Reviews/Analyses

HIV-associated tuberculosis in developing countries: clinical features, diagnosis, and treatment

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This article reviews the clinical aspects and diagnosis of HIV-associated tuberculosis in developing countries, and summarizes WHO's recommendations for treatment. According to WHO estimates (early 1992) over 4 million persons worldwide have been infected with HIV and tuberculosis; 95% of them are in the developing countries.

Clinical features of HIV-associated pulmonary tuberculosis in adults are frequently atypical, particularly in the late stage of HIV infection, with non-cavitary disease, lower lobe infiltrates, hilar lymphadenopathy and pleural effusion. More typical post-primary tuberculosis with upper lobe infiltrates and cavitations is seen in the earlier stages of HIV infection. Extrapulmonary tuberculosis is reported more frequently, despite the difficulties in diagnosing it.

WHO's recent guidelines recommend 6-month short-course chemotherapy with isoniazid, rifampicin, pyrazinamide and ethambutol for patients with HIV-associated tuberculosis. The older 12-month regimen without rifampicin is much less effective. Streptomycin should not be used, because of the risk of transmitting blood-borne pathogens through contaminated needles. Thioacetazone should be abandoned, because of severe adverse reactions observed among HIV-infected patients. The roles of preventive chemotherapy and BCG vaccination for prevention of tuberculosis are also briefly discussed.

Introduction

In January 1992 WHO estimated that 9–11 million adults and about one million children, mostly in the developing countries, had been infected with the human immunodeficiency virus (HIV) worldwide. Further, more than 1.5 million adult and over half a million paediatric cases of acquired immunodeficiency syndrome (AIDS) may have occurred since the beginning of the pandemic (*1*). At the same time, WHO has estimated that (i) about 1700 million people, i.e., one third of the total human population, are infected with *Mycobacterium tuberculosis*; (ii) more than 8 million new cases of active disease occurred in 1990; and (iii) in the same year, nearly 2.9 million deaths were caused by tuberculosis, 90% of them in the developing countries (*2, 3*).

Considering that the great majority of HIV infections occur in 15–49-year-olds, and assuming that the risks of infection with HIV and tuberculosis are independent, it has been estimated that worldwide more than 4 million persons, mostly in the developing countries, have been infected with both HIV and *M. tuberculosis* (Table 1).

This article briefly describes the clinical, diagnostic, and therapeutic issues of HIV-associated tuberculosis in the developing countries, and suggests suitable approaches to treatment.

Epidemiological background

In the developing countries, the overlap between HIV infection and tuberculosis is shown by the high HIV seroprevalence among patients presenting with active tuberculosis. Data from a number of African countries and Haiti (collected between 1985 and 1990) show that seroprevalence ranges between 17% and 66% (*4–13*). In contrast, in the USA the median

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Table 1: **Distribution of individuals estimated to have been infected with HIV and tuberculosis (Tb), January 1992, 15–49-year-old age group**

Region	HIV infected (x 1000)	Tb infected (%)	HIV + Tb infected (x 1000)	
Africa[a]	6500	48	3120	(77.8)[b]
Americas[c]	1000	30	300	(7.5)
Eastern Mediterranean[a]	50	23	11	(0.3)
South East Asia[a] & Western Pacific[d]	1020	40	408	(10.2)
Europe[a] & others[e]	1550	11	170	(4.2)
Total	10120	34	4009	(100)

[a] Includes all countries in the WHO region.
[b] Figures in parentheses are percentages of the total.
[c] Includes all countries of the American Region of WHO, except USA and Canada.
[d] Includes all countries of the Western Pacific Region of WHO, except Japan, Australia and New Zealand.
[e] USA, Canada, Japan, Australia and New Zealand.

HIV seroprevalence in patients with tuberculosis was 3% among 3039 patients identified at 29 clinics in 7 metropolitan areas (*14*).

HIV infection, by progressively impairing cell-mediated immunity, appears to be the highest risk factor for reactivation of tuberculosis into active disease (*15*). Data from the USA suggest that the annual risk of reactivation in tuberculin-positive HIV-infected individuals is 7.9% (*16*). However, the proportions of HIV-related tuberculosis resulting from reactivation of a latent infection (secondary tuberculosis) and from progression to disease of a recent primary infection or re-infection remain to be clarified and undoubtedly vary according to the epidemiological circumstances. Whatever the mechanism, HIV infection accounts, at least in part, for the rapid and dramatic resurgence of tuberculosis experienced by several developing countries. Although large epidemiological surveys are still not available, in western African countries like Côte d'Ivoire the HIV-2 epidemic also appears to have an impact on the incidence of tuberculosis (*13, 17*).

From a global perspective, tuberculosis may indeed represent one of the most common HIV-related opportunistic infections. It was diagnosed in 44% of 62 AIDS patients from Zaire who underwent autopsy (*18*), and is the most frequent pulmonary disease detected in HIV-infected patients in Zimbabwe (*19*). In a study in Dar es Salaam, Tanzania, 19% of 274 patients with AIDS had tuberculosis (*20*), and over one third of HIV-infected Ethiopians presented with pulmonary or extrapulmonary tuberculosis (*21*). In a study in Rio de Janeiro tuberculosis was observed among AIDS patients who died in 24.4% of all cases (*22*). Tuberculosis is second only to candidiasis as manifestation of HIV infection in Mexico, where it is diagnosed in up to a quarter of all patients (*23, 24*). Finally, 18% of Haitian AIDS patients were found to have tuberculosis (*25*) (Table 2).

These epidemiological data have led to growing concern about the resurgence of tuberculosis as a major public health problem, posing a serious threat to control programmes worldwide.

Clinical features

Owing to the relative virulence of *M. tuberculosis*, in contrast to other less pathogenic organisms such as *M. avium* or *M. intracellulare, Toxoplasma gondii* and *Pneumocystis carinii*, tuberculosis is often an early manifestation of HIV infection. Clinical features of HIV-associated pulmonary tuberculosis in adults are frequently atypical, resembling those of primary tuberculosis and consisting of interstitial or miliary infiltrates, hilar lymphadenopathy, and pleural effusion, which are uncommonly seen in the non-HIV-related classical form. This is particularly true when the disease occurs in patients who are severely immunosuppressed, i.e., in the very late stages of HIV infection, and may often be due to new infection with tubercle bacilli. On the other hand, more typical post-primary tuberculosis with upper lobe infiltrates and cavitations is seen in patients during the early stages, when cell-mediated immunity is only partially compromised, and may often be due to reactivation of a latent infection (*28, 29*) (Table 3). By and large, this should hold true in developing countries. Similarly, tuberculin reactivity reflects the stage of HIV infection. Data from developing countries show figures of PPD (purified protein derivative) reactivity which vary considerably. For instance, the proportion of anergy among tuber-

Table 2: **Percentage incidence of tuberculosis among AIDS patients in various regions and countries**

Region or country	Sources	Tuberculosis (%)	References
Africa	Clinical/autopsy	20–44	*18–21*
Latin America: Mexico, Brazil, Argentina	Survey, clinical/ autopsy	7–25	*22–24*[a]
Caribbean: Haiti	Clinical	18	*25*
Southern Europe: Italy	Surveillance	11	*26*
USA	Surveillance	4	*27*

[a] Data for Argentina from I.N. Kantor, personal communication, 1992.

Table 3: **Pulmonary patterns of HIV-associated tuberculosis (Tb)**

Manifestations	Typical or post-primary Tb (early HIV stages)	Atypical or primary Tb (late HIV stages)
Infiltrates	Upper lobes	Diffuse interstitial or miliary
Cavitations	Often present	Usually absent
Lymphadenopathy	Usually absent	Often present
Pleural effusion	Rare	Often present

culosis patients was 33% in Zaire (*7*) and over 90% in Brazil (*30*). One study distinguished between patients with AIDS and patients with early HIV infection presenting with tuberculosis: anergy reflected the degree of immunosuppression, with 100% in the advanced stage and 43% in earlier stages (*12*). Similarly, data from the USA show that over one third of patients with HIV infection are still able to mount a positive reaction to PPD at the time tuberculosis is diagnosed (*31*). In developing countries, one factor which complicates interpretation of PPD testing is the high coverage with BCG vaccination, as shown in a recent study in Uganda (*32*). With all these limitations, the usefulness of PPD in aiding disease diagnosis is limited and of little relevance in the developing countries (*33*).

Pulmonary disease

Pulmonary tuberculosis is the most frequent type of tuberculosis in patients with HIV infection, occurring in 42–80% of cases in Africa (*4, 9, 13*) and 77% of cases in Brazil (*30*). Indeed, many cases with extrapulmonary involvement have evidence of lung disease at the same time.

Presentation. Several reports have described the characteristic clinical presentation of tuberculosis in HIV infection (Table 4). For instance, up to 85% of HIV-seropositive patients from Africa have already experienced a significant weight loss (often more than 10 kg or 20% of body weight) when they are diagnosed with tuberculosis (*5–7, 9, 11*) In addition, the duration of preceding fever is longer than in HIV-seronegative persons, i.e., for more than 1 month in at least half of the cases (*6, 7*). About half have chronic diarrhoea, chest pains and dyspnoea (*4, 6–9*). However, most of these signs and symptoms are also manifestations of other HIV-related conditions, which makes it difficult to ascribe them to one or the other. Other common features accompanying the presentation of HIV-associated tuberculosis in Africa are oral candidiasis (*4, 7, 8*), generalized lymphadenopathy (*4, 7, 8*), and a recent history of herpes zoster (*4, 8, 9*); all three are uncommon in seronegative patients, and therefore are valuable indicators of concurrent HIV infection.

Table 4: **Estimated frequency of clinical signs and symptoms in patients with tuberculosis and with or without HIV infection in developing countries**

Clinical signs or symptoms	HIV(+) patients (%)	HIV(–) patients (%)	References
Weight loss (>20% body weight or >10 kg)	30–85	11–55	*5–7, 11*
Length of fever (>2–4 weeks)	30–90	15–30	*6, 7, 11*
Diarrhoea	10–51	1–23	*4, 7–9*
Oral thrush	5–11	<1	*7, 8*
Lymphadenopathy	11–80	3–44	*4, 8, 11*
Cough	50	50–75	*7, 8, 11*
Haemoptysis	15	20	*6, 11*
History of herpes zoster	8–15	<1	*7–9*

On the other hand, cough is a symptom reported less frequently than in seronegative patients (*7, 8, 11*), probably owing to decreased local inflammation with less cavitation and endobronchial irritation. Similarly, haemoptysis, which results from caseous necrosis of the bronchial arteries inside cavities, is less common in seropositive patients, having been described in no more than 15% of cases as opposed to at least 20% in seronegative patients (*6, 11*).

Although prospective studies are still needed to better define the infectiousness of patients with HIV-associated tuberculosis, the available information seems to indicate that infectiousness may be similar to that of other patients with pulmonary tuberculosis (*29, 34*) However, owing to the greater proportion of non-cavitary disease, the overall infectiousness may be lower among HIV-seropositive patients.

Diagnosis: sputum microscopy. In the USA, sputum smears have been found to be positive in 31–82% of HIV-seropositive patients with pulmonary tuberculosis, with the higher fractions in less immunocompromised individuals (those with typical reactivation tuberculosis) and the lower fractions in advanced HIV disease (*29*).

In the developing countries, rapid diagnosis of pulmonary tuberculosis is based on simple diagnostic techniques: sputum smear microscopy and chest radiography, when available. In a series of 62 HIV-positive patients from Zambia sputum smears were positive in 63% of culture-proven pulmonary tuberculosis cases, but showed a low number of bacilli (defined as 1 to 10 in this study) in 35%, as compared to 82% and 25%, respectively, in 61 HIV-

seronegative patients (*8*). More detailed data are available from Haiti. In a study which distinguished between patients meeting the clinical criteria for definition of AIDS and HIV-seropositive subjects without AIDS, it was found that positive smears could be obtained in 90% of the former and 67% of the latter. Some 80% of subjects with tuberculosis without HIV-infection were smear-positive (*12*). Similarly, in Brazil 87% of 263 cases of HIV-associated pulmonary tuberculosis had a positive smear (*30*).

The tuberculosis detection rate based on sputum smear examination may thus be comparable to that described for HIV-seronegative patients, at least during the early stages of HIV disease. On the other hand, when the immune system is severely compromised, the sensitivity of sputum smear examination may be reduced. However, it has been observed that even in the absence of cavitation and without liquefaction of caseation necrosis, the profound impairment of the immunity seen in HIV infection may permit tubercle bacilli to multiply in such large numbers as to become visible on smear examination (*12*).

Diagnosis: chest radiography. In a radiological investigation of 81 HIV-related tuberculosis cases from Bujumbura, Burundi, reticulo-nodular infiltrates, either bilateral or, less commonly, unilateral, were found in over two thirds of the cases. A miliary pattern was seen in 32% and pleural involvement in 11% of the cases, as compared to 3% and 3%, respectively, in HIV-seronegative patients (*35*). In Uganda, chest X-ray findings not typical of tuberculosis were observed in 41% of HIV-seropositive subjects as compared to only 16% of HIV-negative patients (*11*).

Cavitation is less common in HIV-infected patients with tuberculosis and may range between 16% and 48%, whereas usually more than half of the immunocompetent patients present with pulmonary cavities (*7, 8, 35*). The lack of cavitating lesions in HIV-infected patients probably depends on the host's altered immune response; an abnormal interaction between host and bacillus results in an outcome different from the expected (*8*). Upper lobe involvement is seen less frequently in HIV-seropositive patients, whereas hilar or mediastinal lymphadenopathy is common (*7, 8*).

In a study on tuberculosis in Haiti involving 10 patients with AIDS, 57 HIV-seropositive patients without AIDS, and 158 seronegative patients, a post-primary pattern was seen in 20%, 51%, and 80% of patients respectively, whereas an atypical primary-like pattern was seen in 80%, 30%, and 11% respectively, which supports the observation that the more advanced the stage of disease, the more common the atypical presentation. In this study cavities were significantly less common in HIV-seropositive patients, while hilar or mediastinal adenopathy without parenchymal infiltrates was more common (*36*). In Brazil, an atypical chest X-ray was reported from 81% of AIDS patients as compared to 6% of non-HIV infected persons (*37*). In another study from Brazil, interstitial infiltrates were seen in 71% of 104 HIV-seropositive patients, while 22% had no evidence of radiographic abnormalities (*38*). Similarly, observations from the USA suggest that the chest radiographic manifestations of HIV-related pulmonary tuberculosis reflect the stage of HIV infection, with a typical reactivation pattern early in the course, and an atypical one in the more advanced stages (*29, 39*) (Table 5).

Other and new diagnostic methods. Diagnosis of HIV-infected patients with clinical presentations compatible with pulmonary tuberculosis, but with negative smears, represents a challenge to physicians in developing countries with limited resources. Small hospitals and clinics often provide only basic diagnostic tools such as sputum microscopy and basic radiological facilities. Mycobacterial culture in laboratories is necessary to make a definitive diagnosis in smear-negative patients, but such laboratories are mostly located only in the main hospitals and research institutions, and transportation of sputum samples is often not feasible.

The application of endoscopic bronchoalveolar lavage (BAL) may, however, improve the diagnosis of pulmonary tuberculosis in referral centres in developing countries. A recent study from Kigali, Rwanda, has shown that BAL and transbronchial biopsy may be useful procedures to diagnose tuberculosis in patients with pulmonary infiltrates of unknown etiology (*40*). Another method designed to detect tuberculostearic acid (TBSA), which is a structural component of mycobacteria, in BAL or bronchial aspirates has probably higher sensitivity than microscopy (*41*).

Table 5: **Estimated frequency of chest radiograph findings in patients with tuberculosis and with or without HIV infection in developing countries**

Chest radiograph finding	HIV(+) patients (%)	HIV(–) patients (%)	References
Typical pattern[a]	46–59	80–85	*35–38*
Atypical pattern[b]	40–81	6–16	*35–38*
Upper lobe infiltrates	50–69	72–92	*6, 30*
Cavitations	16–48	35–87	*4, 6–8, 30, 35*

[a] "Post-primary pattern": upper lobe infiltrates, cavitations.
[b] "Primary-like pattern": intrathoracic adenopathy, with or without parenchymal disease, localized non-cavitary disease in middle or lower lobes, isolated pleural effusion or no abnormalities.

A preliminary report from India has emphasized the relevance of applying the polymerase chain reaction (PCR) for the diagnosis of tuberculosis in developing countries, and initial results are encouraging (*42*). It is possible that some of the other new laboratory techniques, once they become widely available, will have an impact in the developing countries. For instance, nucleic acid hybridization probes for specifically identifying the DNA or RNA of mycobacteria in clinical specimens and immunoassays (either radioimmunoassay or ELISA for detecting mycobacterial antigens in sputum or other clinical specimens) are believed to be relatively simple and not very expensive techniques, and meet the requirements for proper handling available in the developing countries. These methods, when made ideally sensitive and specific, could become alternatives to sputum smears and improve case detection (*43*).

Extrapulmonary disease

In developing countries extrapulmonary tuberculosis is a common finding among HIV-infected patients. Available information shows that HIV-seroprevalence is higher in patients with extrapulmonary disease than in those with pulmonary disease alone (*4, 8, 9*). In Africa during the pre-AIDS era only a small fraction of cases occurred in extrapulmonary sites (about 11% among solely extrapulmonary and combined pulmonary and extrapulmonary) (*28*). A change in the distribution has occurred in recent years. For instance, in a series of adult HIV-related tuberculosis cases from the Central African Republic 31% had at least one extrapulmonary site of disease (*4*). In two other series from Malawi and Kenya, 57% and 53%, respectively, of HIV seropositive patients had extrapulmonary tuberculosis, compared to 20% and 19% of HIV seronegatives (*9, 44*). In Brazil, among 339 tuberculosis cases, 62% had proven extrapulmonary disease, either alone or accompanying pulmonary disease (*30*). Similarly, a recent study from San Francisco, USA, has shown that only 38% of tuberculosis cases diagnosed in patients with advanced HIV infection occur in the lungs alone, while 30% were entirely extrapulmonary and 32% both pulmonary and extrapulmonary (*45*).

Reports from Africa and Brazil have shown that while tuberculous lymphadenitis is the most common site, pleural and pericardial disease are also common as well as disseminated miliary forms. For instance, in two series from Zambia and Malawi, pleural tuberculosis was a very common extrapulmonary manifestation (*8, 9*); HIV-related tuberculous pericarditis is also frequently reported in developing countries (*4, 6, 8, 9, 46, 47*).

Lymphadenopathy, both intra- and extrathoracic, remains the most frequent form of extrapulmonary tuberculosis as reported from Central African Republic (*6*), Zambia (*8*), Kenya (*44*), and Brazil (*48*). Although uncommon in Uganda a few years ago (probably not exceeding 5% of all cases of tuberculosis), tuberculous lymphadenitis has become common in recent years; a biopsy study involving 16 HIV-seropositive patients revealed poor cellular reactivation and abundant acid-fast bacilli in nine cases, and caseation with scanty or no bacilli in the other seven (*49*).

Disseminated miliary forms are also frequent (*6, 44, 48*) and may occasionally be encountered in children (*4*). However, mycobacteraemia may be difficult to diagnose in developing countries in the absence of routine blood cultures. Further, virtually all organs have been reported as extrapulmonary sites of tuberculosis, and they include the gastrointestinal tract, liver, meninges, genito-urinary tract, peritoneum, and bone (*4, 6, 9, 44, 48*).

Considering the data on extrapulmonary tuberculosis, our knowledge of its distribution depends to a large extent on the available diagnostic means, like facilities to perform biopsies or other procedures yielding tissue or fluid samples. If these cannot be obtained, physicians should make a presumptive diagnosis and treat those cases whose clinical presentation strongly suggests extrapulmonary tuberculosis, after having carefully excluded other conditions.

Treatment

Efficacy of old and new regimens

The efficacy of short-course treatment has recently been evaluated in Zaire (*50*). The study involved 152 HIV-positive and 192 HIV-negative patients with pulmonary tuberculosis. All patients received 2 months of intensive treatment with isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E), followed by isoniazid-rifampicin twice weekly for 4 months. Later, HIV-positive patients were randomized to receive continued treatment or placebo for another 6 months. Failure rates after the first 6 months of treatment did not differ significantly between HIV-infected (9%) and non-infected subjects (6%). More importantly, relapse rates after 12 months did not differ significantly between HIV-seropositive patients who had been on continuous treatment for the whole 12 months (5%) and those treated only for 6 months (10%), showing that short-course chemotherapy is efficacious in HIV-infected patients. Similarly, in Brazil a standard course of isoniazid-rifampicin-pyrazinamide for 2 months followed by isoniazid-rifampicin for at least 4 months confirmed that sputum conversion was obtainable in 92% of the cases during treatment (*30*).

On the other hand, another study from Zaire has clearly shown that 12-month "standard" antituberculous chemotherapy (which included isoniazid-streptomycin and, in most cases, thioacetazone) was less effective in HIV-seropositive patients than in HIV-seronegative patients, with a much higher mortality during both the year of chemotherapy (31.3% vs 4.4%) and the year after chemotherapy (26.3% vs 2.2%). Further, relapse rates were higher among HIV-seropositive (18.1 per 100 patient-years) than among HIV-seronegative patients (6.0 per 100 patient-years), with a relative risk of 3.0 (*51*). Although lower rates were reported from the Central African Republic and Côte d'Ivoire (*4, 17*), one report from Zambia indicated that, at the end of treatment, 12% (6 of 52) of HIV-positive patients relapsed as opposed to 6% (2 of 35) of HIV-negative individuals, thus showing a trend towards a higher relapse rate among HIV-infected patients (*52*). These findings suggest that while short-course chemotherapy is probably efficacious in HIV-seropositive patients, the "standard" 12-month regimen has a considerably lower efficacy.

In the pre-AIDS era, the overall mortality of untreated, confirmed forms of tuberculosis had been consistently shown to be 50–60% at 5 years (*53*). On the other hand, data from the Tanzania National Tuberculosis and Leprosy Programme (NTLP) have shown that the mortality during treatment was reduced to about 4% before the effects of the HIV epidemic were seen. However, an increase to 11% during recent years in those regions with the highest HIV seroprevalence has been reported (data from the Tanzania NTLP report to WHO, 1991). Despite the good results of short-course chemotherapy in both sputum smear conversion and prevention of relapse, the case fatality of tuberculosis in HIV-infected African patients is higher than in HIV-negative individuals. This has been reported from the Central African Republic, Zaire and Zambia (*6, 51, 52*). In Malawi, 19% of 80 patients were dead at 16 months (*9*). In another study from Zaire, 25% of 73 HIV-seropositive sanatorium patients died during a 2-month period of observation compared with 9% of HIV-seronegative patients; the duration of preceding fever and severe weight loss were independent predictors of fatality (*7*).

Extrapulmonary disease was associated with a higher mortality than pulmonary disease alone in HIV-positive patients in Kenya (*44*). Finally, it is of interest to note that HIV-2, in contrast to HIV-1, does not appear to increase the mortality from tuberculosis (*17*).

In conclusion, what determines the observed higher mortality rate among HIV-1-infected patients remains unclear. A large part of it is probably secondary to other HIV-related disorders that are often very common among HIV-seropositive patients, like chronic diarrhoea with resulting malnutrition, aggressive Kaposi sarcoma, severe anaemia, or other opportunistic infections (W. Nkhoma, personal communication, 1991; *54*). As recently suggested, this must be confirmed by showing that most deaths occur after sputum conversion and when the tuberculosis has improved clinically, which would indicate that tuberculosis is not the actual cause of death (*55*).

Recommendations for treatment

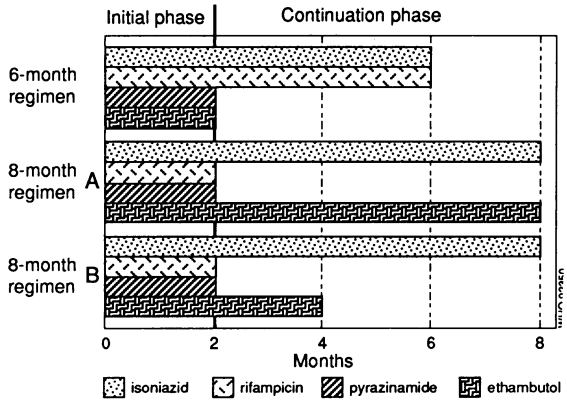
WHO recommends that, whenever possible, new cases of infectious pulmonary and other severe forms of tuberculosis in Africa be treated using short-course chemotherapy.[a] This approach is more efficacious and cost-effective than the "standard" long-course chemotherapy (*56*).

The short-course regimens consist of a fully supervised intensive phase of daily isoniazid-rifampicin-pyrazinamide-ethambutol for 2 months, followed by 4 months of thrice weekly isoniazid-rifampicin or by 6 months of daily isoniazid and ethambutol (or, if cost must be controlled, by daily isoniazid and ethambutol for at least the first 2 months of the continuation phase, followed by isoniazid alone for the last 4 months). This should become the new standard treatment of HIV-infected people in Africa and other developing countries who present with smear-positive pulmonary tuberculosis or other severe forms of tuberculosis (multibacillary forms). For patients with tuberculous meningitis, disseminated tuberculosis or spinal disease with neurological complications, isoniazid-rifampicin should be given daily during the continuation phase and for 6–7 months. In its guidelines, WHO recommends that streptomycin be replaced by ethambutol as the fourth drug during the initial phase of treatment in HIV-infected patients to avoid the potential of transmission of HIV and other blood-borne pathogens through contaminated needles and syringes, and that thioacetazone be replaced by ethambutol during the continuation phase of the 8-month regimen because of the risk of severe adverse reactions when thioacetazone is used in HIV-infected patients. WHO also recommends prologing the initial phase for 2–4 weeks if the sputum is still smear-positive at the end of the second month (Fig. 1).

For HIV-infected patients with smear-negative pulmonary tuberculosis or less severe extrapulmon-

[a] **World Health Organization.** *Guidelines for tuberculosis treatment in adults and children in national tuberculosis programmes.* Unpublished document WHO/TUB/91.161, 1991.

Fig. 1. **Treatment of newly diagnosed tuberculosis in HIV-seropositive patients.** In the 6-month regimen, isoniazid and rifampicin may be given daily or thrice weekly during the continuation phase.



ary cases (paucibacillary forms), self-administered thrice weekly isoniazid-rifampicin-pyrazinamide for 2 months followed by a short continuation phase of 2 months with thrice weekly isoniazid-rifampicin or of 6 months with daily isoniazid and ethambutol may be sufficient. For the same paucibacillary forms an alternative treatment under evaluation in Malawi consists of 2 months of thrice weekly isoniazid-rifampicin-pyrazinamide, followed by 2 months of daily isoniazid-ethambutol and 4 months of daily isoniazid alone (W. Nkhoma, personal communication, 1991). In patients with smear-positive pulmonary tuberculosis who have relapsed or failed treatment WHO recommends the use of 4 drugs (isoniazid-rifampicin-pyrazinamide-ethambutol) during the 3-month fully supervised intensive phase supplemented with streptomycin for the first 2 months, followed by thrice weekly isoniazid-rifampicin-pyrazinamide for the 5 months of the continuation phase.

Safety of antituberculous chemotherapy

A strong limiting factor in the treatment of HIV-related tuberculosis is the high incidence of intolerance to some drug regimens manifested by HIV-infected individuals. In fact, several reports have shown that skin rashes occur frequently in this population during antituberculous chemotherapy.

In 1988 a study from Burundi reported allergic reactions attributed to thioacetazone with a number of deaths due to toxic epidermal necrolysis (TEN) (*57*). Later, a study from Zaire among adult patients receiving treatment with thioacetazone showed that the rate of skin eruptions was significantly higher in HIV-infected patients than in the HIV-seronegative patients (20% vs 7%), and two cases of Stevens-Johnson syndrome (SJS) also occurred (*7*). Similarly, in Zambia there were 8 cases of SJS among HIV-infected patients treated with a combination of several drugs including thioacetazone (*8*), although it was not conclusively shown that thioacetazone caused the reaction. In Kampala, Uganda, one case of SJS, two cases of exfoliative dermatitis, and 5 other skin eruptions occurred in 25 HIV-infected adult patients with tuberculosis treated with thioacetazone-containing regimens (32%), whereas no reactions were seen among 15 HIV-seronegative patients. On the basis of rechallenge, all were proven to be secondary to thioacetazone (*11*).

A recently published study from Kenya showed that 22 (20%) out of 111 HIV-seropositive patients experienced cutaneous hypersensitivity reactions while on antituberculous chemotherapy, compared to 2 (1%) out of 176 HIV-seronegative patients (*58*). There were three deaths from toxic epidermal necrolysis as a consequence of drug hypersensitivity among HIV-infected patients. This study also compared 93 HIV-positive patients on a regimen including thioacetazone (plus streptomycin-isoniazid) with 18 HIV-seropositive patients on a regimen without it (streptomycin-isoniazid-rifampicin-pyrazinamide) during the initial phase: in the first 8 weeks of treatment, eighteen skin reactions occurred among the 93 patients on the thioacetazone-containing regimen (19%) and none among those on the other regimen. Upon rechallenge, no reactions were observed after isoniazid and streptomycin, but 6 of 7 patients challenged with thioacetazone reacted. Therefore, thioacetazone was probably responsible for most of the eruptions which were mainly of the erythema multiforme type (*58*).

Some of these studies may have overestimated the hypersensitivity reactions among HIV-seropositive patients with tuberculosis, as they were not specifically designed to properly address this issue. Some reports did not conclusively show that thioacetazone was the drug responsible for the reaction, as rechallenge was not done. However, the cohort study from Kenya strongly suggested that thioacetazone was the agent responsible for the cutaneous hypersensitivity reactions (*58*).

On the basis of these reports, the recent WHO guidelines for treatment of tuberculosis have emphasized that thioacetazone should not be given to patients who are known to be HIV-infected or at increased risk of HIV infection, e.g., young adults

from countries where HIV infection is prevalent (*59*). The recommendations state that ethambutol, instead of thioacetazone, should be used with isoniazid in the 6-month continuation phase of the 8-month regimen.[b]

Role of prevention

Although preventive chemotherapy has not been an integral part of tuberculosis control programmes in developing countries in the past, the recent increased burden of HIV-associated tuberculosis requires an intervention to limit the occurrence of active tuberculosis in HIV-infected individuals. The use of isoniazid as preventive agent has been stressed recently in the USA, where current recommendations propose a daily course for a minimum of 12 months for HIV-positive individuals with a positive (>5 mm) tuberculin skin test (*60*). Whether preventive therapy should be reserved to tuberculin reactors only—with all the limitations of skin testing in HIV infection—or given to all HIV-seropositive individuals is still unclear. However, results of a decision analysis in the USA showed a benefit from the use of isoniazid as preventive therapy for HIV-seropositive persons regardless of skin test results (*61*).

A recent single-blind, placebo-controlled study from Zambia has evaluated the efficacy of 300 mg of isoniazid daily compared to placebo in preventing HIV-associated tuberculosis. Over an approximately 12-month follow-up period, there were 23 deaths and 3 cases of tuberculosis in the isoniazid group, compared to 27 deaths and 20 tuberculosis cases in the placebo group. Although no appreciable difference in mortality was observed, the annual incidence of tuberculosis among persons on isoniazid was only 1.0%, compared with 7.6% in the placebo group (*62*). Based on animal studies showing that short courses of rifampicin alone or rifampicin-pyrazinamide are superior to isoniazid in preventing tuberculosis (*63*), a field trial has been initiated in Haiti comparing 2 months of rifampicin-pyrazinamide to 6 months of isoniazid. Preliminary results show that the two regimens are equally well tolerated (*64*).

The role of BCG vaccination in preventing tuberculosis when given to HIV-infected children is unknown. Two recent studies from Zaire and Rwanda found that skin reactivity to PPD in BCG-vaccinated children with HIV infection was lower than in HIV-seronegative children (*65, 66*). Furthermore, some adverse reactions, such as lymphadenopathy or adenitis, have been observed among HIV-infected individuals receiving BCG, although most of the cases resolved without major complications (*67, 68*). Thus, it is generally believed that BCG vaccine is relatively safe in asymptomatic HIV-infected children (*66, 69*). Therefore, in countries where tuberculosis is common the WHO recommendations should be followed, and BCG administered to infants as early in life as possible, including when the mother is known to be or suspected of being HIV-infected. Uninfected children born to HIV-infected mothers may benefit from BCG as they are more likely to become infected with tuberculosis from their immunocompromised mothers. However, BCG should be withheld from symptomatic HIV-infected patients (*70–72*).

Conclusions

In developing countries nearly 4 million people have been infected with both HIV and tuberculosis. HIV seroprevalence among active tuberculosis cases is high and tuberculosis is one of the most frequent opportunistic infections among HIV-infected patients in Africa and some other developing countries.

HIV-associated tuberculosis occurs commonly in the lungs, and may present in two different ways: with a typical post-primary pattern in the early stages of HIV infection, or with an atypical primary pattern in the late stages of HIV infection. Extrapulmonary tuberculosis is common in HIV-infected patients and in the developing countries frequently manifests as lymphadenitis, pleural effusion, or pericarditis, although a number of other sites have been found to be involved.

For patients with smear-positive pulmonary tuberculosis and severe extrapulmonary forms WHO recommends a 2-month intensive phase with isoniazid-rifampicin-pyrazinamide-ethambutol under full supervision, followed by a continuation phase of 4 months with thrice weekly isoniazid-rifampicin or 6 months with daily isoniazid and ethambutol. Thioacetazone should be avoided because of the risk of severe toxicity in HIV-infected patients, and streptomycin should not be used because of the potential of transmission of HIV and other blood-borne pathogens through contaminated needles.

The increased burden of tuberculosis cases in countries with a high HIV seroprevalence poses a serious threat to the already overworked national control programmes. A greater effort and global cooperation are therefore necessary to cope with the resurgent tuberculosis problem.

[b] **World Health Organization.** *Guidelines for tuberculosis treatment in adults and children in national tuberculosis programmes.* Unpublished document WHO/TUB/91.161, 1991.

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Résumé

Tuberculose associée au VIH dans les pays en développement: aspects cliniques, diagnostic et traitement

Selon des estimations de l'OMS, il y avait dans le monde entier, au début de 1992, environ 9 à 11 millions d'adultes infectés par le VIH. La plupart étaient des habitants de pays en développement, où l'infection tuberculeuse est prévalente. L'ampleur du recouvrement entre les populations infectées par le VIH et infectées par le bacille tuberculeux détermine le nombre de sujets porteurs d'une infection mixte et soumis à un risque accru de tuberculose évolutive. D'après des estimations de la prévalence de l'infection tuberculeuse dans le groupe d'âge chez lequel le risque d'infection par le VIH est le plus élevé (15-49 ans), l'OMS estime à plus de 4 millions le nombre de personnes porteuses d'une infection par ces deux agents, pour la plupart dans les pays en développement. L'interaction entre la tuberculose et l'infection par le VIH est démontrée par la séroprévalence élevée du VIH, allant de 17% à 66% dans des études réalisées en Afrique et en Haïti, chez les malades atteints de tuberculose évolutive. La survenue d'une tuberculose chez des malades du sida est un autre signe du recouvrement entre les populations infectées par le VIH et par le bacille tuberculeux, et un certain nombre de pays en développement ont rapporté des pourcentages élevés de sidéens faisant une tuberculose évolutive: 44% au Zaïre, 33% au Zimbabwe et 25% au Brésil et au Mexique.

La forme la plus fréquente de tuberculose chez les malades infectés par le VIH est la tuberculose pulmonaire, bien qu'on observe aussi fréquemment des tuberculoses extrapulmonaires. La tuberculose pulmonaire a souvent des aspects atypiques, notamment aux stades tardifs de l'infection par le VIH, avec des formes non cavitaires, la présence d'infiltrats dans les lobes inférieurs, une adénopathie hilaire et un épanchement pleural. Aux stades précoces de l'infection par le VIH, on peut observer une tuberculose post-primaire typique avec infiltration des lobes supérieurs et cavernes. Dans les pays en développement, le diagnostic de tuberculose pulmonaire est principalement basé sur l'examen microscopique des expectorations et la radiographie pulmonaire, et on ne dispose que rarement de la possibilité d'effectuer des cultures de mycobactéries. Le taux de détection par examen microscopique des expectorations peut être comparable à celui des sujets séronégatifs pour le VIH, en particulier au stade précoce de cette infection. En revanche, la radiographie pulmonaire montre souvent des aspects atypiques. Les nouvelles méthodes de diagnostic, faisant appel à des sondes d'acide nucléique et à la détection des antigènes par titrage immunologique, sont en cours d'évaluation mais ne sont pas encore entrées dans la pratique. Malgré les difficultés de diagnostic, la tuberculose extrapulmonaire, seule ou associée à une atteinte pulmonaire, a été, dans certaines séries de cas, rapportée dans 50 à 60% de l'ensemble des cas de tuberculose associée au VIH. La tuberculose lymphatique est la forme la plus courante mais il n'est pas rare d'observer des tuberculoses pleurales, péricardiques ou généralisées.

La chimiothérapie courte (2 mois de traitement par l'isoniazide, la rifampicine, le pyrazinamide et l'éthambutol, puis 4 mois de traitement par l'isoniazide et la rifampicine) s'est montrée efficace dans la tuberculose associée au VIH. Toutefois, la chimiothérapie classique de 12 mois (isoniazide, streptomycine et thioacétazone) est beaucoup moins efficace chez ces malades. L'OMS recommande que, dans la mesure du possible, les nouveaux cas infectieux de tuberculose pulmonaire et d'autres formes sévères de tuberculose soient traités par chimiothérapie courte. Celle-ci consistera en une phase intensive de 2 mois avec prise quotidienne d'isoniazide, rifampicine, pyrazinamide et éthambutol, suivie d'une phase de 4 mois avec 3 prises par semaine d'isoniazide et de rifampicine ou d'une période de 6 mois avec prise quotidienne d'isoniazide et d'éthambutol. On évitera la streptomycine en raison du risque de transmission du VIH par des aiguilles et des seringues contaminées, si on dispose d'autres options thérapeutiques. La thioacétazone ne devra pas être utilisée en raison du risque de réactions indésirables graves chez les sujets infectés par le VIH. Pour les cas de tuberculose pulmonaire associée au VIH à frottis négatifs ou les formes moins sévères de tuberculose extrapulmonaire, on peut se contenter d'un traitement de 4 mois consistant en 2 mois d'administration trihebdomadaire d'isoniazide, de rifampicine et de pyrazinamide, puis 2 mois d'administration trihebdomadaire d'isoniazide et de rifampicine ou 6 mois d'administration quoti-

dienne d'isoniazide et d'éthambutol. Chez les malades ayant une tuberculose à frottis positifs, qui ont rechuté ou qui sont rebelles au traitement, on utilisera une association d'isoniazide, de rifampicine, de pyrazimide et d'éthambutol pendant 3 mois, complétée par de la streptomycine pendant les 2 premiers mois, et suivie d'une période de 5 mois avec prise trihebdomadaire d'isoniazide, de rifampicine et d'éthambutol.

L'emploi d'une chimiothérapie préventive à titre d'intervention visant à limiter la survenue d'une tuberculose évolutive chez les sujets infectés par le VIH est actuellement en cours d'évaluation dans les pays en développement. Il faudra procéder à des études d'efficacité, y compris sur les nouvelles associations médicamenteuses, et de faisabilité, avant de pouvoir formuler des recommandations à l'intention des pays en développement. D'autre part, la politique de vaccination par le BCG devra être poursuivie dans les pays où la tuberculose est prévalente. Le vaccin sera administré aussitôt que possible après la naissance, car il est relativement inoffensif chez les nourrissons infectés par le VIH mais encore asymptomatiques, et il peut être utile chez les enfants non infectés par le VIH mais nés de mères séropositives pour le VIH et exposés à un risque élevé d'infection tuberculeuse.

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