HIV-ASSOCIATED TUBERCULOSIS IN DEVELOPING COUNTRIES:
EPIDEMIOLOGY AND STRATEGIES FOR PREVENTION

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ABSTRACT

The association between tuberculosis and HIV presents an immediate and grave public health and socio-economic threat, particularly in the developing world. WHO estimates that in early 1992, approximately 6 million people had been infected with both Mycobacterium tuberculosis and HIV, 95% of them were in developing countries. The association between tuberculosis and HIV is evident from the high incidence of tuberculosis, estimated at 5-8% per year, among HIV-infected persons, the high HIV seroprevalence among patients with tuberculosis, the high occurrence of tuberculosis among AIDS patients, and the coincidence of increased tuberculosis notifications with the spreading of the HIV epidemic in several African countries.

The impact of the two epidemics on resource-poor countries has ominous social and medical implications, and the already overstretched health services now have to face a tremendously increasing tuberculosis problem. HIV infection worsens the tuberculosis situation by increasing reactivation of latent tuberculosis infection in dually infected persons as well as by favouring rapid progression of new infections in the HIV-infected. This also results in an increase of the risk of infection and a subsequent increase of cases in the general population. In order to respond to this urgent problem, the highest priority must be given to strengthening tuberculosis control programmes in the countries where they are poorly developed and where the prevalence of HIV and tuberculosis infections is high. Besides improving the cure rate by early diagnosis and prompt treatment of patients with tuberculosis, two major strategies that need consideration include BCG vaccination and preventive chemotherapy among HIV-infected individuals. The latter strategy is considered as the most critical intervention that would help to limit the expected increase in clinical tuberculosis from the pool of HIV and tuberculosis co-infected individuals. However, a number of issues need to be addressed urgently and before such an intervention can be implemented in the developing countries.

1. INTRODUCTION

Tuberculosis remains a health problem of enormous dimensions particularly in the developing world, affecting millions of people each year (1,2). The pandemic of the acquired immunodeficiency syndrome (AIDS) and the evidence of an association between tuberculosis and the human immunodeficiency virus (HIV), which causes AIDS, is now a further cause for world-wide concern (3-6). Since containment of tuberculosis infection in an individual depends on intact cellular immunity, HIV, due to its ability to destroy the immune system, now has emerged as the most significant risk factor for progression of the dormant tuberculosis infection to clinical disease. As a result, the tuberculosis problem not only has begun to worsen but also poses an unprecedented medical, social and economic threat globally, especially to the developing countries. In a previous article we reviewed clinical features, diagnosis, and treatment of HIV-associated tuberculosis in developing countries (7). This paper reviews the epidemiological situation regarding the tuberculosis-HIV relationship in the developing world and outlines strategies for prevention with particular reference to the role of tuberculosis preventive therapy.

2. EPIDEMIOLOGY

2.1 Incidence

In early 1992, the Global Programme on AIDS (GPA) of the World Health Organization (WHO) estimated that at least 9-11 million adults and one million children had been infected with HIV worldwide, and that 1.5 million adult and more than half a million paediatric cases of AIDS had occurred since the beginning of the pandemic. Nearly 85% of the HIV infections had occurred in developing countries (6) and the vast majority in the age group 15-49 years. All epidemiological data collected during the 1980s point to continuing large increases in HIV seroprevalence levels in sub-Saharan Africa and other developing countries.
WHO's Tuberculosis Programme has estimated that about 1700 million people, i.e. one third of the total human population, had evidence of infection with Mycobacterium tuberculosis worldwide in 1990. The overall proportion of infected persons is similar in the industrialized and developing countries (2). However, 75% of infected persons in the developing countries are less than 50 years of age compared to 20% in the industrialized countries. About 95% of the global tuberculosis morbidity (of 8 million) and more than 98% of the mortality (of 2.9 million) is contributed by developing countries.

The impact of HIV infection on the tuberculosis situation is obviously most serious when the prevalence of tuberculosis infection in young adults, who are at risk of HIV infection, is high. Using estimates of the prevalence of tuberculosis infection in various regions, it can be estimated that in early 1992 there had been more than 4 million persons with dual HIV and tuberculosis infection worldwide; a great majority (3.12 million) of whom lived in sub-Saharan Africa (Table 1).

These individuals have an extraordinarily high risk of developing clinical tuberculosis, compared to immuno-competent persons with a positive tuberculin skin test (Table 2). A prospective study among drug abusers in New York showed a rate of clinical tuberculosis of 8% per year for those infected both with tuberculosis and HIV; 7 of 49 HIV seropositive persons with a prior positive tuberculin skin test developed tuberculosis over a 2-year period of follow-up, compared with none of the 62 HIV seronegative tuberculin reactors (8). A similar finding has been reported from Zaire, where investigators conducted a retrospective cohort study of HIV-seropositive and HIV-seronegative women of childbearing age (9). After a median follow-up of 32 months, proven pulmonary or clinically diagnosed tuberculosis was reported in 7.6% of 249 HIV seropositive women (3.1 cases per 100 person-years) compared with 0.3% of 310 HIV seronegative women (0.12 cases per 100 person-years); the relative risk was 26. Assuming that 50% of the population was infected with tuberculosis, the annual risk in the two groups could be calculated as 6.2% and 0.2% per year respectively. In Rwanda, the incidence of clinical tuberculosis was studied in a cohort of 1470 women (997 HIV-seronegative and 473 HIV-seropositive) through six-monthly follow-ups (10). Over a 24-month follow-up period, 20 HIV-seropositive and 2 HIV-seronegative women developed tuberculosis (defined as sputum or smear-positive tuberculosis; or having clinical and radiologically suspected tuberculosis which did not respond to anti-tuberculosis therapy). The annual incidences were 2.5% and 0.1% respectively (relative risk 23). The annual incidence among HIV-seropositive tuberculin skin reactors (with induration of ≥ 10 mm) was 5.5%. Finally, a study in Zaire among factory workers and their spouses showed tuberculosis incidences in HIV-seropositive and HIV seronegative persons of 2.8 and 0.43 per 100 person-years of follow-up respectively (relative risk 6.5) (11). Assuming again that 50% of the study population was infected with tuberculosis, since tuberculin skin tests were not performed, the annual risk in dually infected persons can be calculated as 5.62 per year.

In summary, these studies show that the risk of progression to active tuberculosis among individuals infected with HIV is much greater than in HIV seronegative persons and that the estimated annual risk of breakdown among those infected with both HIV and tuberculosis varies from 5% to 8%, with a cumulative lifetime risk of 30% or more. The annual breakdown rates in dually-infected individuals of 5%-8% can be used to estimate that, at this stage of the epidemic, an additional 150 to 250 thousand cases of tuberculosis occur each year in sub-Saharan Africa.

The result of this increased risk is also evident from the data available on the reported numbers of tuberculosis cases. After years of declining incidence both in developed and to some extent in developing countries, the number of reported cases of tuberculosis during the 1980s increased dramatically in many countries of sub-Saharan Africa. For example, the tuberculosis control programme in Tanzania, which has a reliable reporting system, recorded 22 544 cases in 1990, an increase of 86% over 12 089 cases reported in 1984. The increases in some other countries, namely
Burundi, Malawi and Zambia, during the same period have been even greater, i.e. 140%, 180% and 154%, respectively (see also figure 1).

Besides Africa, tuberculosis continues to be a major problem in the South-East Asia and the Western Pacific regions, which contribute more than 60% of the global tuberculosis incidence. In addition, HIV is making rapid inroads in several Asian countries namely Thailand, India and Myanmar (6). This may result in a great increase of tuberculosis cases in Asia, as the absolute numbers of persons infected with M. tuberculosis are very high in those countries.

In the developed countries too, particularly in the urban areas, increases have been seen in the tuberculosis incidence among HIV infected populations. In the United States, tuberculosis cases began to increase for the first time in 1984 after a continued decline over the last 30 years, and from 1985 through 1990 an estimated 28,000 excess cases nation-wide have occurred which are believed to have been mainly the result of HIV infection (12).

2.2 HIV seroprevalence

HIV seroprevalence rates of greater than 40% are common among patients with tuberculosis in many African countries (13-28) (Table 3). In Kampala, Uganda, 66% of newly diagnosed tuberculosis patients were HIV-positive; in Zambia, 60% of tuberculosis patients were HIV-infected and in Kenya, 30% of newly diagnosed tuberculosis patients in a Nairobi hospital were HIV-seropositive (18, 21, 28). The rates are higher among patients with extrapulmonary tuberculosis (range 44-77%) than among those with pulmonary tuberculosis (range 17-49%). Overall these rates are much higher than those seen in the general population. For example, in Côte d’Ivoire, 26% of 2043 tuberculosis patients and 7.2% of 2127 blood donors were HIV seropositive (27). In Haiti, an HIV seroprevalence of 24% was found in 274 bacillary positive tuberculosis patients compared to 3% among a control group of patients i.e. those attending the same hospital for other types of illness; the risk of pulmonary tuberculosis in HIV-seropositive individuals was 16 times that of HIV-seronegative patients, 20-39 years of age (22). More recently, in Cité Soleil, Haiti, the HIV seroprevalence was 73% among male tuberculosis patients 35 to 44 years of age (R. Boulos, pers.com. 1992). In four Uganda hospitals located outside Kampala, the HIV seroprevalence among 1072 new patients with tuberculosis tested in an unlinked anonymous manner was 43% compared to 16.6% among 3324 women attending antenatal clinics of the same hospitals (T. Aisu, pers.com. 1992). Based on these data, it is possible to estimate that between 30-40% of incident tuberculosis cases in Africa and the Caribbean are attributable to HIV infection (9, 22, 27).

In South-East Asia, where the HIV infection began its spread in more recent years, the HIV seroprevalence among tuberculosis patients is also on the increase. For instance, in Chiang Mai, Thailand, it increased from 5.1% in late 1989 to 13.8% in early 1991 (K. Limsakernjanarat, pers.com.1992). In India, 12 of 183 (6.3%) tuberculosis patients admitted to a hospital in Bombay were HIV-infected (O. Bhave, pers.com.1992). In South America, recent data from a hospital in Buenos Aires, Argentina, show that the HIV seroprevalence among tuberculosis cases increased from 3% in 1988 to 6% in 1990 (I.N. Kantor, pers.com.1992).

Although not much information is currently available on the HIV infection rates among children with tuberculosis, limited data suggest that they may be similarly high in many areas. In the Central African Republic, 11% of 37 children with tuberculosis were HIV-seropositive; all of them had extrapulmonary tuberculosis (14). In a recent study in Zambia, 37% of 237 children with tuberculosis attending the University Teaching Hospital in Lusaka have been identified as HIV-seropositive compared to 10.7% among 242 children seen in that hospital for other illnesses (C. Chintu, pers. com. 1992). In an earlier study, 24% of Zambian children with tuberculosis were found to be HIV-infected (29).
2.3 Tuberculosis in patients with AIDS

In many developing countries tuberculosis has now emerged as the most common opportunistic disease associated with HIV infection. Twenty to 44% of AIDS patients in Africa (30-32), 18% of patients in Haiti (33) and up to 25% of patients in some Latin American countries, namely Brazil, Mexico and Argentina, had clinical tuberculosis during the course of HIV infection (34-36, and I.N.Kantor, pers.com.1992) (Table 4). In the United States, only 4% of AIDS cases reported nationally also had tuberculosis, although the proportion in selected areas like Florida and New York was much higher than the national figure (37). In a Southern European industrialized country, Italy, 11.4% of AIDS cases reported during the biennium 1988-1989 had tuberculosis (38).

2.4 Impact on Health services

The overlap between tuberculosis and HIV has ominous social and medical implications particularly for the resource-poor countries. With the further increases in tuberculosis cases, considerable pressure has been put on the already fragile and overstretched health services with more demand for diagnostic services, anti-tuberculosis drugs, hospital beds, and other supplies and services. In some eastern African countries, the phenomenal increase in tuberculosis cases has forced the tuberculosis control programmes to change policies regarding hospitalization of certain types of tuberculosis patients such as those with smear-negative and extrapulmonary disease. These patients are instead being treated on an ambulatory basis with intermittent regimes. Hospital tuberculosis wards in other countries are overflowing with patients in their twenties, most of whom are HIV-positive, and increasing numbers are now being admitted in non-tuberculosis wards. Moreover, HIV-infected patients have a higher frequency of extrapulmonary tuberculosis, which is more difficult to diagnose than pulmonary tuberculosis. Also, recent reports indicate that HIV-infected adults and children with tuberculosis are likely to develop adverse reactions of the Stevens-Johnson syndrome type, life-threatening in some cases, to therapeutic regimes containing thioacetazone, thus making patient management more difficult and decreasing the credibility of control programmes (39). In the absence of rapid and effective interventions, increasing numbers of AIDS and tuberculosis cases and deaths are likely to occur among young adults in their economically most productive years. This may have tremendous social and economic implications.

2.5 Infectiousness

The fear is also that the increasing numbers of HIV-positive patients with tuberculosis will lead to increases of the transmission of tuberculosis in the rest of the population and, thereby, to increased size of the population infected with tubercle bacilli in the future. How infectious to contacts HIV-infected tuberculosis patients are is not clear, as data from published, mainly cross-sectional, studies show conflicting results. For instance, a recent report from Zaire shows that household contacts of HIV-seropositive index cases had a risk of pulmonary tuberculosis similar to that of household contacts of HIV-seronegative index cases (40). Another study from Zambia, while demonstrating a higher frequency of tuberculin positivity among contacts of HIV-seronegative patients (72%) than in those of HIV seropositive patients (54%), indicated the possibility that pulmonary tuberculosis is less infectious in HIV-positive patients (41). Data for other areas including the United States show that patients with HIV-related smear-positive tuberculosis may be as infectious as any patient with positive sputum smears or cavitation (42,43).

Based on the available information, it is difficult to reach any conclusion on the relative infectiousness of HIV-associated tuberculosis. However, given the increased proportions of extrapulmonary and smear-negative disease, the average HIV-infected patient with tuberculosis may be less infectious than the average HIV-
seronegative patient. Furthermore, the transmissibility may depend on the stage of HIV infection, i.e., patients who are immunosuppressed are less likely to cavitate and therefore are less infectious than patients who are at an early stage of HIV infection. Studies are required which would address these questions in a prospective manner. Nonetheless, it is possible that the rises in the absolute number of tuberculosis cases in many countries will increase tuberculosis transmission both to the HIV-positive and HIV-negative populations (44, 45).

In summary, the HIV pandemic will worsen the tuberculosis situation in developing countries in three ways over and above the existing situation: 1) by reactivation of latent tuberculosis infection among dually infected persons; 2) by new infection with tubercle bacilli and rapid progression to active disease in HIV-infected persons; and 3) by increasing the number of cases in the general population whose infection and disease will result from transmission from HIV-positive individuals developing tuberculosis by either reactivation or recent infection (47, 48). Nevertheless, preliminary data from the second round of the National Tuberculosis Survey in Tanzania, where the National Tuberculosis Control Programme is continuously achieving an 80% cure rate of newly diagnosed smear-positive cases during the last 5 years and a 65% case detection rate, suggest that in the regions studied so far, the annual risk of infection in school children did not change appreciably from 1983-1985 to 1989-91, despite the increase in the number of detected new smear-positive cases (NTLP Tanzania, Progress Report No. 25, 1991). This indicates that good control programmes are able not only to cope with the increasing case load produced by the HIV epidemic and other factors, such as the arrival of refugees from areas where tuberculosis is poorly controlled, but also to reduce to some extent the increased chance of transmission.

2.6 Mortality

Although HIV-infected tuberculosis patients respond as well to anti-tuberculosis chemotherapy as HIV-negative patients (47), they may have a higher short-term mortality (48). In Zaire, the case-fatality ratio among HIV-seropositive patients was 31.3% (47 of 150) at one year after diagnosis compared to 4.4% (22 of 501) for HIV-seronegative patients (48). Similar results were reported from the Central African Republic, Zambia and Kenya (26, 18, 28). Furthermore, data from some programmes in East Africa suggest that mortality among tuberculosis patients has increased significantly since the mid 1980s.

A number of reports further suggest that tuberculosis is a common life-threatening complication associated with HIV infection in Africa. For example, in a retrospective cohort study of 249 HIV-seropositive and 310 HIV-seronegative women of childbearing age in Zaire, 11% of HIV-seropositive women died during 2 years of follow-up compared with none of the HIV-seronegative women (9). Among HIV-seropositive women with proven or clinically diagnosed tuberculosis, mortality was even higher; 5 (26%) of the 19 HIV-seropositive women with proven tuberculosis died during 2 years of follow-up compared with 10% of the 224 HIV-seropositive women not diagnosed as having tuberculosis (relative risk 2.7). Similarly, national surveillance data in Mexico demonstrate that 52% of AIDS cases with clinical tuberculosis were dead at the time of reporting, a proportion considered significantly higher than that seen among all AIDS patients (49). In Haiti, up to 14% of fatal HIV infections in children were associated with tuberculosis (50).

The reason for higher mortality among patients with HIV infection may be related to HIV-associated complications such as diarrhoeal diseases and malnutrition resulting from this (51). Further evidence for this comes from reports from the United States. Of the tuberculosis cases reported between 1981 and 1985 in San Francisco, 35 (12%) also had AIDS (52). The case-fatality ratio in patients with both tuberculosis and AIDS was 77% compared to 11% in tuberculosis patients without AIDS. In New York City, a cohort study of young males hospitalized with a diagnosis of pulmonary tuberculosis showed that most patients with HIV infection had depressed cell-mediated immunity and a poor prognosis for survival. The median survival of 21 months from diagnosis of tuberculosis among all seropositive patients was similar
to the median survival of 20 months observed in 1452 tuberculosis patients who already had AIDS (53).

3. STRATEGIES FOR PREVENTION

The main strategy of tuberculosis control in developing countries is to improve the cure rate by treating as early as possible the largest number of diagnosed tuberculosis cases, and subsequently to improve case-finding: that is, to diagnose cases as quickly as possible and as many as possible (1). By doing this, the tuberculosis mortality can be reduced, and the tuberculosis incidence can be subsequently decreased as a result of the removal of a significant portion of sources of infection through efficient treatment and case-finding.

The principle of this strategy still holds in the face of the HIV pandemic. Short-course chemotherapy is as effective among HIV-positive patients with tuberculosis as it is among HIV-negative patients in terms of cure rate (47). Thus, besides decreasing individual suffering, effective tuberculosis control programmes can limit the increase in transmission of infection, despite a large increase in tuberculosis incidence. Furthermore, while the short-term mortality of treated HIV-positive patients is higher than that of HIV-negative patients (16,48), effective treatment of patients with tuberculosis, whether they are HIV-positive or -negative, will decrease the mortality compared to no treatment (54). However, the strategy of increasing the cure rate and improving case detection can at the most contain the increase in incidence secondary to the HIV epidemic. As a large part of the increase in tuberculosis due to the HIV epidemic depends upon reactivation of latent infection, more direct preventive methods must supplement this strategy in order to curb the upsurge of tuberculosis.

The two major strategies used in different countries for preventing tuberculosis are BCG vaccination and preventive chemotherapy. We would therefore focus here on the roles of BCG and chemotherapy in the prevention of HIV-associated tuberculosis.

3.1 Role of BCG

BCG is widely used in the developing world for the prevention of disseminated tuberculosis. However, some isolated case reports of adverse reactions associated with this vaccine among children and adults with HIV infection have raised concerns regarding its safety (55-59). This concern was heightened by observed increases in lymphadenitis in several African countries at the same time (60-62).

However, outbreak investigation reports from Zimbabwe and Zaire reveal that rates of lymphadenitis among HIV-infected infants were similar to those in other children (60,62). In a study in Zaire, 9% of 223 HIV-seropositive infants had lymphadenitis, and 2% had fistulae; in HIV-seronegative children these proportions were 5% and 1%, respectively (61). Whereas the risk of lymphadenitis in HIV-seropositive children may be somewhat increased, it certainly is not alarming. The sudden increases in lymphadenitis could be ascribed to switching over to a different vaccine, notably to BCG from the Institut Pasteur, which is more reactogenic than the vaccines used before. A similar situation occurred recently in Uganda, where the introduction of the Institut Pasteur vaccine led to an increased incidence of lymphadenitis (T. Aisu, pers. com. 1992). Among 55 children (age range 5-25 months) with BCG-associated lymphadenitis, the HIV status was known in 45; 4 (8%) were seropositive. Another 6 children born to HIV-infected mothers and seropositive themselves could not be retested after 15 months of age, as 3 died and 3 were lost to follow-up. None had disseminated infection. Given an estimated HIV seroprevalence among children of 7-10%, children with HIV infection were not more likely to develop lymphadenitis than HIV-seronegative children.
The results of a prospective follow-up study conducted recently in Brazzaville, Congo also show that the recommended practice of immunizing asymptomatic infants with BCG should be continued (63). In this study, 64 babies of HIV-seropositive mothers and 130 control babies were followed-up for a mean duration of 36 months for the occurrence of complications of BCG vaccination given at birth. Neither chronic deep ulcerations at the site of injection, nor disseminated forms of BCG infection were observed. The frequency of BCG-related lymphadenitis in the group of HIV-infected children (24%) did not differ significantly from that of the uninfected children (19%), but the response to BCG in terms of tuberculin sensitivity induced by the vaccination appeared to be reduced. Similarly, a study from Kigali, Rwanda, showed that HIV-seropositive infants who received BCG vaccination during the first week of life were not at any increased risk of regional adenitis or disseminated BCG disease than HIV-seronegative children. However, they were more likely to have no scarring after vaccination and a negative skin test reaction at 6 months of age, suggesting that the immunological response may be decreased among HIV-infected children (64).

These reports conclude that BCG vaccination is safe, irrespective of the HIV serological status of the infant. Since infants born to HIV-seropositive mothers are at an increased risk of becoming infected with tuberculosis from their immunocompromised parent, the potential benefits from BCG far outweigh the theoretical risk of disseminated BCG infection in the HIV-infected infants. These data further support the existing recommendations issued in 1987 in a joint statement from the WHO Global Programme on AIDS and the Expanded Programme on Immunization (65) that for asymptomatic HIV-infected individuals from countries with a high prevalence of tuberculosis BCG is recommended at birth or as soon as possible thereafter, in accordance with standard policies for immunization of non-HIV infected children. In 1989, a joint WHO/UNICEF statement (66) and a joint WHO/CDA and Tuberculosis Programme statement (67) more specifically recommended that "BCG should be administered to infants as early in life as possible, including when the mother is known to be or suspected of being HIV-infected. BCG should be withheld from individuals with symptomatic HIV infection".

3.2 Preventive chemotherapy

In view of the high risk of tuberculosis in dually-infected persons, prevention of tuberculosis in such persons is clearly a high priority. Administration of preventive chemotherapy to HIV/tuberculosis co-infected persons has therefore been considered as one of the most critical interventions to limit the increase in clinical tuberculosis that is expected from the pool of HIV/tuberculosis co-infected individuals.

3.2.1 Rationale

The rationale for the use of preventive therapy is two-fold. Firstly, data from some countries show that tuberculosis in dually-infected persons is caused predominantly by endogenous reactivation of dormant foci; it therefore should be preventable by chemotherapy (8,68). The efficacy of isoniazid in preventing tuberculosis has been established in numerous clinical trials (69-71), and preliminary observations among HIV-infected individuals indicate that isoniazid may be effective in preventing tuberculosis in this group as well (8,72). In a single-blind, placebo-controlled clinical trial in Zambia, 944 HIV-positive individuals were randomized to receive either isoniazid 300 mg (298 persons) or vitamin B complex daily for 6 months (246 persons) (72). The 298 persons receiving isoniazid were followed for 293 person-years: 23 deaths and 3 tuberculosis cases occurred. The 246 persons receiving placebo were followed for 262 person-years: 27 deaths and 20 tuberculosis cases occurred. The annual incidence of active tuberculosis was shown to be significantly lower among persons on isoniazid (1.0% per year) than among those on placebo (7.6% per year).
At present only isoniazid has been studied in preventative therapy among HIV-infected persons. The data indicate the risk of side effects is low. However, it must be administered for at least 6 months, which may compromise compliance. The use of a short-term (two-month) regimen may be preferable since this would likely increase the degree of compliance and, depending on the regimen used, perhaps also the effectiveness (73,74). Recently other regimens have been investigated in animal studies which show that rifampicin and pyrazinamide (2 months) or rifampicin alone (3 months) are more effective than isoniazid given for 6 months (76). Preliminary results of a study in Haiti comparing 2 months of rifampicin and pyrazinamide versus 6 months of isoniazid among co-infected adults show that the two regimens are equally well tolerated (75).

Secondly, the risk of tuberculosis in HIV-infected persons is far higher than in any other risk group so that in terms of drug costs, preventative chemotherapy is likely to be more cost-effective than treatment of tuberculosis cases that will occur in the future among the HIV/tuberculosis co-infected pool. For instance, of the estimated 3.1 million newly-infected persons in sub-Saharan Africa, 1 million may develop tuberculosis within 10 years. In terms of drug cost only, this would require approximately 34 million dollars, calculated at the rate of 34 dollars per patient in Africa (76). In contrast, the cost of isoniazid for all HIV/tuberculosis co-infected persons would be about 6 million dollars, as a six-month supply of isoniazid costs less than 2 dollars per person.

Isoniazid daily for 12 months is routinely used in the United States for prevention of tuberculosis in individuals with positive tuberculin skin test. However, preventative chemotherapy has never been an integral part of tuberculosis control programmes in developing countries, primarily because of 1) difficulties in identifying high risk groups among the large numbers of tuberculosis infected individuals; 2) problems in ensuring drug supplies and compliance to preventive therapy; and 3) limited benefit, since the rate of active disease in HIV seronegative persons is low. Therefore, the limited resources were used primarily for passive case-finding and treatment of sputum smear-positive patients. It may now be possible to provide preventative chemotherapy by establishing voluntary HIV testing and tuberculin testing centres. These testing centres should not only identify newly-infected individuals but also provide them with preventative therapy. In this area, collaboration between national tuberculosis and AIDS programmes is essential.

3.2.2 The problem of tuberculin anergy

The use of preventative chemotherapy is presently being studied mostly for HIV-infected persons who react to tuberculin PPD (purified protein derivative), i.e. those who have been exposed to M. tuberculosis during their lifetime. The Mantoux test, a technique that utilizes the injection of PPD intradermally and measures the induration 48-72 hours after the injection, has been used traditionally to identify persons infected with M. tuberculosis. However, HIV-infected individuals with impaired cell-mediated immunity may not be able to mount an adequate reaction to PPD, and at times more than 50% of the infected individuals can be missed if a positive PPD reaction (for instance, with 5 mm induration or more) is used as criterion for providing preventative therapy (77-79) (Table 3). The stage of HIV infection may be an important factor in determining the capability to react, with reasonably preserved reactivity in less immunocompromised individuals and suppressed reactivity in persons with advanced stages of HIV infection or AIDS (22). Many studies, however, tend to equate nonreactivity to PPD as anergy to tuberculin, although a proportion of those who do not react may be uninfected persons. Recently, multiple puncture devices delivering various delayed-type hypersensitivity (DTH) antigens have been used in the USA in the attempt of better defining the degree of cutaneous anergy. However, these methods, although probably more sensitive due to the high number of antigens used, are more costly than Mantoux-type tests which should be preferred particularly in the setting of developing countries. It has been shown that mumps, Candida or tetanus toxoid are the best DTH antigens. Therefore, in the USA it has been recommended that PPD with two DTH skin-test antigens (mumps
and Candida, for instance) administered by the standard Mantoux method (0.1 ml intradermally) be used to detect tuberculosis infection and anergy rates among HIV-infected persons (80).

One of the methods to increase the detection of the tuberculosis infected persons, particularly those with impaired immunity, is based on the so-called "boosting" following administration of PPD. This procedure has been used in the USA among elderly persons and has been shown to detect increased numbers of infected individuals by simply repeating the skin test one to four weeks after an initial low response (81,82). The "boosting" may persist for at least a year. Repeated PPD can also be combined with administration of multiple antigens (79). However, no data are available on the usefulness of repeat PPD testing in HIV-infected persons. In addition, "mass" isoniazid preventive chemotherapy in HIV-infected persons, regardless of PPD status, may need to be studied in areas where the prevalence of tuberculosis infection is high. Indeed, this approach may be more cost-effective than limiting prevention to individuals with a positive reaction to PPD (83).

3.2.3 Priorities and issues related to implementation

WHO has accorded a high priority to studies on preventive therapy in order to
1) determine the efficacy of old and new regimens in preventing clinical tuberculosis in those infected with both tuberculosis and HIV; and 2) study operational aspects of a preventive therapy programme at local and national levels, provided that the efficacy of preventive therapy is confirmed. The latter studies are crucial to determining implementation of such programmes in resource-poor countries in terms of costs and sustainability. Another major question relates to the issue of compliance: whether HIV-infected persons, who are otherwise healthy, would continue to take drugs for the duration it is intended. Many of these issues need to be addressed urgently and before any such intervention can be proposed for introduction in developing countries as a part of the national programme.

An informal consultation organized by WHO in February 1990 developed guidelines for studies of preventive tuberculosis chemotherapy; these are available from the Tuberculosis Programme, World Health Organization, 1211 Geneva 27, Switzerland (84).

A number of clinical trials are currently ongoing in Africa, Latin America and the Caribbean to evaluate efficacy of isoniazid daily for 6 months and of regimens consisting of rifampicin and pyrazinamide given only for a two-month or a three-month period in HIV-infected adults. In addition, WHO support is being provided to a study in Uganda which assesses the operational feasibility of tuberculosis preventive therapy as an intervention strategy, notably in terms of compliance to therapy, resource requirements and sustainability. The result of these studies may have major implications for HIV and tuberculosis control programmes in all countries. If the inexpensive preventive therapy regimens are shown to be effective and feasible in developing countries, a policy of targeted preventive chemotherapy should be considered. Such a programme will not only decrease morbidity among HIV-infected persons, and possibly prolong their lives, but also likely to reduce the number of tuberculosis cases in the future. Demonstrating that a treatment is effective could stimulate voluntary HIV testing and counselling, thus facilitating prevention of HIV infection and increasing the credibility of both tuberculosis and AIDS control programmes.
REFERENCES


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Table 1. CUMULATIVE DISTRIBUTION OF INDIVIDUALS WHO HAVE BEEN INFECTED WITH TUBERCULOSIS AND HIV
15-49 YEAR-OLD GROUP, EARLY 1992

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<td>11</td>
<td>170</td>
<td>4.2</td>
</tr>
<tr>
<td>ALL REGIONS</td>
<td>10 120</td>
<td>34</td>
<td>4 009</td>
<td>100</td>
</tr>
</tbody>
</table>

¹ Includes all countries of WHO region.
² Includes all countries of the American Region of WHO, except USA and Canada.
³ Includes all countries of the Western Pacific Region of WHO, except Japan, Australia, New Zealand
⁴ USA, Canada, Japan, Australia, New Zealand
<table>
<thead>
<tr>
<th>Country</th>
<th>Year of report</th>
<th>Study methods</th>
<th>% Annual risk of TB</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>1989</td>
<td>Prospective study, intravenous drug users</td>
<td>7.9</td>
<td>0</td>
</tr>
<tr>
<td>Zaire</td>
<td>1991</td>
<td>Retrospective study, women of childbearing age</td>
<td>6.2*</td>
<td>0.2</td>
</tr>
<tr>
<td>Rwanda</td>
<td>1991</td>
<td>Prospective study, women attending antenatal clinics</td>
<td>5.5*</td>
<td>0.2</td>
</tr>
<tr>
<td>Zaire</td>
<td>1991</td>
<td>Prospective study, factory workers and spouses</td>
<td>5.6*</td>
<td>0.8</td>
</tr>
</tbody>
</table>

* Tuberculin test not performed. Risk calculated assuming a prevalence of tuberculosis infection of 50%.
### TABLE 3
HIV SEROPREVALENCE AMONG PATIENTS WITH TUBERCULOSIS
IN DEVELOPING COUNTRIES

<table>
<thead>
<tr>
<th>Selected country</th>
<th>Year</th>
<th>Total No of TB cases</th>
<th>HIV(+) (%)</th>
<th>No of pulmonary TB cases</th>
<th>HIV(+) (%)</th>
<th>No of ex. pulm. TB cases</th>
<th>HIV(+) (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaire</td>
<td>1985</td>
<td>159</td>
<td>33.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>13</td>
</tr>
<tr>
<td>Zaire (sanatorium)</td>
<td>1985/87</td>
<td>485</td>
<td>38.0</td>
<td>419</td>
<td>37.0</td>
<td>46</td>
<td>48.0</td>
<td>17</td>
</tr>
<tr>
<td>Zaire (outpatients)</td>
<td>1985/87</td>
<td>509</td>
<td>17.0</td>
<td>509</td>
<td>17.0</td>
<td>-</td>
<td>-</td>
<td>17</td>
</tr>
<tr>
<td>Burundi</td>
<td>1986</td>
<td>328</td>
<td>54.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>15</td>
</tr>
<tr>
<td>Central African Rep.</td>
<td>1986/87</td>
<td>72</td>
<td>54.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>16</td>
</tr>
<tr>
<td>Central African Rep.</td>
<td>1987/88</td>
<td>183</td>
<td>31.1</td>
<td>153</td>
<td>25.0</td>
<td>30</td>
<td>60.0</td>
<td>14</td>
</tr>
<tr>
<td>Central African Rep.</td>
<td>1987/88</td>
<td>37</td>
<td>10.8</td>
<td>14</td>
<td>0</td>
<td>23</td>
<td>17.0</td>
<td>14</td>
</tr>
<tr>
<td>Malawi</td>
<td>1988</td>
<td>125</td>
<td>26.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>20</td>
</tr>
<tr>
<td>Zambia</td>
<td>1988/89</td>
<td>346</td>
<td>60.0</td>
<td>149</td>
<td>49.0</td>
<td>124</td>
<td>77.0</td>
<td>18</td>
</tr>
<tr>
<td>Malawi</td>
<td>1988/89</td>
<td>153</td>
<td>52.0</td>
<td>92</td>
<td>37.0</td>
<td>61</td>
<td>75.0</td>
<td>19</td>
</tr>
<tr>
<td>Uganda</td>
<td>1988/89</td>
<td>59</td>
<td>66.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>21</td>
</tr>
<tr>
<td>Burkina Faso*</td>
<td>1988/89</td>
<td>573</td>
<td>22.7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>23</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>1988/89</td>
<td>591</td>
<td>40.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>26</td>
</tr>
<tr>
<td>Côte d'Ivoire*</td>
<td>1988/90</td>
<td>2043</td>
<td>40.2</td>
<td>609</td>
<td>37.2</td>
<td>159</td>
<td>50.8</td>
<td>27</td>
</tr>
<tr>
<td>Côte d'Ivoire*</td>
<td>1988/90</td>
<td>4221</td>
<td>34.3</td>
<td>-</td>
<td>26.6</td>
<td>-</td>
<td>43.3</td>
<td>24</td>
</tr>
<tr>
<td>Haiti</td>
<td>1986/89</td>
<td>274</td>
<td>24.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>22</td>
</tr>
<tr>
<td>Haiti</td>
<td>1989/90</td>
<td>143</td>
<td>39.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>25</td>
</tr>
<tr>
<td>Kenya</td>
<td>1989/90</td>
<td>240</td>
<td>30.4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>28</td>
</tr>
</tbody>
</table>

* Including HIV-2 infected patients

Note: in some studies, confirmed and presumed pulmonary tuberculosis cases were combined.
TABLE 4
TUBERCULOSIS AMONG AIDS PATIENTS

<table>
<thead>
<tr>
<th>Country/Region</th>
<th>Source</th>
<th>%</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>clinical/autopsy</td>
<td>20-44</td>
<td>30-32</td>
</tr>
<tr>
<td>Latin America: Mexico,</td>
<td>survey</td>
<td>7-26</td>
<td>34-36</td>
</tr>
<tr>
<td>Brazil, Argentina</td>
<td>clinical/autopsy</td>
<td>19</td>
<td>33</td>
</tr>
<tr>
<td>Caribbean: Haiti</td>
<td>clinical</td>
<td>11</td>
<td>33</td>
</tr>
<tr>
<td>Southern Europe: Italy</td>
<td>surveillance</td>
<td>4</td>
<td>37</td>
</tr>
</tbody>
</table>

TABLE 5
TUBERCULIN SKIN TEST RESULTS IN HIV(+) AND HIV(-) ADULTS, SELECTED COUNTRIES, 1991

<table>
<thead>
<tr>
<th>Induration (mm)</th>
<th>Uganda (%)</th>
<th>Zambia (%)</th>
<th>Haiti (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV+</td>
<td>HIV-</td>
<td>HIV+</td>
</tr>
<tr>
<td>0</td>
<td>50</td>
<td>20</td>
<td>68</td>
</tr>
<tr>
<td>1-4</td>
<td>13</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>5-9</td>
<td>15</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>&gt;10</td>
<td>14</td>
<td>59</td>
<td>30</td>
</tr>
<tr>
<td>N</td>
<td>106</td>
<td>44</td>
<td>1014</td>
</tr>
</tbody>
</table>

Reference (78) (77) (79)
Figure 1: Annual Tuberculosis Notification Rates in Selected African Countries (All Cases) 1983 - 1990

- BURUNDI
- MALAWI
- TANZANIA
- ZAMBIA

Cases per 100,000 population vs. Year of Notification