Epidemiology of AIDS and Tuberculosis[1]

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This article reviews literature on the epidemiology, pathogenicity, and control of HIV and Mycobacterium tuberculosis *coinfection. Regarding pathogenicity, immune system deterioration makes HIV-infected people more likely to develop active tuberculosis on primary or secondary exposure to the bacillus or to suffer reactivation of latent infections, and to experience considerably higher rates of extrapulmonary manifestations, relapses, and death. Regarding epidemiology, as of 1990 there were an estimated 3 million people coinfected with HIV and* M. tuberculosis, *with some 300 000 active tuberculosis cases and 120 000–150 000 tuberculosis deaths occurring annually among those coinfected. Over 500 000 coinfected people are thought to reside in the Americas, over 400 000 of them in Latin America.*

In general, the impact of coinfection is evident. Relatively high and increasing prevalences of HIV infection have been detected among tuberculosis patients around the world, and tuberculosis has become a frequent complication of AIDS cases. Moreover, there is no longer any doubt that coinfection obstructs tuberculosis prevention and control. Among other things, it affects BCG vaccination policies, suggests the need to administer preventive chemoprophylaxis to HIV-infected individuals at high risk of harboring or contracting tuberculosis infections, and complicates both detection and treatment of active tuberculosis cases. The recent proliferation of M. tuberculosis *strains resistant to multiple drugs, most notably in the United States, compounds the problem.*

Tuberculosis prevention and control are still technically and economically feasible. However, more must be done to establish surveillance programs with laboratory support. More research is needed to determine what case prevention measures are best-suited to current circumstances and the HIV/AIDS presence. More effective preventive treatment regimens that are well tolerated, well complied with, and do not pose the risk of multiresistance need to be devised. More health workers need to be trained to suspect tuberculosis and to conduct timely and appropriate tests confirming this diagnosis. And finally, more must be done to standardize the types and durations of the various curative treatment regimens employed.

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The HIV/AIDS epidemic has had a major impact on the epidemiology of tuberculosis around the world—including the Americas, where its consequences have been observed in both industrialized and developing countries. This article reviews certain pathogenic aspects of the interrelationship between infections caused by the human immunodeficiency virus (HIV) and *Mycobacterium tuberculosis*. It then analyzes the epidemiologic status of coinfection worldwide, particularly in the Americas, and examines the problems confronting

efforts to control tuberculosis following the appearance of coinfection.

HIV AND *M. TUBERCULOSIS* COINFECTION: PATHOGENIC CONSIDERATIONS

The progression from infection with *M. tuberculosis* through tuberculous disease has been described thoroughly. In countries where the tuberculosis prevalence is high, infection generally occurs in early infancy. Less than 10% of the individuals infected with *M. tuberculosis* subsequently develop active tuberculosis after an interval ranging from 1 to 50 years (*1–3*). Activation of the infection is contingent upon the integrity of the host's immune system. Advanced age (*4*), pregnancy, associated diseases such as diabetes mellitus (*5*), and treatment with corticosteroids (*6*) have all been associated with development of active tuberculosis. The ensuing lethality of the disease, however, depends primarily on access to health services. In a pattern strongly reflecting the presence or absence of such access, it is typical for between 10% and 50% of those with active cases to die after an interval ranging from 1 to 10 years (*7*).

Knowledge of the natural history of HIV infection has progressed considerably in recent years. At present, it is believed that some 44% of those infected with HIV as a result of sexual transmission develop AIDS within a 13-year period. Over 90% of those with AIDS then die after an interval generally ranging from 6 months to 2 years, though intervals exceeding 2 years have been reported (*8*).

The natural history of *M. tuberculosis* and HIV infection changes when both infections coexist in the same individual. Some studies have pointed out that the likelihood of an HIV-infected individual contracting tuberculosis upon exposure to the bacillus is greater than that of an individual uninfected with HIV. Similarly, once tuberculosis infection has been contracted, the presence of an HIV infection increases the subject's chances of developing active tuberculosis (*9, 10*). Along these lines, a study conducted by Daley et al. (*9*) found that at least 50% of a group of HIV-positive patients exposed to *M. tuberculosis* contracted tuberculosis infection and 37% developed active tuberculosis. These frequencies are higher than those that would normally be expected among uninfected individuals.

Molecular biology techniques have made it possible to demonstrate exogenous reinfection and development of active tuberculosis among individuals who have had the disease previously. Small et al. (*11*), by using a "DNA fingerprinting" technique—restriction fragment length polymorphism (RFLP) analysis—demonstrated the existence of reinfections caused by multiresistant strains in HIV-positive patients who had already been treated for a prior episode of tuberculosis caused by sensitive strains. These studies indicate that such patients do not develop immunity and accordingly become reinfected upon reexposure to the tuberculosis bacillus.

A relationship between HIV and *M. tuberculosis* infections is also evident in cases where the bacillus is reactivated following deterioration of an HIV-positive host's immune system. *M. tuberculosis* had been identified as a potential opportunistic agent even before the advent of the AIDS era. In connection with HIV, its high pathogenicity reflects the fact that it becomes active before other opportunistic agents such as *Pneumocystis carinii* or *Toxoplasma gondii*. In this regard, it is noteworthy that the CD4 lymphocyte counts in coinfected patients are higher (between 300 and 400/mm^3) following development of active tuberculosis (*12*).

At present, HIV infection constitutes one of the most important risk factors determining whether an individual with signs of tuberculous infection, such as cutaneous reactivity to PPD, will develop

active tuberculosis. Selwyn et al. (*13*) have demonstrated the risk that HIV infection represents for the development of tuberculosis in coinfected subjects. These authors studied a group of intravenous drug users. Among other things, they found that HIV-infected individuals' risk of developing tuberculosis was 26 times higher if they had positive PPD skin test results than if they had negative results. Again studying intravenous drug users, Selwyn and colleagues (*14*) found that when an HIV-infected individual's negative response to PPD was associated with anergy to other cutaneous immunogens, that person's risk of developing tuberculosis was relatively high. Moreover, when these coinfected patients developed tuberculosis, the clinical characteristics of the disease were found to differ from those observed in individuals who were not coinfected. Notably, extrapulmonary localizations (including miliary tuberculosis and infections involving the lymphatic system, central nervous system, soft tissues, bone marrow, genitourinary tract, liver, or blood) were found to be more frequent. Specifically, the frequency of extrapulmonary manifestations was found to be 15% in subjects not infected with HIV, 20–40% in asymptomatic HIV-positive individuals, and 70% in AIDS patients (*15*).

Other authors have found that 71% of a group of tuberculosis patients coinfected with HIV exhibited extrapulmonary manifestations (*16, 17*). Morais et al. found that 18.3% of 420 HIV-infected patients in Rio de Janeiro had extrapulmonary tuberculosis (*18*). Casiro et al. (*19*) estimated that 40% of the AIDS patients in Argentina in 1982–1990 had disseminated tuberculosis, and that in the year 1991 this percentage reached 60.6%. On the other hand, the frequencies of pulmonary tuberculosis found for these two periods were 25.7% and 21.2%, respectively, and those for tuberculous lymphadenitis were 17.1% and 9%, respectively.

The percentage of tuberculosis relapses in HIV-positive individuals is also higher. As Table 1 indicates, it has been estimated that such patients suffer relapses between 3.7 and 16 times more frequently than those who are not HIV-positive. Specifically, Hawken et al., studying subjects in Kenya, found that relapses were 16 times more frequent in HIV-positive patients with tuberculosis (*20*). Idigbe et al., studying the frequency of tuberculosis relapses among HIV-infected patients in Nigeria, found that compared to HIV-negative subjects the relative risk of relapse was 3.6 among those infected with HIV-1, 1.7 among those infected with HIV-2, and 4 among those coinfected with HIV-1 and HIV-2 (*21*). And Nunn et al., working with subjects in Nairobi, estimated that HIV-positive patients suffered tuberculosis relapses 13 times more frequently than those who were HIV-negative (*22*).

Table 1. The frequency of tuberculosis relapse among HIV-positive and HIV-negative patients as reported by several studies in Africa, showing the relative risks and 95% confidence intervals derived from these data.

Authors	Year of report	Place	Patients (No.)	% relapses HIV+	% relapses HIV−	Relative risk	95% CI
Hawken et al. (*20*)	1992	Nairobi	209	16 per 100 person-years	0.7 per 100 person-years	16	2.4–677
Idigbe et al. (*21*)	1992	Nigeria	75	37	10	3.7	—
Nunn et al. (*22*)	1992	Nairobi	—	—	—	13	1.6–102

In addition, as indicated in Table 2, a number of authors have reported that the mortality produced by active tuberculosis cases is 2.7 to 19 times higher in HIV-positive subjects than in those who are HIV-negative. Kibuga and Gathua (1990) estimated that mortality in Nairobi was 3.4 times higher among tuberculosis patients who were HIV-positive (*23*). Yesso et al. in Abidjan (1991) and Stoneburner et al. in New York (1992) estimated that mortality was 7 to 7.5 times higher among tuberculosis patients who were HIV-positive (*24, 25*). Mukadi et al. (1990) in Kinshasa found that tuberculosis mortality was 18 times higher among HIV-positive subjects (*26*). And various studies conducted in a number of African countries that were reported in 1992—Hawken et al. (*20*), Idigbe et al. (*21*), Nunn et al. (*27*), and Kassim et al. (*28*)—also detected higher mortality from tuberculosis cases among HIV-infected patients.

Specific mortality rates for HIV-infected tuberculosis patients are not comparable between studies, as the types of patients and follow-up times differ. For example, Stoneburner et al. (*25*) followed a hospitalized cohort of male intravenous drug users and determined their mortality from 1985 through 1991. Their data are not generalizable to tuberculosis patients diagnosed in outpatient clinics or to other populations and regions. These studies do show, however, that mortality rates are higher among coinfected patients than among noncoinfected patients.

It should also be noted that mortality among coinfected individuals has not been associated with tuberculosis in all cases. Some studies have found that excess mortality is not associated with the failure of antituberculous treatment. In particular, Nunn et al. found that most deaths were the result of bacteremias and not tuberculosis (*27*).

It has been suggested by some that *M. tuberculosis* infection could stimulate the replication of HIV, as it has been observed that this mycobacterium activates HIV expression *in vitro* (*29*). According to this hypothesis, *M. tuberculosis* infection *in vivo* could activate HIV replication and accelerate progression of the clinical picture.

HIV-2 AND *M. TUBERCULOSIS* COINFECTION

The frequency of HIV-2 in the Americas is low. In 1992 Ueda reported results

Table 2. Tuberculosis mortality among HIV-positive and HIV-negative patients as reported by eight studies in Africa and the United States, showing the relative risks and 95% confidence intervals derived from these data.

Authors	Year of report	Place	Patients (No.)	Mortality		Relative risk	95% CI
				HIV+	HIV−		
Kibuga and Gathua (*23*)	1990	Nairobi	210	42%	12.4%	3.4	2.4–10.9
Mukadi et al. (*26*)	1990	Kinshasa	273	13.6%	0.75%	18.1	2.8–97.7
Yesso et al. (*24*)	1991	Abidjan	455	25.5%	3.6%	7.0	—
Stoneburner et al. (*25*)	1992	New York	57	83%	11%	7.5	2.3–11.6
Hawken et al. (*20*)	1992	Nairobi	199	19%	1%	19	4.1–140
Idigbe et al. (*21*)	1992	Nigeria	75	18%	7.5%	2.7	0.2–27.2
Nunn et al. (*27*)	1992	Kenya	281	32.7%	7.5%	4.4	2.4–7.9
Kassim et al. (*28*)	1992	Abidjan	—	23.8%	1.6%	14.9	—

from a study of 222 high-risk individuals examined at the Referral Center of São Paulo, Brazil, in order to evaluate the presence of HIV-2 antibodies. The author found that 30.6% were seropositive for this virus. However, a search for antibodies inhibiting the reverse transcriptase of HIV-2 indicated that only 3.1% of all of the samples analyzed possessed anti-HIV-2 antibodies (*30*). Santos et al., also in Brazil, analyzed 748 blood samples taken from adults with seropositivity for HIV-1. None were seropositive for HIV-2 (*31*).

Comparative studies have been conducted on coinfection with *M. tuberculosis* and both retroviruses. Gnaore et al., working in Côte d'Ivoire, reported in 1991 that tuberculous patients exhibited a higher frequency of HIV-1 infection (30%) than of either HIV-2 infection (4.3%) or coinfection with both retroviruses (9%) (*32*). Also in Côte d'Ivoire, Yesso et al. (*24*) reported in 1991 that the highest lethality rate was found among tuberculosis patients with HIV-1 infection (25.5 deaths per 100 person-years), followed closely by that among tuberculosis patients infected with both retroviruses (20.2 deaths per 100 person-years). By comparison, a far lower lethality rate (4.6 deaths per 100 person-years) was observed among tuberculosis patients infected with HIV-2. These studies indicate that the presence of HIV-1 and active tuberculosis exhibits greater pathogenicity than the presence of HIV-2 and active tuberculosis.

PREVALENCES OF TUBERCULOSIS, HIV/AIDS, AND COINFECTION

Table 3 shows WHO Tuberculosis Unit estimates of the worldwide prevalence of tuberculous infection and annual tuberculosis morbidity and mortality (*33*). The estimate for tuberculosis infections in 1990 (1 722 million infections) was calculated using a model that took the annual risks of tuberculosis infection for different age groups, assessed by surveys conducted during the 10 preceding years, and applied these risks (by age group) to the general population. It was also estimated that 8 million new cases of tuberculosis occurred throughout the world in 1990. This latter estimate was derived from two assumptions—regarding the number of bacillipherous cases per unit of annual risk of infection and the number of cases with negative bacilloscopy for each bacillipherous case. Finally, it was estimated that between 2.6 and 2.9 million deaths from tuberculosis occurred in 1990. This estimate, based on the apparent degree of health services coverage, was calculated by comparing the number of cases reported to the number expected in 1990 and assuming that the total number of deaths equals 50% of the untreated (un-

Table 3. Estimated worldwide cases of infection, morbidity, and mortality attributed to tuberculosis, HIV/AIDS, and tuberculosis/HIV coinfection.

	Tuberculosis (1990)	HIV/AIDS (1993)	Tuberculosis/HIV coinfection (1990)
Infection	1 722 million (prevalence)	>14 million (cumulative)	3 million (cumulative)
Disease	8 million cases per year	>2.5 million cases (cumulative)	305 000 cases per year
Mortality	2.6–2.9 million deaths per year	2 million deaths (cumulative)	120 000–150 000 deaths per year

Sources: World Health Organization documents WHO/TUB/91.158 and WHO/GPA/CNP/EUA/93.1 (*33, 35*).

reported) cases plus 15% of those reported. More recently (*34*), a group of WHO experts estimated that 90 million new tuberculosis cases would occur between the years 1990 and 2000 and that the number of tuberculosis deaths in this period would total 30 million, of which 22 000 would occur in North America and 1 210 000 in Latin America and the Caribbean.

With regard to the prevalence of HIV infection and AIDS morbidity and mortality, the WHO Global Program on AIDS has noted that as of January 1993 more than 600 000 cases of AIDS had been reported worldwide. However, the actual cumulative figure, taking into account underrecording, reporting delays, and diagnostic errors, was estimated to exceed 2.5 million cases as of June 1993 (*35*). The cumulative total number of deaths from AIDS as of 1993 was estimated at 2 million (see Table 3). In addition, it was estimated that the cumulative number of HIV-infected individuals throughout the world as of June 1993 totaled more than 14 million, based on studies of the HIV infection's prevalence in diverse groups and regions, the estimated size of those groups, the infection's prevalence in neighboring regions, and time trends.

Regarding coinfection with HIV, the WHO Tuberculosis Unit estimated that the cumulative number of individuals coinfected with HIV and *M. tuberculosis* as of 1990 totaled 3 million (*33*). This figure was calculated from the tuberculosis infection prevalence found among subjects between the ages of 15 and 49 who were presumably infected with HIV. It was also estimated (assuming an annual rate of tuberculosis development of 10% in coinfected people) that roughly 300 000 coinfected individuals developed active tuberculosis cases in 1990. Finally, it was estimated that between 120 000 and 150 000 deaths from tuberculosis occurred among coinfected individuals in 1990. In calculating these latter figures, two criteria were used. The lower (120 000) figure was calculated the same way tuberculosis mortality was calculated for individuals uninfected with HIV, assuming 50% lethality in untreated (unreported) cases and 15% in reported cases. The higher (150 000) figure was calculated assuming 50% lethality among tuberculosis patients with HIV infection, irrespective of treatment.

The distribution of coinfected cases differs in different regions and is determined by the prevalence of tuberculosis in specific regions. In Europe, it is estimated that there are some 500 000 HIV-positive people, of whom 55 000 may be coinfected with *M. tuberculosis*. Africa has the highest number of HIV-infected individuals (8 million), of whom 3.8 million may be coinfected. Similarly, it has been estimated that some 1 million HIV-infected individuals live in the United States and Canada, while another 1.5 million reside in other countries of the Americas. However, because of the higher prevalence of tuberculosis infections, the estimate for coinfected people in these latter countries is almost four times that for coinfected people in Canada and the United States (450 000 as compared to 110 000) (*33, 35*).

THE IMPACT OF COINFECTION

The impact of HIV upon tuberculosis is clearly visible. Consider the example of the United States, where a system for epidemiologic tuberculosis surveillance began operating in 1953. This system made it possible to detect a leveling off in the prevailing downward trend of tuberculosis mortality in 1985. Since then, a rising trend in the number of new tuberculosis cases in the United States has been observed. Also, an analysis by ethnic groups has indicated that blacks, Hispanics, and other ethnic minorities account for a higher percentage of coinfected tuberculosis-AIDS patients than of total AIDS patients. It thus appears that

the greatest number of coinfected cases in the United States has occurred among ethnic groups that traditionally exhibit higher prevalences of tuberculosis than the general population (*36*).

In other countries of the Americas, no dramatic impact on overall tuberculosis morbidity has emerged. In Mexico, for example, reported tuberculosis morbidity has decreased in recent years—from 16.1 cases per 100 000 inhabitants in 1980 to 10.0 cases in 1992 (*37*).

However, the impact of tuberculosis on HIV infection has manifested itself to a greater extent in certain African countries, where the prevalence of both infections is among the highest in the world. In Tanzania, for example, the surveillance system detected an increase of 43.7% in new tuberculosis cases over the 1979–1989 period. Of these, 32.7% involved patients with positive bacilloscopies, a finding of particular significance in terms of the contagiousness of the disease (*38*).

Coinfection analysis can be conducted from a number of different standpoints. HIV infection frequency in patients diagnosed as having active tuberculosis for the first time is a useful indicator. Relatively high and increasing prevalences of HIV infection among tuberculosis patients have been detected in a number of different countries (Table 4). In the United States, Laroche et al. analyzed tuberculosis cases reported to the New York State epidemiologic surveillance system. Their analysis, based on 1979–1985 and 1979–1988 data, found HIV infection frequencies of 2.2% for the 1979–1985 period and 8.1% for the 1979–1988 period (*39*). More broadly, the United States Centers for Disease Control conducted sentinel studies at 20 clinics providing medical care to tuberculosis patients in 14 cities during 1988–1989. These studies indicated a median clinic seroprevalence of HIV infection among 3 077 patients of 3.4% within a range of values extending from 0% to 46.3%. Estimated prevalences for the Northeast and Atlantic Coast regions were relatively high (*40*).

Elsewhere in the Americas, in 1989 Clermont et al. found that 39% of 143 tuberculosis patients in a poor urban area of Haiti were infected with HIV (*41*). In Mexico, sentinel studies conducted by the Ministry of Health in 11 states from 1990–1993 have found HIV seroprevalences in tuberculosis patients ranging from 0% to 5% (*42*). In Brazil, Ribeiro et al. reported that 453 tuberculosis patients seen at a health center in 1987–1988 had an HIV infection prevalence of approximately 3.3% (*43*). Thus, while the highest prev-

Table 4. Prevalences of HIV infection in tuberculous patients found by various surveys in the United States, Latin America, France, and Africa.

Place	Year	Patients (No.)	Prevalence (%)	Authors
New York, U.S.A.	1979–1985	11 640	2.2	Laroche et al. (*39*)
"	1979–1988	13 820	8.1	"
U.S.A. (14 cities)	1988–1989	3 077	0–46.3	Onorato et al. (*40*)
Haiti	1989	143	39	Clermont et al. (*41*)
Mexico	1992	1 201	0–5	Valdespino et al. (*42*)
Brazil	1987–1988	453	3.3	Ribeiro et al. (*43*)
Nairobi, Kenya	1989	240	30	Nunn et al. (*44*)
Burkina Faso	1988–1990	573	22.7	Malkin et al. (*45*)
Abidjan, Côte d'Ivoire	1989	263	11.8	Sassan et al. (*47*)
Zimbabwe	1988–1989	927	40.1	Mahari et al. (*49*)
France	1985–1990	68	53	Beaulieu et al. (*50*)

alences of HIV infection among tuberculosis patients in the Americas have been detected in U.S. cities, prevalences found in other countries (principally those cited above) are also noteworthy.

In parts of Africa, very high prevalences of HIV infection have been reported among tuberculosis patients. Studies conducted in Nairobi, Kenya, by Nunn et al. in 1989 found an HIV infection prevalence of 30% among 240 tuberculosis patients (*44*). In Burkina Faso, Malkin et al. found an HIV infection prevalence of 22.7% among 573 patients followed from 1988 to 1990 at a regional tuberculosis treatment center (*45*). In a related work, Malkin et al. reported annual increases of HIV prevalences in tuberculosis patients of 12.5%, 22.5%, 29.3%, and 23.5% for the years 1987, 1988, 1989, and 1990, respectively (*46*). At tuberculosis treatment centers in Abidjan, Côte d'Ivoire, Sassan et al. found an HIV infection prevalence of 11.8% (10.3% for HIV-1, 0.4% for HIV-2, and 1.1% for HIV-1 and HIV-2 combined) among 263 pediatric tuberculosis patients as compared to an HIV prevalence of 2.6% among apparently healthy children seen at the clinic (*47*). In the same country, Yesso et al. (*48*) reviewed the records of all outpatients treated for tuberculosis at two tuberculosis treatment centers in Abidjan during the 1985–1989 period. For 1989 the observed prevalences of HIV infection by sex and age group were 19% for males under age 20, 47% for males 20–39, 53% for males 40 and over, and 22%, 37%, and 21%, respectively, for females in these age groups. Among the 1989 patients, the rate of HIV infection was significantly higher in those seen for a second episode of tuberculosis (65%) than in those seen for the first time (39%; $P < 0.001$). These data indicate that the probability of reinfection and relapse was highest in the HIV-infected group. In Zimbabwe, a 1988–1989 study by Mahari et al. (*49*) examined 927 tuberculosis patients in an urban area for HIV infection. The observed prevalence of HIV infection was 40.1%.

Africa is not the only area where very high prevalences of HIV infection have been found in tuberculosis patients. In France, Beaulieu et al. reviewed the clinical files of 68 tuberculosis patients seen at a hospital center from 1985 to 1990. The estimated prevalence of HIV infection in these patients was 53% (*50*).

Another useful indicator is the frequency of active tuberculosis in AIDS patients. As might be expected, examination of available data for regional variations indicates that the prevalence of tuberculosis in AIDS patients is highest in countries with a high frequency of tuberculosis infection (Table 5).

In Mexico, trend analysis of AIDS and tuberculosis cases based on data from the National Case Register has shown that AIDS cases with tuberculosis as their initial manifestation were infrequent in the early years of the epidemic. During the 1987–1990 period, 6.7% of all AIDS cases had a tuberculosis infection at the time of reporting (*51, 52*). This frequency increased to 10.6% for 1991–1993 (*53*). Initially, the AIDS epidemic tended to affect individuals with relatively high socioeconomic status, in whom the frequency of *M. tuberculosis* infection was lower. Since then, however, the disease has gradually extended to individuals with lower socioeconomic status who reside in suburban and rural areas, among whom the frequency of *M. tuberculosis* infection is higher.

Tuberculosis has come to constitute the most frequent endemic infection among Mexican AIDS patients at the time of reporting (*54–56*). It has also been found that the proportions of young adults, intravenous drug users, and fatalities (*57*), as well as individuals with low socioeconomic status (*58*), are higher among patients with AIDS-tuberculosis coinfection than among all patients with AIDS. In

Table 5. Tuberculosis frequencies among AIDS patients found by various surveys in Latin America, Mozambique, and Europe.

Place	Years	Patients (No.)	Prevalence (%)	Authors
Mexico	1983 to 1992	1 017	8.3	García et al. (53)
Mexico	1986 to 1991	310	50	Romo & Salido (59)
Mexico	1983 to 1987	93	4	Ruiz Palacios et al. (60)
Mexico	1984 to 1989	650	7.7	Cano et al. (61)
Mexico	1985 to 1988	58*	27	Jessurrum et al. (62)
Mexico	1984 to 1988	177*	25	Mohar et al. (63)
Brazil	1982 to 1984	150	8	Chequer et al. (64)
Brazil	1988	Not available	22	"
Brazil	1986 to 1988	42	33.3	De Paula et al. (65)
Brazil	1983 to 1991	142*	40	Brandão-Mello et al. (66)
Argentina	1988 (publication date)	53	18.9	Cahn et al. (67)
Dominican Republic	1983 to 1991	1 420	13	Ducos et al. (68)
Colombia	1992 (publication date)	27	18.5	Estrada et al. (69)
Mozambique	1986 to 1991	340	24	Fernandes et al. (70)
San Sebastián, Spain	1985 to 1988	112	36	Iribarren et al. (72)
France	1982 to 1988	427	12	Chrétien & Papillon (74)
Frankfurt	1984 to 1988	328	37	Müller et al. (76)
Italy	1986 to 1988	42	24	Piersantelli & Guida (78)
Austria	1985 to 1989	Not available	30	Simader et al. (79)

*Autopsy studies.

this same vein, the frequency of tuberculosis among hospitalized AIDS patients with low socioeconomic status appears higher than it does among AIDS patients with relatively higher socioeconomic status. Specifically, Romo and Salido, surveying patients at a Mexico City hospital specialized in caring for the underprivileged, estimated that between 1986 and 1991 the frequency of tuberculosis among AIDS patients was 50% (*59*). In contrast, Ruiz Palacios et al. found *M. tuberculosis* and *Mycobacterium* spp. infecting only 4% and 26.8%, respectively, of 93 AIDS patients at a Mexico City referral hospital (*60*). Similarly, Cano et al. found that only 7.7% of 650 AIDS patients had tuberculosis at a Mexico City Social Security Hospital that gives medical care to people with established jobs (*61*).

Also in Mexico, high frequencies of tuberculosis infection have been found among AIDS patients at autopsy. Jessurrum et al. found a tuberculosis prevalence of 27% in 58 autopsies conducted between 1985 and 1988 at a Mexican general hospital providing care to poor patients (*62*). Similarly, Mohar et al. reported finding a tuberculosis incidence of 25% in 177 autopsies performed on AIDS patients at several Mexico City hospitals between 1984 and 1988 (*63*).

In Brazil, Chequer et al. analyzed cases reported to the national epidemiologic surveillance system from 1982 to 1988. The percentage of active tuberculosis among AIDS cases increased during this period from 8% in 1982 to 1984 to 22% in 1988 (*64*). Also in Brazil, De Paula et al. followed 42 children with AIDS between 1986 and 1988. They found that 33.3% of these subjects developed pulmonary tuberculosis. The authors attribute the increased frequency of infection to the high prevalence of tuberculosis in the country (*65*). As in Mexico, a relatively high frequency of tuberculosis infection was detected at autopsy. Specifically, Brandão-Mello et al. recorded a 40% frequency of *M. tuberculosis* infection in

142 AIDS patient autopsies that were performed between 1983 and 1991 (*66*). The relatively high frequency of tuberculosis infections detected at autopsy suggests that a considerable number of active tuberculosis cases among AIDS patients are probably not diagnosed during the patients' lifetimes.

In Argentina, Cahn et al. reported that 10 of 53 AIDS cases exhibited disseminated tuberculosis. The authors concluded that disseminated tuberculosis is an indicator of AIDS in Argentina and the second most frequently observed AIDS-related opportunistic infection (*67*).

In the Dominican Republic, Ducos et al. found the frequency of tuberculosis infection among AIDS cases reported to the National Surveillance System from 1983 to 1991 to be 13% (*68*).

In Colombia, Estrada et al. studied 27 patients with AIDS to determine the etiology of pulmonary infection; 18.5% were found to have *M. tuberculosis* infections (*69*).

Relatively few studies of this sort have been conducted in Africa. In Mozambique, Fernandes et al. found the prevalence of tuberculosis among a group of AIDS patients to be 24% (*70*). This figure probably understates the magnitude of the problem in that region.

In Europe, various published studies indicate that the frequency of tuberculosis among AIDS patients is considerable.

In Spain, Casabona et al. analyzed cases reported to the AIDS Epidemiologic Surveillance System in Catalonia during 1988–1989. They found that the sole criterion for AIDS diagnosis in 40.7% of the study cases was extrapulmonary tuberculosis, and that another 23% of the cases presented extrapulmonary tuberculosis associated with some other opportunistic infection (*71*). In San Sebastián, Spain, Iribarren et al. conducted a prospective study on 112 AIDS patients at a hospital center, finding a tuberculosis frequency of 36% (*72*). In Barcelona, Spain, Ruiz et al. studied 55 patients with AIDS who had abdominal lymphadenopathy diagnosed by echography. In 43 out of 45 (95%), the authors observed that disseminated tuberculosis coexisted with Kaposi's sarcoma (*73*).

In France, Chrétien and Papillon studied 427 pneumology service patients at a Paris hospital center between 1982 and 1988. They found the tuberculosis frequency to be 12% among patients with AIDS and 7.5% among HIV-positive patients (*74*). Also in France, Lüizzi et al. studied 258 HIV-positive subjects in whom the observed tuberculosis prevalence was 4.6% (*75*).

In Germany, Müller et al. reported that the frequency of tuberculosis among 328 AIDS patients in Frankfurt during 1984–1988 was 37% (*76*). Heise et al., describing the microbiologic findings for 330 HIV-positive patients in Berlin, confirmed the diagnosis of mycobacteriosis in 21.2%. However, 80% of these infections were due to nontuberculous mycobacteria (*77*).

In Italy, Piersantelli and Guida conducted a study on 42 AIDS patients in the 1986–1988 period, 24% of whom were diagnosed as having pulmonary tuberculosis (*78*). This finding contrasts with that of other studies which have identified disseminated tuberculosis as the most frequently observed tuberculous infection of AIDS patients.

In Austria, Simader et al. observed that 30% of the AIDS patients seen at a hospital from 1985 to 1989 were initially seen for extrapulmonary tuberculosis (adenitis, meningitis, miliary tuberculosis). *M. tuberculosis* was isolated in all cases (*79*).

These studies of the tuberculosis frequency among subjects with HIV and AIDS are not generally comparable—because of differences in the types of patients studied, primarily with regard to the degree of immunodeficiency developed, the type of tuberculosis involved (pulmonary or disseminated), and the bacteriologic results. However, virtually

Table 6. The prevalence of PPD reactivity among HIV-positive and HIV-negative subjects as reported by studies in the United States, Mexico, and Italy.

Authors	Year of report	Country	Subjects (No.)	PPD positive (%)	
				HIV+	HIV−
Graham et al. (*81*)	1992	United States	260	13.8	25.2
Canessa et al. (*82*)	1990	Italy	145	17.5	34
García et al. (*80*)	1993	Mexico	375	24	53

all of the studies found the tuberculosis frequency to be high, especially among AIDS patients.

Theoretically, a third indicator of coinfection is PPD reactivity among HIV-positive groups. However, PPD reactivity is determined by two factors: prior infection with the tubercle bacillus and the integrity of the tested individual's cellular immunity. In coinfected patients, PPD reactivity decreases as immunodeficiency progresses.

In studies involving only asymptomatic patients, high prevalences of PPD reactivity related to the prevalence of tuberculosis infection have been reported (Table 6). In Mexico, investigators found a positive PPD response among 24% of 258 HIV-infected subjects and among 53% of 117 uninfected subjects (*80*). In the United States, Graham et al. have carried out PPD testing among intravenous drug users. A positive response (diameter of induration 5 mm) was obtained in 13.8% of the 109 HIV-seropositive cases and 25.2% of the 151 seronegative cases ($P < 0.02$) (*81*). In a study conducted on prisoners in Italy, Canessa et al. observed PPD reactivities of 17.5% in 40 HIV-seropositive subjects and 34% in 105 uninfected (HIV-negative) subjects (*82*).

TUBERCULOSIS CONTROL

The tools available for tuberculosis control vary in accordance with the particular stage of the disease. In order to prevent active disease prior to onset of *M. tuberculosis* infection, the instrument available is vaccination of children with BCG (*83*). WHO recommends that BCG vaccine be administered to neonates in regions where the prevalence of *M. tuberculosis* infection is high. However, administration of the vaccine is contraindicated for older children and asymptomatic adults, as cases have been reported of *M. bovis* dissemination in subjects with HIV infection to whom the vaccine was administered (*84*).

In the case of susceptible contacts or subjects who have positive PPD results and appear at risk of developing active tuberculosis, the tool available for preventing development of tuberculosis is chemoprophylaxis (*85, 86*). Since 1989, the U.S. Centers for Disease Control and Prevention have recommended administering isoniazid to HIV-infected individuals with positive PPD reactivity (diameter of induration ≥ 5 mm) or the existence of confirmed anergy who belong to groups at risk for tuberculosis (*85, 86*). Recently, PAHO has broadened this recommendation and suggested the administration of chemoprophylaxis with isoniazid to all HIV-positive subjects, regardless of the results of PPD reactivity testing, who reside in regions where tuberculosis is highly endemic (*87*). It is also recommended that people residing in regions of low tuberculosis endemicity receive chemoprophylaxis in accordance with the results of a PPD test. This recommendation underscores the need to consider the local epidemiologic status of both diseases as well as the results of future research studies.

Although the effectiveness of antituberculous chemoprophylaxis has been

demonstrated in diverse groups (Table 7), the studies performed on HIV-positive subjects are preliminary. Sckell et al. found tuberculosis incidence rates of 0 and 9.7 cases per 100 person-years in treated groups (12 months isoniazid) and untreated groups (no treatment or less than 12 months isoniazid), respectively (*88*). Wadhawan et al. reported rates of 2.6 and 11.3 cases per 100 person-years in groups treated with isoniazid and placebo, respectively (*89*). Pape et al. determined that the average number of months without AIDS was 37.5 for HIV-positive subjects who received isoniazid versus 29.7 months for a placebo group (*90*).

On the other hand, it has also been found that the incidence of active tuberculosis increases in the period following chemoprophylaxis. Such activation of the mycobacterial infection was observed primarily in patients with grades III and IV on the Walter Reed Scale (*88*). Hence, the duration of the protection provided by chemoprophylaxis needs to be determined on the basis of long-term studies.

Schuermann et al. (*91*) and Mukadi et al. (*92*) consider that prolonged administration of antituberculous chemotherapy is unnecessary. Another point to be considered is the possible appearance of resistant strains due to administration of chemoprophylaxis. To date, there is no proof that this has occurred. Johnson et al. (*93*) reported on the case of an HIV-positive patient with disseminated tuberculosis from *M. avium* and *M. intracellulare* who received chemoprophylaxis with isoniazid for 12 months. Eighteen months later, this patient developed an abscess in the psoas from which *M. tuberculosis* that was sensitive to isoniazid, rifampin, and pyrazinamide was cultured.

Other aspects to be considered involve the toxicity of the drugs used in chemoprophylaxis and the patient's adherence to the treatment. Preliminary data appear to indicate that the frequency of toxicity resulting from chemoprophylactic administration of isoniazid to these patients is low (*27, 94–96*). Also, the results of available recent studies indicate that patient adherence to chemoprophylaxis has been good (in the range of 70–80%) (*97, 98*).

In view of these considerations, routine use of chemoprophylaxis in a given region depends on several factors. One of these involves the distinction between exogenous infection and reactivation of latent infection. Chemoprophylaxis is useful in preventing reactivation of a latent infection—which explains why PAHO/WHO recommends that chemoprophylaxis be administered to all at-risk individuals residing in high-prevalence areas. It should be borne in mind, however, that any given region contains groups with differing frequencies of tuberculous infection. Hence, as is indicated in the recommendation, the local epidemiologic situation needs to be evaluated.

As an alternative to indiscriminate administration of chemoprophylaxis to all HIV-positive individuals, especially considering the likelihood of adverse effects, it is possible to identify groups that will

Table 7. Effectiveness of isoniazid in tuberculosis chemoprophylaxis for HIV-positive persons.

Authors	Year of report	Place	Subjects (No.)	Rate for the treated group	Rate for the untreated group	Relative risk
Sckell et al. (*88*)	1992	New York, U.S.A.	120	0	9.7 cases per 100 person-years	
Wadhawan et al. (*89*)	1992	Zambia	649	2.6 cases per 100 person-years	11.3 cases per 100 person-years	4.3
Pape et al. (*90*)	1992	Haiti	118	Avg. of 37.5 months without AIDS	Avg. of 29.7 months without AIDS	

benefit to a relatively great degree from chemoprophylaxis. In Mexico, the Secretariat of Health is carrying out a survey of the prevalence of a number of different immunologic markers in collaboration with PAHO/WHO and the United States National Institutes of Health. The markers involved include tuberculin, other intradermally administered antigens, and the CD4 lymphocyte count. Use of these markers, taking into consideration the infrastructure available in different countries, may permit examination of the groups at highest risk of developing tuberculosis that stand to benefit the most from chemoprophylaxis.

Once the effectiveness of antituberculous chemoprophylaxis has been demonstrated in long-term follow-up studies, it will be necessary to evaluate the cost-benefit ratio of its administration and the feasibility of community-based programs (*96*).

After the opportunity for prevention has passed and active tuberculosis has developed, the tools available for preventing mortality are case identification and treatment. These are the key measures of any tuberculosis control program in developing as well as developed countries (*98*). In the latter, one circumstance that makes case identification particularly important is the fact that a considerable number of cases are the result of primary or secondary reinfection. It is also important to note that diagnosis of tuberculosis in coinfected patients needs to take account of the disease's particular clinical manifestations in subjects with HIV infection or AIDS.

Among other things, the sputum smear test exhibits a lower degree of sensitivity in HIV-infected tuberculous patients (*99*). PPD reactivity is modified by the degree of integrity of the subject's immune system. Indeed, in a selected series of patients with HIV and active tuberculosis, only 10–30% showed a reaction to PPD (*16, 17*). Accordingly, in order to determine whether the patient is anergic, it is recommended that PPD be combined with other cutaneous antigens (*100*).

Chest X-rays of coinfected patients are atypical, showing diffuse interstitial infiltrates in the inferior lobes with involvement of the hilar and paratracheal lymph nodes and pleural effusion (*16, 17*). Neves et al. analyzed the chest films of 152 HIV-positive patients with active tuberculosis and found, in order of frequency, diffuse interstitial infiltrates (in 46.6%), foci of pulmonary consolidation (in 21.3%), adenopathy (in 12.6%), cavitated appearance (in 12.6%), and apical infiltrates (in 10.6%). Pleural involvement was observed in 18.4% of the cases (*101*). This type of patient should be diagnosed using invasive methods (bone marrow, lymph nodes, cerebrospinal fluid, blood) (*99*).

The CDC (*86*), WHO (*102*), and PAHO (*87*) have published recommendations regarding tuberculosis treatment regimens for HIV-positive patients. It should be noted that an elevated number of adverse reactions to chemotherapy have been found in such individuals (*23, 96*). A retrospective study by Carvalho et al. reviewed the clinical histories of 152 HIV-positive patients with tuberculosis. The regimen used to treat these patients employed rifampin, isoniazid, and pyrazinamide. Side-effects occurred in 26.9% of the patients treated. (Tests of hepatic function were abnormal in 41.4% of those with side-effects; cutaneous reactions occurred in 34.7%; and gastrointestinal manifestations occurred in 19.5%.) Most of these reactions involved pyrazinamide intolerance (*94*). In a similar vein, Kibuga and Gathua have studied the frequency of adverse reactions to treatment in 105 tuberculous patients. Adverse reactions to chemotherapy, especially to thiacetazone, were five times more frequent in HIV-positive subjects (*23*).

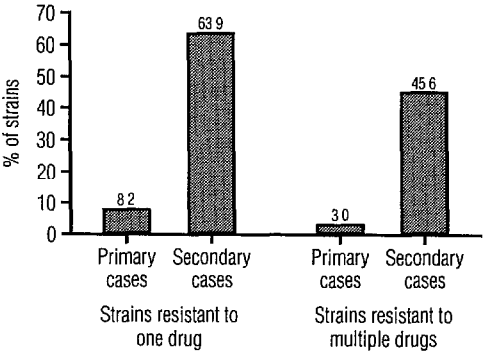
Recently, the appearance of multiresistant *M. tuberculosis* strains has posed an

additional problem for treatment of these patients. The U.S. epidemiologic surveillance system has shown a marked increase in the frequency of *M. tuberculosis* strains resistant to various drugs. For example, 3.3% of the strains studied have been found resistant to isoniazid and rifampin (*103*). Proof of nosocomial transmission of multiresistant strains also exists. Specifically, Fischl et al., Dooley et al., and Edlin et al. all described outbreaks of nosocomial tuberculosis in HIV-infected patients that were caused by multiresistant strains (*104–106*). These findings are supported by the work of Busillo et al., who conducted a genetic analysis of *M. tuberculosis* strains and observed that 14 out of 15 strains isolated in patients hospitalized at a New York medical center between December 1990 and May 1991 were identical, which suggests the existence of nosocomial transmission (*107*).

Analysis of data for 1991 on HIV-positive patients in New York City showed that 32% of the *M. tuberculosis* strains studied were resistant to three drugs (*108*). A research study conducted by the European Tuberculosis Study Group, which recruited tuberculosis patients from 30 centers in eight European countries, demonstrated the existence of resistance to one or more drugs (*95*). Jenny et al. found that resistant *M. tuberculosis* can cause fatal progressive primary disease in HIV-positive patients (*109*). The authors described a four-patient cluster occurring within a three-month period in a New York City hospital. Patients had no clinical, bacteriologic, or radiologic evidence of prior tuberculosis, PPD reactivity, or community exposure. High levels of mortality have also been observed among HIV-positive tuberculosis patients, and it has been found that many of the *M. tuberculosis* strains isolated from these patients are resistant to several drugs (*103*).

Information available about multiresistant *M. tuberculosis* strains in parts of the Americas outside the United States indicates that, although the magnitude of the problem is not yet alarming, accumulating evidence is starting to indicate that the situation may change. In Mexico, analysis of 1 637 strains received at the tuberculosis referral laboratory showed that 8.2% of the strains isolated from primary cases and 63.9% of those isolated from secondary cases in 1989–1991 were resistant to one drug, while 3% of the strains isolated from primary cases and 45.6% of those isolated from secondary cases exhibited multiple resistance (Figure 1). A third of the strains isolated from secondary cases were resistant to rifampin. Although the prevailing trends in resistance patterns of strains isolated from primary cases remained stable over the study period, those isolated from secondary cases showed a slight increase (*110*).

Figure 1. Percentages of 1 637 *M. tuberculosis* strains isolated from primary or secondary tuberculosis cases in Mexico during 1989–1991 that were found resistant to one drug and multiple drugs (*110*).



CONCLUDING REMARKS

The data presented underscore the worldwide magnitude of coinfection with HIV and *M. tuberculosis*. In the Americas, coinfection occurs in both industrialized and developing countries. In the former,

it has affected mostly minority groups characterized by a coexistence of conditions favoring both infections, such as crowding and intravenous drug use. In the latter, although HIV infection is not quite so prevalent, poor health conditions and limited access to health services in many areas are responsible for the fact that *M. tuberculosis* currently infects a substantial share of the population. For example, surveys conducted in Mexico in the 1970s and 1980s indicated that close to 40% of the adult population was infected (*111*). The situation is probably similar in the rest of Latin America.

In the United States, the HIV/AIDS epidemic's impact on new cases of tuberculosis has already been noted. Although this impact has yet to be documented in the rest of the hemisphere, sentinel studies have found high frequencies of HIV infection in tuberculous patients; and in some countries, such as Mexico, tuberculosis has been found to constitute the most frequent endemic infection in AIDS patients (*52–54*).

The WHO goal of eliminating tuberculosis by the year 2000 in industrialized countries has had to be postponed, at least for a few five-year periods, owing to the impact of the AIDS epidemic. This impact is even more critical in developing countries, and also among minority and socially disadvantaged groups in developed countries.

In addition to its more customary depredations, tuberculosis has come to have a particular impact upon the prognosis and quality of life of HIV-infected individuals. Tuberculosis control is feasible from the technical and economic standpoint. However, the available control measures—vaccination, chemoprophylaxis, case identification, and treatment—all encounter special circumstances when HIV-infected patients are involved.

Case prevention has especially great importance from the standpoint of costs and benefits. For this reason, it is essential to continue to conduct research on case prevention, above all with regard to chemoprophylaxis. It is also necessary to develop immunologic markers permitting detection of those individuals at high risk of developing active tuberculosis and those most likely to benefit from chemoprophylaxis. More effective preventive treatment regimens that do not produce multiresistance and that are well tolerated must also be developed.

Case identification requires that health personnel be trained to suspect the presence of tuberculosis and to conduct appropriate tests confirming the diagnosis. Such training is especially important in view of evidence that individuals infected with HIV are more prone to exogenous *M. tuberculosis* reinfections than those not infected, and that they also develop progressive primary or secondary tuberculosis more rapidly.

Finally, the types and durations of the various treatments currently employed need to be standardized. In this regard, the appearance of multiresistant strains has posed new challenges and has created a powerful need to establish surveillance programs with laboratory support.

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Monitoring of Drug-Resistant Diseases

At a four-day meeting last December, a WHO Working Group called for urgent action to combat the spread of antibiotic-resistant bacterial diseases in many parts of the world. While resistance to existing drugs is appearing everywhere, the problem is most severe in the developing world, where the sale of antimicrobial drugs is largely unrestricted.

The group of scientific experts from 23 countries issued a set of recommendations to help tackle the problem. They recommended, among other things, establishing policies to control the availability of antibiotics and to promote their appropriate use; setting up methods and standards for evaluation of hospital-based infection and antibiotic resistance prevention and control programs; encouraging basic research toward new approaches to the development of antimicrobials; and global expansion of the network of antimicrobial resistance surveillance activities through the WHO computerized system *WHONET*.

In collaboration with the microbiology laboratory of Brigham and Women's Hospital in Boston, Massachusetts (U.S.A.), WHO created the computerized integrated system known as *WHONET* for surveillance of bacterial resistance. It is based on a network of clinical laboratories linked by common software for analyzing and sharing their routine antimicrobial test results. About 150 laboratories in 30 countries are currently linked. *WHONET* also enables groups of participants to form local, national, or regional networks, and Latin American countries are leading the way in this regard with well-established systems in Argentina, Chile, and Venezuela.

Source: World Health Organization. WHO calls for action on spread of drug-resistant diseases. Geneva: WHO; 5 December 1994. (Press release WHO/95).