HUMAN IMMUNODEFICIENCY VIRUS INFECTION IN TUBERCULOSIS PATIENTS IN SAN FRANCISCO

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ABSTRACT

To assess the impact of human immunodeficiency virus (HIV) infection on tuberculosis morbidity in San Francisco, retrospective and prospective analyses were undertaken.

In a population-based study, acquired immunodeficiency syndrome (AIDS) and tuberculosis registries were matched from the period of 1981 through 1985. Of 287 tuberculosis cases in non-Asian-born males aged 15-60, 35 (12%) also had AIDS. Patients with tuberculosis and AIDS were more likely to be nonwhite and heterosexual intravenous drug users than were AIDS patients without tuberculosis. Although the lungs were the most frequent site of tuberculosis in both AIDS and non-AIDS patients, 60% of the AIDS group had at least 1 extrapulmonary site of disease compared to 28% of the non-AIDS group ($p<0.001$). Non-significant tuberculin skin tests were more common in AIDS patients (14 of 23 tested) than in non-AIDS patients (12 of 129 patients tested; $p<0.0001$). Chest radiographs in AIDS patients showed predominantly diffuse or miliary infiltrates (60%), whereas non-AIDS patients had predominantly focal infiltrates and/or cavitation (68%). Response to antituberculosis therapy was favorable in AIDS patients, although adverse drug reactions occurred more frequently than in non-AIDS patients ($p<0.02$). Overall mortality was high, was almost always caused by AIDS, and did not differ when measured from the time of tuberculosis diagnosis or from the time of AIDS diagnosis.

To determine the full clinical spectrum of tuberculosis in HIV-infected patients (not only those HIV-seropositives with AIDS) a

prospective seroprevalence study of San Francisco non-Asian-born tuberculosis patients aged 18 through 65 was undertaken. Of 128 eligible patients, 60 agreed to participate. Seventeen (28%) were seropositive for antibodies to HIV. Seropositive patients were more likely to be between the ages of 18 and 40 ($p<0.01$), male ($p<0.05$), black ($p<0.01$) and American-born. They were less likely to have a history of prior tuberculin reactivity ($p<0.05$). HIV risk factors in seropositives were gay man-29%, intravenous drug user-29% and gay man and intravenous drug user-18%. Fifteen of 17 (88%) seropositives had no clinical evidence of HIV infection prior to the diagnosis of tuberculosis. There were no significant differences between seropositive and seronegative patients in site of disease, smear or culture sensitivities for Mycobacterium tuberculosis, tuberculin reactivity or radiographic features. Seropositive patients were immunosuppressed on the basis of absolute CD4 lymphocyte counts (mean of 328, versus 934 in seronegative patients; $p<0.0001$). Both groups responded well to antituberculosis drugs and had similar rates of adverse drug reactions.

These data indicate that tuberculosis is the initial opportunistic infection in most HIV-infected patients who develop tuberculosis. Atypical clinical features (extrapulmonary disease, tuberculin anergy and atypical chest films) occur most frequently when tuberculosis afflicts patients with other clinical evidence of HIV infection. Treatment for tuberculosis is effective regardless of a patient's HIV status.

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Introduction

The acquired immunodeficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV), a retrovirus that preferentially infects cells bearing the CD4 glycoprotein and causes profound deficits in cell-mediated immunity (1-4). As a consequence, patients with HIV infection are vulnerable to a multitude of infectious agents defensed by the cellular immune system. Among these is Mycobacterium tuberculosis.

Ecological studies were the first to suggest a tuberculosis-AIDS association: New York City health districts reporting the highest incidence of AIDS also reported the highest incidence of tuberculosis (5). Subsequent retrospective studies comparing tuberculosis and AIDS patients in Miami, New York and Newark revealed a prevalence of tuberculosis in AIDS patients ranging from 7.8% to 34% (6-9). These figures exceeded the estimated national tuberculosis incidence and reinforced an association between HIV and tuberculosis in those Haitian, intravenous drug using and hospitalized patients studied.

Although patients with AIDS in San Francisco have considerably different demographic characteristics than the groups in which a high prevalence of tuberculosis had been reported previously, it has been noted that an increased number of tuberculosis cases in non-Asian-born males might be related to HIV infection. To test this hypothesis, a population-based study was undertaken in which the the tuberculosis and AIDS registries of San Francisco were cross-matched and features of tuberculosis in AIDS patients were analyzed. Reporting and referral bias that may occur in single-institution

studies were avoided by using county-wide surveillance data on tuberculosis and AIDS in a setting where both diseases are common. Results indicated that clinical features of tuberculosis in AIDS patients differ significantly from manifestations of tuberculosis in patients without AIDS.

At the time of completion of this retrospective analysis a prospective study from Miami indicated that most HIV-infected patients with tuberculosis have no evidence of HIV infection prior to the diagnosis of tuberculosis (10). Retrospective studies looking only at patients with a late stage of HIV infection--namely AIDS--tend to overlook those with asymptomatic infection. As a result, many HIV-related tuberculosis cases were not analyzed in the retrospective study. Hence, a prospective serologic study of newly diagnosed cases of tuberculosis in San Francisco was undertaken to assess the prevalence of HIV infection in these patients, the clinical features of HIV-associated tuberculosis and the response to therapy. In this manner the full spectrum of HIV-related tuberculosis can be described.

METHODS

Retrospective analysis

All verified case reports of tuberculosis in non-Asian-born males 15 to 60 years of age reported to the San Francisco Department of Public Health from 1981 through 1985 were reviewed. Reports were based on positive cultures for M. tuberculosis and other standard diagnostic methods used in the Verified Case Report of tuberculosis (11). Because of the near total absence of women and Asian-born immigrants among patients with AIDS in San Francisco, these groups were excluded from the review. Cases identified from the Tuberculosis Registry were then matched to the AIDS Registry which includes all reported cases of AIDS diagnosed in San Francisco. To identify tuberculosis cases that might have had AIDS diagnosed in other jurisdictions, the list of cases from the Tuberculosis Registry was also cross-matched with the case list of the San Francisco General Hospital AIDS Clinic, a large outpatient facility that enrolls approximately 40% of San Francisco AIDS patients. Cases from the Tuberculosis Registry that also appeared on the AIDS Registry or the AIDS Clinic rolls, and had documented diagnoses of AIDS (12), were defined as cases of tuberculosis and AIDS. Cases appearing on the Tuberculosis Registry but not on either the AIDS Registry or the AIDS Clinic list were defined as cases of tuberculosis without AIDS. From the list of tuberculosis cases without AIDS a subset of age- and race-matched control cases was selected consecutively and alphabetically

for each tuberculosis and AIDS case. Finally, cases appearing in the AIDS registry but not in the Tuberculosis Registry were defined as cases of AIDS without tuberculosis.

Demographic, clinical and laboratory data were obtained on all tuberculosis cases from the Tuberculosis Registry. The date of diagnosis was defined as the day on which the first positive culture for M. tuberculosis was obtained. Data on AIDS diagnoses were obtained from the AIDS Registry. The date of AIDS diagnosis was defined as the date on which the index diagnosis was first established, as reported to the Department of Public Health. Because of reporting delays, date of reporting of AIDS cases was not used in the analysis. Survival data were obtained from a combination of sources, including the AIDS Registry, Tuberculosis Registry, review of clinic and hospital charts and phone calls to physicians caring for patients. The date of follow-up was considered to be the last documented physician visit or the date of death. For subjects who died, the cause of death as listed on the death certificate was obtained if available. Follow-up was complete for all subjects through July 15, 1986.

Chest radiographs of the patients with tuberculosis and AIDS and the control patients who were seen at San Francisco General Hospital were obtained from files of the Radiology Department. Films were read by an observer who was unaware of the patients' clinical status and were judged to be normal or to show any of the following abnormalities: diffuse infiltration, miliary pattern, focal infiltration, cavitation, intrathoracic lymphadenopathy and pleural effusions.

Statistical analysis was done using the continuity corrected chi-square of Fisher's exact test for univariate comparisons (13). Survival analysis was done by the product-limit method using a computer software package (BMDP); comparison was made of the length of time from tuberculosis diagnosis to death and length of time from AIDS diagnosis to death in each subject (14). Differences in median survival from the date of AIDS diagnosis and the date of tuberculosis diagnosis in subjects with both diseases were compared using paired and unpaired t tests (15).

Prospective analysis

Patients meeting the definition of a verified case of tuberculosis and who received their care at the San Francisco Department of Public Health Tuberculosis Clinic from July 1, 1986 to May 1, 1988, were recruited. Asian-born immigrants and persons less than 18 or greater than 65 years and patients who did not receive their medications and/or medical care at the clinic were excluded.

After providing informed consent, each patient answered a brief questionnaire administered by a trained interviewer in order to obtain demographic data, behavioral risks for HIV infection and medical history. Complete cell counts were performed by a standard cell sorter. Lymphocyte phenotyping was performed by monoclonal antibody staining and flow cytometry. Absolute CD4 lymphocyte counts wre calculated by multiplying the white blood cell count by the per cent of lymphocytes determined by manual inspection of the peripheral blood smear and by the per cent of CD4 lymphocytes

determined by lymphocyte phenotyping. Testing for antibodies to HIV was performed by commercial ELISA; repeatedly positive specimens were confirmed by immunofluorescence assay (IFA). Specimens reactive by ELISA and IFA were considered positive. For patients desiring knowledge of antibody status, counselling sessions were arranged and results given in a confidential manner. Antibody status was not divulged to the clinic staff nor entered in patient charts. The study was approved by Human Studies Committees of the University of California, San Francisco, San Francisco County Department of Public Health and the California Department of Health Services.

Clinical data including site of tuberculosis, tuberculin reactivity, smear and culture results, chemotherapeutic regimen, drug toxicity requiring the discontinuation of an antituberculosis drug and relapse were abstracted from clinic charts. The date of the diagnosis of tuberculosis was defined as the day on which the first culture positive for M. tuberculosis was obtained. For cases not proven bacteriologically, the date of the diagnosis of tuberculosis was defined according to clinic chart notes, most often as the date on which antituberculosis therapy was begun. Time to sputum conversion was defined as the time between initiation of antituberculosis medications and first persistently negative smear and culture result in pulmonary cases with an initially positive culture.

Chest radiographs obtained within one month of the tuberculosis

diagnosis date were read by an observer who was unaware of patients' clinical status Films were judged to be normal or to show one or more of the following abnormalities: diffuse infiltration, miliary pattern, focal infiltration, cavitation, intrathoracic adenopathy and pleural effusions.

Confirmation of HIV-related diagnoses in HIV-seropositive patients was done through review of charts at the San Francisco General Hospital AIDS Clinic or through contact with patients' personal physicians. AIDS was defined according to surveillance criteria in effect at the time of tuberculosis diagnosis (12). AIDS-related condition (ARC) was defined as a physician confirmed diagnosis of oral candidiasis, hairy leukoplakia or persistent diarrhea.

Follow-up was done on all patients through April 22, 1989 by review of files at the Tuberculosis Clinic and San Francisco General Hospital AIDS Clinic as well as through contact with patients' personal physicians.

Statistical analysis was done using the continuity corrected chi-square of Fisher's exact test for univariate comparisons (13). Kaplan-Meier curves of time to sputum conversion were constructed for each group and comparisons made using paired and unpaired t tests (14,15).

RESULTS

Retrospective analysis

Between January 1, 1981 and December 31, 1985, 287 non-Asian-born males 15 to 60 years of age were identified as having tuberculosis. This represented 19% of the total cases of tuberculosis reported during the 5-year period in San Francisco. Of these 287 cases, 35 (12%) also had AIDS. Thirty-one patients had AIDS diagnosed in San Francisco and were identified through the Department of Public Health AIDS Registry, and 4 patients had AIDS diagnosed elsewhere, and were located by review of the AIDS Clinic list. Demographic characteristics of these patients are presented in Table 1. When compared with patients with AIDS but not tuberculosis, patients with both diseases were more likely to be Black or Latino than White ($p<0.005$). In comparison to patients with tuberculosis but not AIDS, patients with both diseases were more likely to be White ($p<0.001$). AIDS risk categories of patients with tuberculosis and AIDS also differed significantly from AIDS patients without tuberculosis, with a higher frequency of heterosexual intravenous drug users and fewer homosexual/bisexual men ($p<0.00001$).

In Figure 1, the time of the diagnosis of tuberculosis is shown relative to the time of diagnosis of AIDS. Eighteen (51%) patients had tuberculosis diagnosed prior to AIDS (range, 1 to 23 months), 4 patients (11%) had both AIDS and tuberculosis diagnosed with 14 days of one another, and 13 patients (37%) had tuberculosis diagnosed after the diagnosis of AIDS (range, 1 to 15 months). One

patient had tuberculosis diagnosed 6 years prior to the diagnosis of AIDS. He had been treated with isoniazid and ethambutol for 6 months in 1978, and in January, 1984 he developed pulmonary, lymphatic and urogenital tuberculosis; AIDS was diagnosed in September, 1984.

The presenting AIDS diagnoses were Pneumocystis carinii pneumonia in 16 patients (47%), Kaposi's sarcoma in 12 patients (34%) and other opportunistic infections in 7 patients (20%). The distribution of AIDS diagnoses in these patients did not differ based on whether tuberculosis or AIDS occurred first.

The source of specimens that yielded M. tuberculosis for patients with and without AIDS is shown in Table 2. Patients with tuberculosis and AIDS had significantly more extrapulmonary involvement than did patients with tuberculosis without AIDS; 21 of 35 (60%) patients with tuberculosis and AIDS had at least one documented extrapulmonary site in comparison to 71 of 252 (28%) patients with tuberculosis without AIDS ($p<0.001$). Five patients (14%) with tuberculosis and AIDS had more than one extrapulmonary site of disease compared with 7 (3%) of the non-AIDS patients. The lungs were the most common site of involvement in both groups, with 74% of the AIDS group and 82% of the non-AIDS group having positive cultures from sputum or other lung-derived specimens. There were no significant differences in rate of purely extrapulmonary tuberculosis between patients with and without AIDS.

The most common sites of extrapulmonary involvement in the

AIDS group were lymphatic (31%), urogenital (14%), bone marrow or blood (both 11%), and musculoskeletal (9%). Central nervous system and skin and soft tissue each accounted for 3% of cases. In the non-AIDS group, the most common extrapulmonary sites were pleural (10%) and lymphatic (7%). There were no cases of pleural tuberculosis in the AIDS group, though the frequency with which pleural fluid was examined or pleural biopsies were performed on this group could not be determined.

Of patients with tuberculosis and AIDS, 9 of 23 (39%) for whom skin test results were known had a significant reaction (greater than 9 mm of induration) at the time tuberculosis was diagnosed (Table 2). Of 129 non-AIDS patients for whom test results are available, 117 (91%) had significant reactions ($p<0.0001$). There were no differences in the frequency of significant reactions to tuberculin tests among patients with tuberculosis and AIDS relative to onset of AIDS, site of tuberculosis or primary AIDS diagnosis (Kaposi's sarcoma versus opportunistic infection).

Chest radiographs were reviewed for 20 AIDS and tuberculosis patients and 22 age-, race- and sex-matched patients who did not have AIDS (Table 2). Of the AIDS group, 12 (60%) had diffuse or miliary radiographic abnormalities, 4 (20%) had intrathoracic lymphadenopathy, 7 (35%) had focal infiltrates and 4 (20%) had pleural effusions. Only 1 AIDS patient had a cavitary lesion. Of the control group, 15 (68%) had focal pulmonary abnormalities on chest radiographs, including 5 cavitary lesions, 7 (32%) had diffuse or miliary abnormalities, 5 (23%) had pleural effusions and none had

intrathoracic lymphadenopathy.

In general, patients with AIDS and tuberculosis had a favorable response to antituberculosis therapy. Of the 26 pulmonary cases, 12 had additional sputum cultures after initiation of treatment. All of these patients had negative sputum cultures within 3 to 10 months of starting antituberculosis drugs. One AIDS patient with hepatic and urogenital tuberculosis converted urine cultures after 3 months of treatment. There was one relapse after sputum conversion in a patients who was noncompliant with treatment. A second patient, who had an isoniazid-resistant isolate, developed central nervous system tuberculosis despite sputum conversion and continuation of appropriate antituberculosis therapy.

Adverse reactions to antituberculosis medications necessitating a change in therapy occurred in 9 patients (26%) with AIDS but in only 1 of 35 (3%) control patients with tuberculosis without AIDS ($p<0.02$). Of tuberculosis and AIDS patients with adverse drug reactions, 6 had a rash and/or itching that responded to discontinuation of isoniazid in 2 and rifampin in 4 instances. Another patient had hepatitis attributed to isoniazid that resolved when the drug was stopped. Thrombocytopenia attributed to rifampin was diagnosed in 1 patient and resolved when the drug was withheld. One patient had an unspecified reaction to rifampin that resolved when the drug was discontinued.

Mortality in patients with tuberculosis and AIDS was high. The case-fatality rate in this group was 77%, compared to 11% of control tuberculosis patients without AIDS ($p<0.001$); Figure 2 is a life table

plot of patients with tuberculosis and AIDS showing survival both from the time of tuberculosis diagnosis and from the time of AIDS diagnosis. Median survival from tuberculosis diagnosis was 7.4 months, with the longest survival being 29 months. Median survival from the time of AIDS diagnosis was 8.1 months (range, 0 to 31 months) and did not differ significantly from survival from tuberculosis diagnosis ($p>0.30$). The cause of death in patients with tuberculosis and AIDS was almost always AIDS, not tuberculosis. Of the 26 patients in the AIDS group who died, 22 died of AIDS-related diagnoses. Four of 26 patients who died had no cause of death listed. Three patients had tuberculosis listed on their death certificates as a contributing cause of death, and in one of these tuberculosis was the primary cause listed. Only one subject, a patient with central nervous system tuberculosis, was documented to have active tuberculosis at the time of death, and he died of respiratory complications caused by P. carinii pneumonia. Another patient was reported to have died of Kaposi's sarcoma, though no autopsy was performed. Cultures obtained premortem from bronchoalveolar lavage and transbronchial biopsy were reported as showing M. tuberculosis after the patient had died. No antituberculosis therapy was given.

Prospective analysis

From July 1, 1986 to May 1, 1988, 320 verified cases of tuberculosis in non-Asian born patients were reported to the San Francisco Department of Public Health. One hundred and twenty-

eight (40%) of these were between the ages of 18 and 65 and received at least some of their care at th San Francisco Tuberculosis Clinic. Forty-five patients (35%) could not be enrolled in the study because they died (5 patients) or failed to return to the clinic after confirmation of tuberculosis (40 patients). Twenty-three patients (18%) refused to participate. Enrolled candidates did not differ significantly from unenrolled patients, though more were female and between the ages of 18 and 40 (Table 3).

Of the sixty patients who entered the study 17 (28%) had antibodies to HIV detected. The mean time from date of diagnosis of tuberculosis to time of detection of antibodies to HIV was 3 months (range 1 to 9 months).

Demographic data are shown in Table 4. Males were more likely to be seropositive than females (36% versus 6%, $p<0.05$). The median age of seropositive patients was 34 years (range 23 to 59 years) as compared to 43 years in seronegative subjects. Seropositive patients were significantly more likely to be between the ages of 18 and 40 than 41 or older (44% versus 11%, $p<0.01$).

Forty-eight per cent of Black patients had antibodies to HIV, versus 14% of Latinos and 10% of Whites ($p<0.01$). Seropositives tended to be American-born though not significantly more so than seronegative patients.

No seropositive patient had a history of prior tuberculin reactivity while 14 (33%) of seronegative patients reported prior tuberculin reactivity ($p<0.05$). Seven seropositives gave a history of a prior negative tuberculin test as compared to 12 seronegative patients.

HIV risk factors in seropositives were intravenous drug use-29%, homosexual-29% and homosexual and intravenous drug use-18%. While the presence of an HIV transmission risk factor was predictive of underlying infection, 24% (4 of 17) of seropositives did not report risk behavior other than heterosexual intercourse.

Of the 17 seropositive patients, 15 had no clinical evidence of HIV infection prior to the diagnosis of tuberculosis. One patient had oral candidiasis and one patient had AIDS (Kaposi's sarcoma). Among the fifteen seropositive patients without evidence of HIV infection prior to the diagnosis of tuberculosis, four had extrapulmonary tuberculosis and thereby satisfied Centers for Disease Control surveillance criteria for AIDS (23).

The lung was the only site from which M. tuberculosis was isolated in 13 (76%) seropositive and 31 of 43 (72%) seronegative patients (Table 4). No seropositive subject had purely extrapulmonary tuberculosis, although 14% of seronegative patients did. The lymphatic and urogenital systems were the most frequent extrapulmonary sites of disease in seropositive subjects while the pleura and meninges were the most frequent extrapulmonary sites of disease in seronegative subjects.

Eight of 17 (47%) seropositive patients had acid-fast bacilli on initial smear evaluation and 15 of 17 (88%) were culture positive. In seronegative patients with pulmonary tuberculosis, 19 of 37 (51%) were smear positive on initial screening and 35 of 37 (95%) were culture positive.

Twelve of fifteen (80%) seropositive patients had a tuberculin

reaction of greater or equal to 10 mm versus 93% of seronegative patients. This difference was not statistically significant. The three anergic seropositive patients all had extrapulmonary tuberculosis. One of these patients had an absolute CD4 lymphocyte count of 23--the lowest value of any study subject.

Chest radiographs were reviewed for 13 seropositive and 29 seronegative patients with pulmonary tuberculosis (Table 5). Of the seropositive group, 6 (46%) had focal infiltrates, four (31%) had cavitation, 6 (46%) had diffuse abnormalities and one (8%) had a miliary pattern. Of seronegative patients 14 (48%) had focal infiltrates, 10 (34%) had cavitation and 10 (34%) had diffuse abnormalities. Five (17%) seronegative patients had normal chest radiographs at the time of the diagnosis of tuberculosis.

The average absolute CD4 lymphocyte count in 11 seropositive subjects was 328 (range 23 to 742) versus 934 in 30 seronegative patients (range 145 to 2962, $p<0.0001$, Figure 3).The average CD4 to CD8 lymphocyte ratio in 12 seropositive patients was 0.54 (range 0.02 to 1.07) as compared to a ratio of 1.6 (range 0.35 to 4.36) in 38 seronegative subjects ($p<0.0001$, Figure 4).

Most patients were treated with isoniazid, rifampin, ethambutol and pyrazinamide. There were no significant differences in time to sputum conversion between seropositive and seronegative patients (Figure 5). No patient failed to convert sputum cultures.

Drug toxicity requiring a change in therapy occurred in 24% of seropositive patients and 23% of seronegative patients. This difference was not statistically significant. Relapse following therapy

occurred in two seronegative patients and no seropositive patients. Eleven of 16 seropositive patients who finished therapy were treated for 6 months.

Ten of 16 seropositive patients have been followed at least 6 months since the completion of therapy or until date of death. During the period of follow-up four seropositive patients developed other AIDS-related diagnoses: a patient with pulmonary, urogenital and lymphatic tuberculosis who was anergic developed cytomegalovirus retinitis 2 years after the diagnosis of tuberculosis; a patient with pulmonary tuberculosis who demonstrated tuberculin reactivity, and had a CD4 to CD8 ratio of 0.48 and an absolute CD4 lymphocyte count of 262, developed progressive multifocal leukoencephalopathy 10 months after the diagnosis of tuberculosis; a patient with pulmonary and lymphatic tuberculosis who was anergic, and had a CD4 to CD8 ratio of 0.02 and absolute CD4 lymphocyte count of 23, developed P. carinii pneumonia 2 months after the diagnosis of tuberculosis and died 8 months later from an AIDS wasting syndrome; an ARC patient with pulmonary tuberculosis who demonstrated tuberculin reactivity and had a CD4 to CD8 ratio of 0.14 and absolute CD4 lymphocyte count of 84 developed P. carinii pneumonia 4 months after the diagnosis of tuberculosis. The two patients who developed P. carinii pneumonia had the lowest CD4 to CD8 lymphocyte ratios and absolute CD4 lymphocyte counts found in the study.

One other HIV-seropositive patient died during the period of follow-up. He had converted his sputum cultures and was receiving

antituberculosis medications when he died from a respioratory arrest. Lung cancer as well as pulmonary tuberculosis were listed as contributing causes of death.

DISCUSSION

Infection with HIV may cause a profound deficit in cell-mediated immunity and set the stage for a wide variety of infections that normally are controlled by cellular immune defenses. An increased frequency of tuberculosis would therefore be expected in persons infected with HIV, particularly those persons likely to be infected with M. tuberculosis as well. Moreover, because many of the manifestations considered typical of tuberculosis are a result of interactions between M. tuberculosis and normal host responses, the depression of cellular immunity that occurs secondary to HIV infection would be predicted to alter the clinical features of tuberculosis associated with HIV infection.

In San Francisco, an area with a high prevalence of HIV and M. tuberculosis infection, the HIV epidemic has greatly influenced tuberculosis morbidity. From 1981 to 1985 patients with AIDS accounted for 12% of the cases of tuberculosis in non-Asian-born males 15 to 60 years. Conversely, 2% of AIDS cases in San Francisco had tuberculosis over the five year period, a figure more than forty times the incidence of tuberculosis in the general population (16).

While providing evidence to substantiate a link between HIV infection and tuberculosis, retrospective analysis matching AIDS and tuberculosis registries underestimates the prevalence of tuberculosis as a HIV related disease because it recognizes only cases of tuberculosis occurring in patients with an advanced stage of HIV infection--namely AIDS. Prospective analysis, by identifying HIV-infected tuberculosis patients without clinical evidence of

immunodeficiency prior to the diagnosis of tuberculosis, overcomes this bias. Indeed, 28% of patients studied prospectively had antibodies to HIV. Because only 47% of eligible patients were studied the true prevalence of HIV infection could have been overestimated if seropositive subjects had been more likely to volunteer. However, of the 68 non-participants in the study, 7 (10%) were known to have AIDS. Hence the minimum prevalence of HIV infection in all patients was 19% (24 of 128). Because the majority (15 of 17) of subjects in the study had no clinical manifestation of HIV infection other than tuberculosis at the time of entry into the study, it is likely this calculation underestimates the true seroprevalence.

The San Francisco seroprevalence figure is similar to the 31% prevalence of HIV infection seen in tuberculosis patients in South Florida (10). Other major metropolitan areas, especially New York City and Newark, which have reported high rates of tuberculosis in AIDS patients, may also have similar rates of HIV-related tuberculosis (7-9,17).

Retrospective studies from many cities including San Francisco show that the diagnosis of tuberculosis precedes that of AIDS in patients with both diseases (6-9). Prospective analysis confirmed that tuberculosis is the initial opportunistic infection in many HIV-seropositive patients. Of 15 of 17 HIV-seropositive patients in San Francisco, one had Kaposi's Sarcoma and one had oral candidiasis prior to the diagnosis of tuberculosis. The remainder did not have clinical evidence of HIV infection apart from tuberculosis. Similarly,

of 22 HIV-seropositive patients with tuberculosis in Miami, only two met Centers for Disease Control criteria for AIDS (both had P. carinii pneumonia) and four were classified as having ARC by virtue of oral candidiasis, persistent diarrhea or unexplained lymphadenopathy (10). The fact that tuberculosis is frequently the initial opportunistic infection in HIV-seropositive patients indicates why retrospective analysis is limited in its ability to assess the influence of HIV infection on tuberculosis morbidity. For example, if during the prospective study period from 1986 through 1988 only tuberculosis cases with AIDS in San Francisco had been considered, only two cases would have been included! It is clear the retrospective analysis uncovered only the tip of the iceberg of HIV-related tuberculosis. Prospective analysis was a necessary adjunct to characterize the full spectrum of HIV-related tuberculosis.

The demographic make-up of patients with tuberculosis and HIV infection reflects the degree to which populations with M. tuberculosis infection adopt risk behaviors that put them at risk for HIV infection. In San Francisco from 1981 through 1985 for instance blacks, who represented one of every three cases of tuberculosis, accounted for relatively few AIDS cases. Hence, when compared with patients with AIDS but not tuberculosis, patients with both diseases were more likely to be Black than White. In comparison to patients with tuberculosis but not AIDS, patients with both diseases were more likely to be White. In Miami, where M. tuberculosis infection is endemic among Haitians and many are also infected with HIV, it is no surprise that almost all cases of patients with tuberculosis and

AIDS are Haitian (6,10).

HIV infection in tuberculosis patients identified prospectively in San Francisco was more frequent in males, blacks, patients 18 to 40 years of age and in patients with a history of behavior that placed them at risk for HIV infection. These demographic features correlate with epidemiologic data that have documented an increased prevalence of tuberculosis in San Francisco in American-born persons aged 25 to 44 years (18).

Comparison of the two study periods indicate substantial differences in the prevalence of specific HIV transmission factors. Most cases of tuberculosis in AIDS patients from 1981 through 1985 occurred in gay males. Intravenous drug users accounted for only 17% of cases (though intravenous drug use was more commonly associated with cases of tuberculosis in AIDS patients than with cases of AIDS not complicated by tuberculosis). In contrast, during the prospective study period from 1986 through 1988 approximately half the cases of HIV-related tuberculosis occurred in intravenous drug users.

The emergence of intravenous drug use as a major HIV transmission factor in HIV-seropositive patients with tuberculosis is not surprising. Public health efforts in San Francisco have substantially reduced homosexual HIV transmission, while transmission by intravenous drug use remains a major problem (19). The fact that intravenous drug users are at increased risk of M. tuberculosis infection independent of HIV status further compounds the problem (20,21). In the future it is likely that the proportion of

intravenous drug users with HIV infection contributing to tuberculosis morbidity will increase unless effective means for controlling HIV transmission in this group are found. As a result, racial minorities, who are overly represented among intravenous drug users, can be expected to make up a greater proportion of HIV-related tuberculosis cases (22).

Because intravenous drug users are at particular risk of infection by M. tuberculosis as well as by HIV, the Centers for Disease Control recommendation that all HIV-infected persons with demonstrated tuberculin reactivity receive isoniazid prophylaxis is particularly applicable to this group of patients in San Francisco. A similar recommendation has been advocated in New York City (17).

Interestingly 4 of 17 (24%) seropositive subjects denied high risk behaviors despite careful questioning. Since HIV-seropositive patients with tuberculosis are advised to receive a longer course of antituberculosis therapy, identification of all patients with tuberculosis complicated by HIV infection is important to insure proper treatment. Furthermore, those patients with extrapulmonary tuberculosis and evidence of HIV infection will be classified as having AIDS and offered appropriate social services (23). Consequently, it is recommended that in areas where HIV infection is endemic, patients with tuberculosis should have routine HIV antibody testing done to insure that all cases of tuberculosis related to HIV infection are identified and that appropriate medical and public health follow-up is provided.

The pathogenesis of tuberculosis in HIV-seropositives is

uncertain. The lack of atypical clinical features in HIV-seropositives without AIDS suggests that HIV-induced cellular immunodeficiency results in reactivation of M. tuberculosis, a relatively virulent pathogen, in patients immunocompetent enough to control disease caused by less virulent opportunistic agents. Immunologic data confirms this thought, as HIV-seropositive patients identified prospectively were significantly immunocomprimised, yet were not depleted to the point commonly associated with infection with P. carinii and other opportunists (24).

Interestingly, HIV-seronegative patients in San Francisco identified prospectively were more likely to report a history of a positive tuberculin test and 41% of seropositives reported previously having a negative PPD, suggesting recent acquisition of M. tuberculosis. The possibility of inaccurate patient reporting, however, limit the utility of these data. Clinical findings, furthermore, strongly support reactivation of remote infection because of HIV-induced immunosuppression, rather than primary tuberculosis from recent contact with M. tuberculosis, as the major means of pathogenesis. Further investigation is necessary to fully clarify the relationship of HIV infection and M. tuberculosis infection and disease.

The "atypical" clinical nature of tuberculosis in patients with AIDS is demonstrated clearly by retrospective analysis. Patients with tuberculosis and AIDS are much more likely to have extrapulmonary involvement, to have non-significant tuberculin tests and to have unusual radiographic features than patients with

normal cellular immunity. The finding that 60% of the patients we reviewed retrospectively had extrapulmonary sites of disease is consistent with the 50-72% frequency of extrapulmonary disease reported by others (6-9). The findings of frequent dissemination to the lymphatic, urogenital and hematologic systems is also consistent with other studies (6-9). For unclear reasons, tuberculosis in patients with AIDS seems not to frequently involve the pleura (7). Studies have not specified pleural fluid sampling rates, however, and pleural effusions, while of less volume, occur as commonly as in cases of tuberculosis not complicated by AIDS (25).

Because of these atypical features, tuberculosis is more difficult to diagnose in the setting of AIDS and may be confused with other infectious diseases. The diffuse pulmonary involvement may be easily mistaken for P. carinii pneumonia. In this regard, it should be noted that neither P. carinii pneumonia nor generalized lymphadenopathy associated with ARC is associated with intrathoracic adenopathy. Thus, the finding of hilar or mediastinal adenopathy in a patient with AIDS is suggestive of tuberculosis or an infectious process other than P. carinii pneumonia. Peripheral lymphadenopathy can also be mistaken for HIV-associated generalized lymphadenopathy. Even when acid-fast bacilli are identified in lymph node biopsies or aspirates they may be assumed to be Mycobacterium avium complex. In patients with HIV infection, acid-fast organisms should be presumed to be M. tuberculosis, and appropriate treatment should be instituted.

HIV-seropositive patients without AIDS identified prospectively

were significantly immunosuppressed on the basis of absolute CD4 lymphocyte counts and CD4 to CD8 lymphocyte ratios. While tuberculosis alone can cause transient inversion of CD4 to CD8 lymphocyte ratios, the ratios usually revert to normal 4 to 6 weeks after beginning treatment (26). Lymphocyte phenotyping in most study patients was done 3 months after the diagnosis of tuberculosis. Thus, it is unlikely that tuberculosis was the cause of lymphocyte abnormalities in seropositive subjects. Rather, it is likely that the CD4 to CD8 ratio inversion and CD4 lymphocyte depletion in seropositive subjects reflected HIV-induced immunosuppression.

Despite immunosuppression, seropositive patients did not exhibit the distinguishing clinical features of tuberculosis seen in patients with AIDS. Seropositive and seronegative patients had similar rates of extrapulmonary tuberculosis, anergy to tuberculin and atypical radiographic features. Although the power to detect significant differences was limited, the only clinical characteristic in which seropositive patients exhibited even a substantial difference from seronegatives was in tuberculin anergy.

Comparison of clinical features of tuberculosis in AIDS patients (those patients identified retrospectively) and in HIV-seropositive patients without AIDS (those patients identified prospectively) illustrate an important point. Clinical features of tuberculosis in the setting of HIV infection reflect the stage of immunosuppression. AIDS patients are more severely immunocomprimised than HIV-seropositive patients without clinical evidence of infection and can be expected to have higher rates of disseminated tuberculosis and other

atypical clinical features.

Interestingly, reports from South Florida showed that HIV-seropositives without AIDS had rates of atypical clinical features paralleling those of AIDS patients with tuberculosis. It is unclear what accounts for differences between this data and data from the current study. It is possible, however, that host factors are responsible: the largely Haitian population of Florida may be more susceptible to disseminated tuberculosis than the American-born San Francisco population.

The Centers for Disease Control currently include extrapulmonary tuberculosis in an HIV-seropositive patient on the list of AIDS-defining diagnoses (23). Three of four HIV-seropositive patients with extrapulmonary tuberculosis identified prospectively were anergic. One had a CD4 lymphocyte count of 23 per milliliter and went on to develop P. carinii pneumonia two months later. Another developed cytomegalovirus retinitis 2 years later. Nevertheless, from this small sample of patients it is not clear if extrapulmonary tuberculosis or tuberculin anergy is generally associated with a greater degree of immunodeficiency and a poorer prognosis than purely pulmonary disease in HIV-infected populations. Additional studies of the natural history of tuberculosis and HIV infection are needed.

Tuberculosis in HIV-seropositive patients, with or without AIDS, responds well to standard antituberculosis chemotherapy. Sputum conversion in HIV-seropositive patients occurred as quickly as in seronegative patients and no seropositive patient relapsed after

completing therapy. Radiographic abnormalities similarly improved and extrapulmonary foci, while usually not sampled to document microbiologic cure, became clinically unapparent. The lack of mortality attributable to treated tuberculosis further demonstrates the efficacy of treatment. Of the opportunistic infections associated with HIV infection, tuberculosis may be the most responsive to treatment. In this regard, however, it must be noted that in three cases of tuberculosis in AIDS patients (two in Newark and one in San Francisco) with central nervous system involvement and one patient with pericardial tuberculosis, disease progression occurred despite appropriate chemotherapy (7). More importantly, one patient successfully treated in Newark for pulmonary tuberculosis relapsed at an extrapulmonary site despite apparent compliance with four-drug chemotherapy (27).

Based in part on these treatment failures as well as the theoretical concern that inadequate host defenses may allow for persistence of microorganisms, current Center for Disease Control recommendations for the treatment of tuberculosis in HIV-seropositive patients are different than those applicable to patients without evidence of HIV infection. In contrast to the 6-month regimen recommended for HIV-seronegative patients with tuberculosis, treatment of HIV-seropositives should continue 9 months and at least 6 months after culture conversion (28). If either isoniazid or rifampin (both bactericidal antimicrobials) is not, or cannot be, included in the treatment regimen, therapy should continue a minimum of 18 months and at least 12 months after

culture conversion (28).

It should be noted that standard four-drug short-course therapy continues to be used in San Francisco for uncomplicated (purely pulmonary) HIV-related tuberculosis with excellent results (GF Schecter, personal communication). Longer follow-up of large numbers of patients is needed to evaluate optimally the efficacy of current antituberculosis regimens in HIV-infected patients with tuberculosis.

Adverse reactions to antituberculosis medications necessitating a change in therapy occurred in a significant number (26%) of patients with AIDS and tuberculosis in San Francisco, compared to the 3% figure reported for patients with tuberculosis without AIDS. In South Florida, liver function test elevations were common in AIDS patients being treated for tuberculosis though only 8% required discontinuing rifampin because of significant hepatitis (10).

Prospective analysis, focusing mainly on HIV-seropositive patients without AIDS being treated for tuberculosis, did not show increased rates of drug toxicity in patients with HIV infection, as both cases and controls had rates close to the rate seen in AIDS patients with tuberculosis. Clinical experience indicates that the 3% figure reported for tuberculosis patients without AIDS was substantially lower than would be expected, reinforcing the conclusion that adverse drug reaction to antituberculosis drugs are not more common in HIV-seropositives. In no case, identified either retrospectively or prospectively, has therapy failed because of an adverse drug reaction.

These data have important clinical and pathophysiologic implications. Tuberculosis is a significant HIV-related disease and appears to occur earlier in the course of progressive immunodeficiency than other HIV-related opportunistic infections. It should be high on the list of differential diagnosis for patients with or at-risk for HIV infection who have suspected pulmonary disease.

In San Francisco, intravenous drug use is increasingly becoming the most common HIV-transmission factor associated with HIV-related tuberculosis. Tuberculin screening should be aggressively pursued in this population and those with tuberculin reactivity started on isoniazid prophylaxis.

Clinical features of tuberculosis in the setting of HIV infection may be either typical or atypical. Extrapulmonary disease, tuberculin anergy and infrequent apical disease on chest radiograph occur most frequently when tuberculosis afflicts patients with other clinical evidence of HIV infection at the time tuberculosis is diagnosed. These patients are severely immunosuppressed and may be infected with opportunistic organisms at or soon after the time of diagnosis of tuberculosis.

Tuberculosis is a curable disease regardless of a patient's HIV serologic status. Prognosis for HIV-infected patients treated for tuberculosis is poor, but reflects the underlying immunosuppression caused by HIV infection rather than complications stemming from tuberculosis.

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TABLE 1

RACIAL/ETHNIC CHARACTERISTICS AND AIDS TRANSMISSION CATEGORIES OF PATIENTS WITH TUBERCULOSIS AND AIDS, TUBERCULOSIS WITHOUT AIDS, AND AIDS WITHOUT TUBERCULOSIS IN SAN FRANCISCO, 1981–1985. ONLY NON-ASIAN-BORN MALES 15 TO 60 YEARS OF AGE ARE INCLUDED IN THE TUBERCULOSIS CATEGORIES

	TB/AIDS	TB/Non-AIDS	AIDS/Non-TB
Racial/ethnic group*			
White	24 (69%)	86 (34%)	1,470 (88%)
Black	6 (17%)	85 (34%)	84 (5%)
Hispanic	5 (14%)	52 (20%)	100 (6%)
Asian	0	12 (5%)	16 (1%)
Native American	0	10 (4%)	0
Other	0	7 (3%)	0
AIDS transmission category†			
Homosexual	28 (80%)	–	1,635 (98%)
IV drug use	6 (17%)	–	10 (0.6%)
Other	1 (3%)	–	25 (1.4%)

* $p < 0.001$ TB/AIDS versus TB/non-AIDS; $p < 0.01$ TB/AIDS versus AIDS/non-TB.
† $p < 0.00001$.

TABLE 2

DIAGNOSTIC STUDIES IN TUBERCULOSIS PATIENTS WITH AND WITHOUT AIDS

	AIDS (n = 35)		Non-AIDS (n = 252)	
	(*n*)	(%)	(*n*)	(%)
Source of positive culture				
Lung	26	74	206	82
Lymph nodes	11	31	17	7
Urine/kidney	5	14	9	4
Blood	4	11	0	
Bone marrow	4	11	2	1
Musculoskeletal	3	9	8	3
Central nervous system	2	6	4	2
Liver	1	3	0	
Skin/soft tissue	1	3	3	1
Gastrointestinal tract	1	3	4	2
Pleura	0		25	10
Larynx	0		3	1
Any extrapulmonary	21	60	71	28*
Extrapulmonary only	9	26	41	16
Skin test response				
Significant (≥ 10 mm)	9	39	117	91†
Non-significant (< 10 mm)	14	61	12	9
Radiographic pattern	AIDS		Controls‡	
Diffuse/miliary	12		7	
Focal/cavitary	7		15	
Adenopathy	4		0	
Effusions	4		5	

* $p < 0.001$.
† $p < 0.0001$.
‡ Age- and sex-matched controls (see text).

TABLE 3

Demographic and immunodeficiency history of eligible patients.

	participants (60)	non-participants (68)
sex:		
male	44 (73%)	43 (63%)
female	16 (27%)	25 (35%)
age:		
18-40	32 (53%)	44 (65%)
>40	28 (47%)	24 (35%)
birthplace:		
United States	47 (78%)	48 (71%)
foreign country	13 (22%)	20 (29%)
race/ethnicity:		
White	20 (33%)	22 (32%)
Black	25 (42%)	24 (35%)
Latino/other	15 (25%)	22 (32%)
AIDS prior to tuberculosis	1 (2%)	7 (10%)

TABLE 4

Demographic and clinical characteristics of tuberculosis patients with and without HIV infection.

characteristic	HIV+ (N=17)	HIV- (N=43)
sex:		
male	16 (94%)	28 (65%)*
female	1 (6%)	15 (35%)
age:		
18-40	14 (82%)	18 (42%)**
>40	3 (18%)	25 (58%)
race/ethnicity:		
White	2 (12%)	18 (42%)
Black	12 (71%)	13 (30%)**
Latino/other	3 (17%)	12 (28%)
birthplace:		
United States	15 (88%)	32 (74%)
other	2 (12%)	11 (26%)
known prior tuberculin reactivity	0 (0%)	14 (33%)
site of disease:		
pulmonary	13 (76%)	31 (72%)
pulmonary and extrapulmonary	4 (24%)	6 (14%)
extrapulmonary only	0 (0%)	6 (14%)
initial sputum evaluation (pulmonary cases):		
smear positive	8 (47%)	19 (51%)
culture positive	15 (88%)	35 (95%)
tuberculin skin test result:		
>/= 10 mm	12 (80%)	27 (93%)
< 10 mm	3 (20%)	2 (7%)
not tested	2	14

*p<0.05
**p<0.01

Table 5

Radiographic characteristics of patients with pulmonary tuberculosis with and without HIV infection (categories not mutually exclusive).

	HIV+ (N=13)	HIV- (N=29)
characteristic:		
focal	6 (46%)	14 (48%)
cavity	4 (31%)	10 (34%)
diffuse	6 (46%)	10 (34%)
miliary	1 (8%)	0 (0%)
effusion	0 (0%)	1 (3%)
adenopathy	0 (0%)	0 (0%)
normal	0 (0%)	5 (17%)

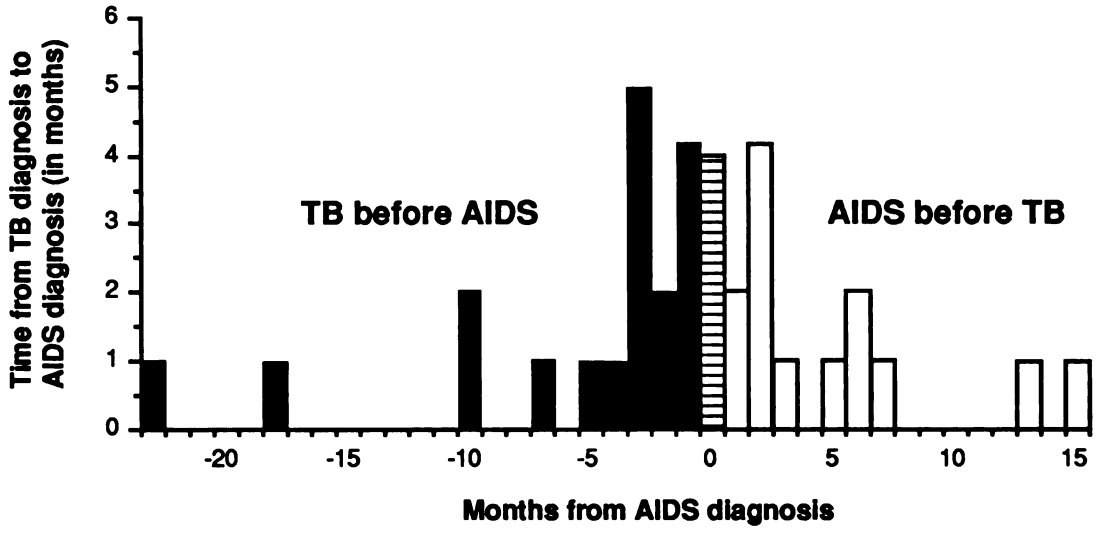

Fig. 1 Time from tuberculosis diagnosis to AIDS diagnosis among non-Asian-born males 15 to 60 years old, 1981-1985. Tuberculosis occurred before AIDS (solid bars), concurrent to AIDS (hatched bar), or after AIDS (open bars).

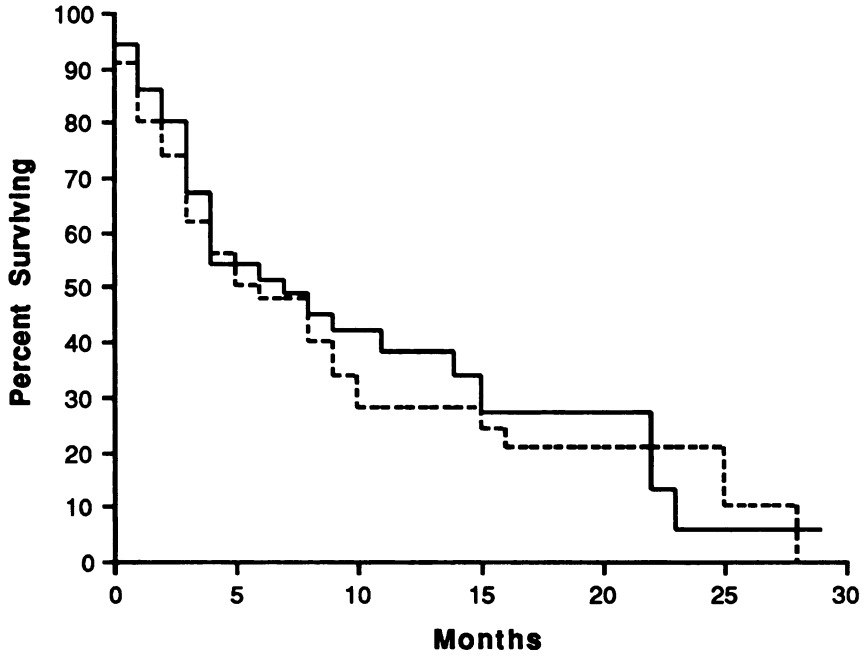

Fig. 2 Survival in AIDS patients with tuberculosis from time that tuberculosis (solid line) and AIDS (interrupted line) were diagnosed

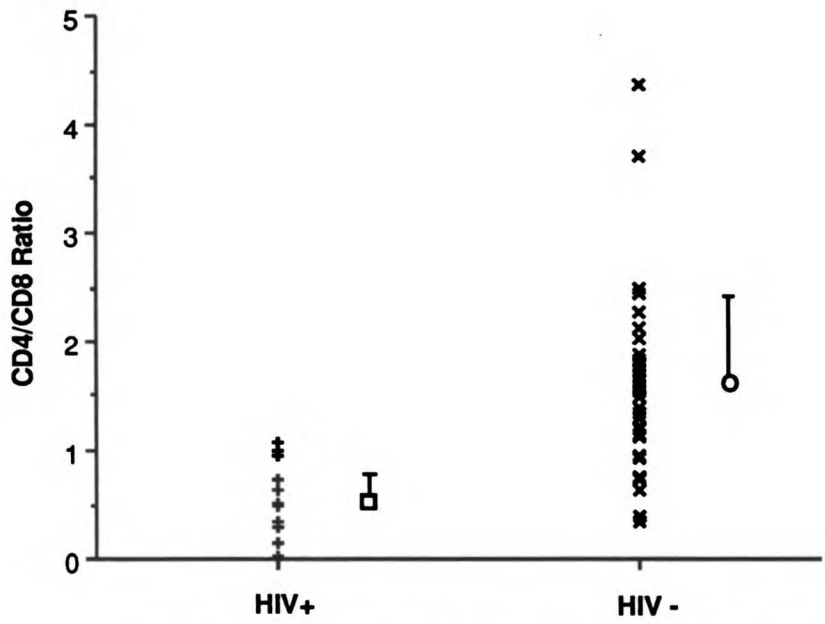

Fig. 3 Comparison of CD4 to CD8 lymphocyte ratios between HIV-seropositive and HIV-seronegative patients with tuberculosis

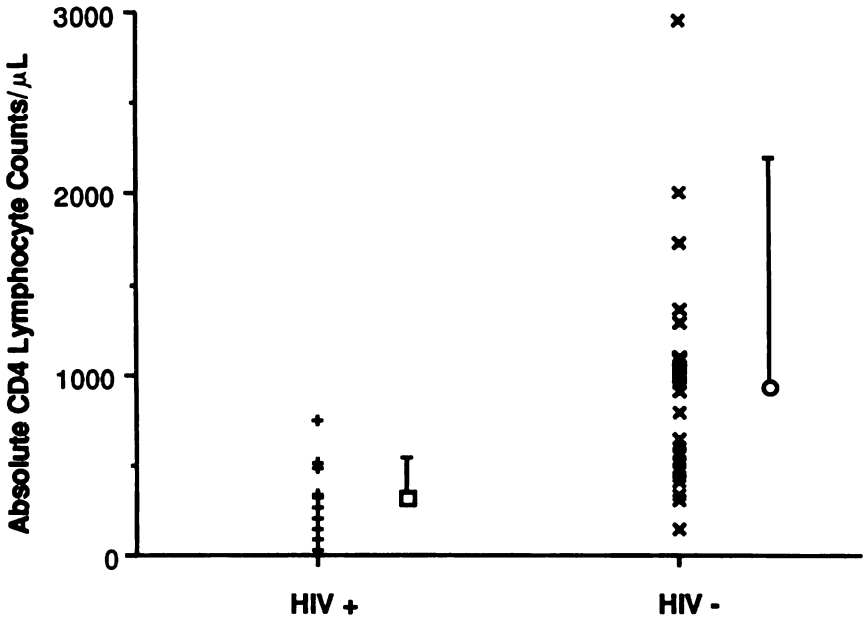

Fig. 4 Comparison of absolute CD4 lymphocyte counts between HIV-seropositive and HIV-seronegative patients with tuberculosis

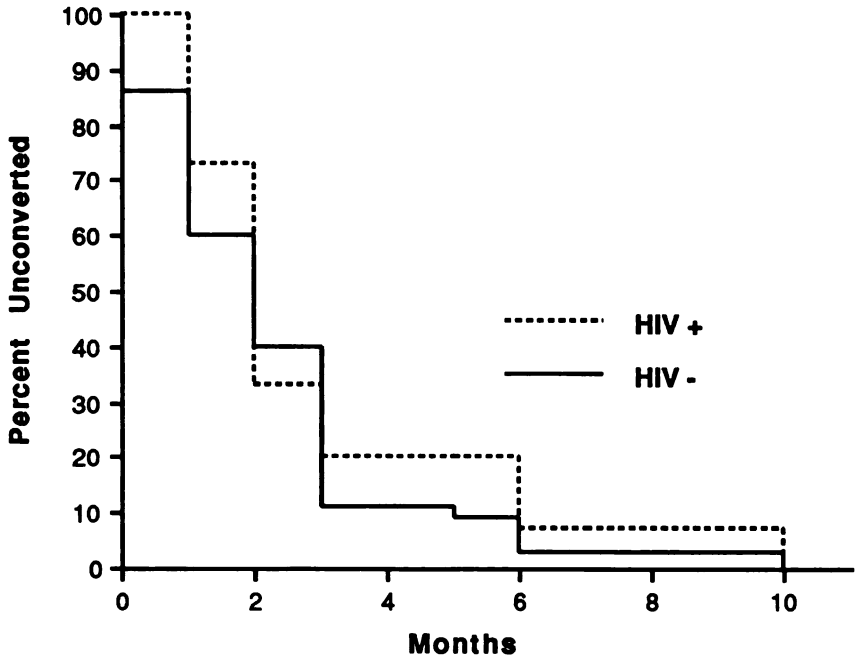

Fig. 5 Sputum conversion in bacteriologically proven pulmonary cases from time of initiation of tuberculosis medications to date of first persistently negative culture and smear