Native American	0.5	0.0–36.3	0.5699			
U.S. born	2.8	2.2–3.5	<0.00005	0.1	0.0–0.2	<0.0005
HIV positive	4.1	3.2–5.2	<0.00005	0.2	0.1–0.4	<0.0005
Sputum smear positive	2.1	1.6–2.6	<0.00005	1.8	1.2–2.5	<0.0005
Initial resistance to isoniazid	0.3	0.2–0.5	<0.00005			
Homeless*	4.0	2.9–5.6	<0.00005			
Injecting drug use*	0.9	0.4–1.9	0.7061			
Noninjecting drug use*	6.6	4.7–9.1	<0.00005	3.7	1.4–9.4	0.007
Excessive alcohol use*	3.0	2.1–4.2	<0.00005			
Substance abuse*	5.3	3.9–7.1	<0.00005	13.5	5.3–34.1	<0.0005
Characteristics of the Secondary Cases						
Male	1.5	1.2–1.9	<0.0006			
Age < 45 yr	2.1	1.7–2.6	<0.00005			
Race						
Asian	Ref			14.5	4.4–47.4	<0.0005
African American	10.3	7.6–14.0	<0.00005	4.0	1.6–9.4	0.003
White	3.9	2.9–5.1	<0.00005			
Latino	2.9	2.0–4.2	0.00005			
Native American	8.1	2.3–27.2	<0.00005			
U.S. born	6.6	5.2–8.3	<0.00005	31.8	10.7–93.9	<0.0005
HIV positive	3.7	2.9–4.7	<0.00005	6.1	3.0–12.7	<0.0005
Sputum smear positive	1.6	1.2–2.0	0.0002			
Initial resistance to isoniazid	0.3	0.2–0.6	<0.00005	0.2	0.1–0.7	0.007
Homeless*	4.5	3.4–6.0	<0.00005			
Injecting drug use*	6.1	4.0–9.1	<0.00005			
Noninjecting drug use*	4.5	3.3–6.1	<0.00005	0.3	0.1–0.9	0.024
Excessive alcohol use*	3.0	2.2–4.4	<0.00005			
Substance abuse* [†]	4.5	3.4–5.8	<0.00005	0.1	0.1–0.3	<0.0005

Definition of abbreviations: CI = confidence interval; OR = odds ratio; Ref = reference value.

Values are based on univariate and multivariate logistic regression analysis.

* Within the 12 months before the diagnosis of tuberculosis.

[†] Substance abuse was defined as reporting at least one of the following behaviors: injecting drug use, noninjecting drug use, or excessive alcohol.

a higher prevalence of HIV than persons with reactivated disease, the average PAF for HIV infection was 35.1%, ranging from 50.1% in 1995 to 10.6% in 2000. An excess of 405 tuberculosis cases attributable to HIV infection occurred during the study period. Approximately 56% of the excess cases were from reactivation of latent tuberculosis infection, whereas 44% were secondary tuberculosis cases from recent transmission of *M. tuberculosis* and rapid progression to disease. Although the PAF for HIV infection was greater for secondary tuberculosis cases, the absolute number of excess cases of tuberculosis due to

HIV infection in San Francisco was greater for reactivation of latent tuberculosis infection.

The percentage of tuberculosis cases among HIV-positive patients in San Francisco that was attributable to their HIV infection (AFE) during the 12-year period was 87.0%, and was highest in 1994 (89.9%) and lowest in 1997 (73.2%) (Table 3).

Treatment Success and Case Fatality Ratios

Treatment success for all patients with tuberculosis was 85.9%, ranging from a low of 70.5% in 1993 to a high of 89.2% in 2001,

TABLE 2. COMPARISON OF GENOTYPE CLUSTERS ACCORDING TO THE HIV TEST RESULT OF THE PATIENTS WITH TUBERCULOSIS IN THE CLUSTERS, SAN FRANCISCO, 1991–2002

Characteristics of Clusters	Total	Clusters with at Least One HIV-positive Patient with TB	Clusters of Only HIV-uninfected Patients with TB	P Value
No. of clusters (%)	158 (100.0)	73 (46.2)	85 (53.8)	<0.0005
No. of cases in cluster (%)	596 (100.0)	377 (63.3)	219 (36.7)	<0.0005
Median cluster size (range)	2 (2–31)	3 (2–31)	2 (2–12)	<0.00005
Median cluster duration, d* (range)	178 (1–2,346)	243 (1–2,346)	96 (1–1,422)	0.009
Median time between successive cases, d (range)	62.0 (1–361)	57.0 (1–354)	78.5 (1–361)	0.018

Definition of abbreviations: TB = tuberculosis.

* First case to last case.

TABLE 3. ESTIMATES OF THE RATE RATIO OF HIV-POSITIVE TUBERCULOSIS CASES VERSUS HIV-UNINFECTED TUBERCULOSIS CASES, POPULATION ATTRIBUTABLE FRACTION, AND EXCESS TUBERCULOSIS CASES, SAN FRANCISCO, 1991–2002

Year*	RR	95% CI	Prevalence of HIV+ (%)	AFE (%)	PAF (%)	Total No. of TB Cases	No. of TB Cases if HIV Were Absent	Excess Cases (Total Cases × PAF)
1991	8.8	6.7–11.6	21.6	88.7	19.2	319	257	62
1992	7.0	5.2–9.2	17.0	85.7	14.6	364	311	53
1993	9.1	6.8–12.0	19.7	89.0	17.5	320	264	56
1994	9.9	7.2–13.4	20.0	89.9	18.0	270	221	49
1995	8.6	6.1–12.0	16.9	88.4	15.0	260	221	39
1996	8.4	5.9–11.7	15.5	88.0	13.6	271	234	37
1997	3.7	2.1–6.2	7.4	73.2	5.4	217	205	12
1998	7.1	4.6–10.5	13.3	85.9	11.4	218	193	25
1999	5.7	3.6–8.7	11.2	82.5	9.2	224	203	21
2000	5.3	2.7–8.9	10.6	81.1	8.6	161	147	14
2001	4.9	2.8–8.0	10.1	79.5	8.0	179	164	15
2002	8.4	5.2–13.0	16.7	88.1	14.7	150	128	22
Total	7.7	7.0–8.47	15.7	87.0	13.7	2,953	2,548	405

Definition of abbreviations: AFE = attributable fraction among the exposed (HIV+ persons); CI = confidence interval; PAF = population attributable fraction, $100 \times [P_{\text{cases}}(RR - 1)/RR]$; P_{cases} = prevalence of HIV-positive persons in the population; RR = rate ratio of HIV+ :HIV-uninfected patients with TB; TB = tuberculosis.

* $P < 0.00005$ for all years.

and has been greater than 85% since 1996. Treatment success was significantly lower among HIV-positive compared with HIV-uninfected patients (76.5 vs. 85.9%, $P = 0.001$).

The case fatality ratio for all patients with tuberculosis was 12.0%, but was higher among patients coinfecting with HIV than among HIV-uninfected patients (22.0 vs. 10.3%, respectively; $P = 0.035$). HIV-positive patients with tuberculosis were just as likely to die with tuberculosis during 1997–2002, after the introduction of HAART, as during 1991–1996 ($P = 0.204$). Similarly, HIV-positive patients were just as likely as HIV-uninfected patients to be diagnosed at death and before initiating antituberculosis treatment ($P = 0.62$), but HIV-positive patients with tuberculosis were twice as likely to die during treatment (RR, 2.1; 95% CI, 1.7–2.6; $P < 0.00005$) and had a shorter survival time ($P < 0.00005$, data not shown).

DISCUSSION

Our study demonstrates the impact that HIV infection has had on tuberculosis transmission dynamics, treatment, and mortality in San Francisco during a 12-year period. Genotypic clusters with at least one HIV-positive patients with tuberculosis in the cluster were larger, lasted longer, and had a shorter time interval between successive cases, relative to clusters with only HIV-uninfected persons. Our study suggests that the high HIV prevalence in San Francisco amplified the local tuberculosis epidemic: 13.7% of San Francisco's tuberculosis cases were attributable to HIV in the population and there occurred an excess of 405 tuberculosis cases, most of them among patients with reactivation of latent tuberculosis infection. The PAF in San Francisco is similar to the PAF (14%) in Harare, Zimbabwe (27).

Although intensified tuberculosis control efforts were underway in San Francisco and the tuberculosis case rates declined among HIV-positive and HIV-uninfected individuals (19), tuberculosis case rates remained significantly higher among HIV-positive individuals. Tuberculosis case rates decreased more rapidly among HIV-positive persons, particularly those with reactivation of latent tuberculosis infection (Figures 2A and 2B). During the study period, targeted interventions, such as directly observed therapy and isoniazid to treat latent tuberculosis, were used to interrupt transmission of *M. tuberculosis*, particularly

among homeless and HIV-positive persons (19). By 1997, the Department of Public Health began location-based screening and active case finding among IDUs and homeless and HIV-positive persons, and the incidence rate ratios decreased when fully adjusting for confounding by injection drug use, substance abuse, and homelessness in the multivariate model. HAART was widely available in San Francisco by 1997 and likely reduced the risk of rapid progression to disease, thereby decreasing the tuberculosis case rate among HIV-positive persons. Several other studies have documented decreases in the tuberculosis incidence rate soon after the introduction of antiretroviral therapy (28–31). However, such an improvement may be short-lived if it coincides with increased risk-taking behaviors that enhance the opportunities for HIV transmission (9, 28).

There are currently three different approaches to evaluate the infectiousness of *M. tuberculosis* in HIV-positive versus HIV-uninfected persons. First, the annual risk of tuberculosis infection (ARTI) estimates the number of new infections occurring among young schoolchildren, and one would expect the ARTI to increase in populations with an increasing prevalence of HIV. However, the ARTI can be influenced by many factors and provides an ecological analysis at best (32–34). For example, as HIV prevalence increased, the prevalence of tuberculosis infection increased in Kenya (35) but not in Tanzania (36). Second, one can look at the period of infectiousness of a patient with tuberculosis and make inferences about the transmission potential. Corbett and colleagues showed that HIV-positive gold miners in South Africa had a significantly shorter mean duration of smear positivity or infectiousness (0.17 yr) than HIV-negative persons (1.15 yr), a sixfold difference likely due to increased presentation to health care providers and increased case-finding rates among HIV-positive persons (37). In contrast, the estimated duration of infectiousness was similar for HIV-positive and HIV-negative individuals in a community-based study in South Africa (38). A third approach is to assess tuberculosis infections among the contacts of the source cases. A meta-analysis concluded that patients with tuberculosis and HIV-1 infection are not intrinsically more infectious to their contacts than are HIV-1-negative patients with tuberculosis (39), and a study in Brazil showed that HIV-positive index cases may even be less infectious to their contacts (40). Taken

together, multiple studies using the first three approaches demonstrate that patients with HIV-related tuberculosis are not more infectious, and may even be less infectious, than HIV-uninfected patients.

Our study was unable to determine the infectiousness of HIV-positive patients with tuberculosis compared with HIV-uninfected patients. However, by using molecular genotyping methods, we were able to estimate the number of secondary cases that arose from HIV-positive and HIV-uninfected source cases. Glynn and coworkers used a molecular epidemiologic approach to evaluate recent infection with *M. tuberculosis* in northern Malawi, an area in Africa with a high HIV prevalence, and reported the PAF was 57%; more than half of the sputum smear-positive pulmonary tuberculosis cases were attributed to HIV infection (41). Furthermore, nearly half of the tuberculosis cases arising from recent infection in their study population had acquired the infection from an HIV-positive source case (42). Similarly, by assuming that the first case in a cluster is the source case, we estimated that 38.8% of the tuberculosis cases due to recent transmission in San Francisco acquired the infection from an HIV-positive source case. In addition, one in every five secondary cases was caused by transmission from an HIV-positive source case to an HIV-uninfected person, an estimate upheld by sensitivity analysis. HIV-positive persons account for a significant amount of tuberculosis transmission to both HIV-positive and HIV-uninfected populations (5).

Our data suggest that transmission to HIV-positive contacts is important for the amplification of a local tuberculosis epidemic. The prevalence of HIV infection is often greater among the contacts of HIV-positive patients with tuberculosis than among the contacts of HIV-uninfected patients (43, 44). Transmission of *M. tuberculosis* to HIV-positive persons often leads to rapid progression to disease in the newly infected individuals (10), partially explaining why HIV-positive persons were likely to become secondary cases of tuberculosis and within a shorter time interval than HIV-uninfected contacts and HIV-uninfected patients. In a retrospective cohort study among gold miners in South Africa, the tuberculosis case rate was 2.9 cases per 100 person-years in HIV-positive miners and 0.8 cases per 100 person-years in HIV-negative miners (adjusted RR of tuberculosis, 2.9), and unexpectedly, the tuberculosis incidence was doubled (adjusted RR, 2.1) within 1 year of HIV seroconversion (45). In our 12-year study, genotypic clusters with at least one HIV-positive person were larger, lasted longer, and had a shorter time between successive cases relative to clusters with only HIV-uninfected persons in the genotypic cluster. Therefore, unless they compensate for the rapid progression to disease among HIV-positive contacts, current models of tuberculosis incidence could underestimate the effect of HIV infection in areas where tuberculosis is endemic (46, 47).

Our findings document and quantify the relative transmission of *M. tuberculosis* by patients with tuberculosis who are coinfected with HIV before they die or are rendered noninfectious by antituberculosis therapy. The overall CFR was high (12%) and was higher still among HIV-positive patients with tuberculosis ($P < 0.035$). The high CFRs could be due to the difficulties and delays in diagnosing tuberculosis. However, there was no significant difference in the proportion of HIV-positive and HIV-uninfected persons who were diagnosed at death, and theoretically, such untreated persons could still be infectious and transmit *M. tuberculosis* before their death. In addition, confounding factors such as homelessness, higher rates of exposure to HIV-positive contacts, and social networks linked to substance abuse may also facilitate tuberculosis transmission into populations where the HIV prevalence is high.

There are some limitations in the present study. First, not all patients with tuberculosis received HIV counseling and testing;

thus, some misclassification bias by HIV serostatus may have occurred. However, patients who were not tested for HIV came from populations and risk groups that are known to have a low prevalence of HIV infection. Nevertheless, the exclusion of a group at low risk for tuberculosis transmission may have led us to overestimate transmission-related tuberculosis in the entire population. If some individuals who did not have HIV counseling and testing and were classified as HIV uninfected were actually HIV positive, their reclassification would strengthen our conclusions. Second, a genotyping pattern was available for most, but not all, of the culture-confirmed cases. Although undersampling is likely to underestimate the true rate of clustering (22), it is unlikely to change our conclusions, because the availability of genotyping did not differ by HIV serostatus. Third, we initially assumed that the first case in each cluster was the source case for the cluster. Because it is likely that the first patient diagnosed with tuberculosis was not the source case in every single cluster, we performed a sensitivity analysis in which we altered the source case between the first, second, and third case. The sensitivity analysis did not change our results significantly (Table E3). Fourth, children younger than 5 years were a very small portion of our study population (1.9%), so our results have limited inferences for pediatric populations. Finally, we do not have information about the HIV status of all of the contacts in our study, but if HIV-positive persons were more likely to have other HIV-positive persons among their close contacts, we could have overestimated the number of secondary cases attributed to HIV-positive patients with tuberculosis (44).

Our findings have important public health implications. Intensified tuberculosis case finding and treatment can reduce tuberculosis transmission and lower the case number and case rate over time, even in settings with high HIV prevalence. Routine HIV counseling, testing, early diagnosis of infection, and assessment for HAART are appropriate interventions for patients with tuberculosis, their contacts, and populations with a high risk of exposure to tuberculosis and HIV, such as the homeless (48–50). Targeted interventions that prevent infection with HIV, and prevent tuberculosis in persons coinfecting with HIV and *M. tuberculosis*, will reduce the burden of disease in communities (5).

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