Reviews/Analyses

An approach to the problems of diagnosing and treating adult smear-negative pulmonary tuberculosis in high-HIV-prevalence settings in sub-Saharan Africa

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The overlap between the populations in sub-Saharan Africa infected with human immunodeficiency virus (HIV) and Mycobacterium tuberculosis *has led to an upsurge in tuberculosis cases over the last 10 years. The relative increase in the proportion of notified sputum-smear-negative pulmonary tuberculosis (PTB) cases is greater than that of sputum-smear-positive PTB cases. This is a consequence of the following: the association between decreased host immunity and reduced sputum smear positivity; the difficulty in excluding other HIV-related diseases when making the diagnosis of smear-negative PTB; and an increase in false-negative sputum smears because of overstretched resources. This article examines problems in the diagnosis and treatment of smear-negative PTB in high-HIV-prevalence areas in sub-Saharan Africa.*

The main issues in diagnosis include: the criteria used to diagnose smear-negative PTB; the degree to which clinicians actually follow these criteria in practice; and the problem of how to exclude other respiratory diseases that can resemble, and be misdiagnosed as, smear-negative PTB. The most important aspect of the treatment of smear-negative PTB patients is abandoning 12-month "standard" treatment regimens in favour of short-course chemotherapy.

Operational research is necessary to determine the most cost-effective approaches to the diagnosis and treatment of smear-negative PTB. Nevertheless, substantial improvement could be obtained by implementing the effective measures already available, such as improved adherence to diagnostic and treatment guidelines.

Introduction

Background

The global burden of death and disease caused by tuberculosis is immense and is concentrated particularly in low-income countries. In 1995, an estimated 9 million new cases occurred worldwide, with 3 million deaths (*1*, *2*). Some 95% of cases and 98% of deaths from the disease occur in developing countries. The case-notification rate in Africa (97 per 100000 population) is the highest of all the WHO regions (*3*) and in several African countries the rate exceeds 150 per 100000 (*4*).

The global burden of infection with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) is also particularly concentrated in the developing world. In mid-1996, an estimated 21.8 million adults and children worldwide were living with HIV/AIDS, 20.4 million (94%) of whom were in the developing world (*5*). Sub-Saharan Africa is the region worst affected by the HIV pandemic: in mid-1996, an estimated 14 million adults were infected with the virus, representing about 60% of the world's total (*5*). Worldwide during 1995, there were 2.7 million new HIV infections in adults (*5*), of which about 1.4 million (close to 4000 new infections per day) were in sub-Saharan Africa (*5*). By mid-1996, over 6 million adults had developed AIDS since the beginning of the pandemic; of these, 4.5 million (nearly 75%) were in sub-Saharan Africa (*5*).

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In sub-Saharan Africa, there are three broadly defined geographical areas that account for almost 90% of all current cases of HIV infection in adults and adolescents in the region (*5*). Each of two groups of countries contributes about 37% of these cases: Central and East Africa (Cameroon, the Democratic Republic of the Congo, Ethiopia, Kenya, Rwanda, Sudan and Uganda) and southern Africa (Botswana, Malawi, Mozambique, South Africa, the United Republic of Tanzania, Zambia and Zimbabwe). A group of countries in West Africa (Burkina Faso, Côte d'Ivoire, Ghana and Nigeria) contributes about 15% to the total number of adults and adolescents infected with HIV in sub-Saharan Africa.

The impact of the HIV epidemic on tuberculosis depends on the degree of overlap between the population infected with HIV and that infected with *Mycobacterium tuberculosis*. In sub-Saharan Africa the prevalence of both infections is high with considerable overlap between the infected populations, since the age distribution of both infections is concentrated in the 20–50-year age group. In 1994 there were an estimated 4.8 million people worldwide infected with both *M. tuberculosis* and HIV, of whom over 75% were reported to be living in sub-Saharan Africa (*6*). Worldwide estimates of the proportions of new tuberculosis cases attributable to HIV infection were 4% in 1990, 8% in 1995, projected to 14% by the year 2000 (*1*). HIV-related infection thus accounts for a relatively small but increasing proportion of the global tuberculosis burden. In sub-Saharan Africa, however, it accounts for a greater part of the burden: an estimated 30% or more of tuberculosis cases by the year 2000 (*1*).

HIV infection, by impairing cell-mediated immunity, appears to be the highest known risk factor for the reactivation of tuberculosis (*6*). Recent evidence from Europe (*7*) and the USA (*8*) suggests that HIV-infected people may also be more susceptible to new tuberculous infection and may rapidly develop the overt disease. HIV infection is highly prevalent among newly diagnosed tuberculosis patients in sub-Saharan Africa, particularly in East and Central African countries (*9*). Recent studies in Malawi (*10*), Rwanda (*11*) and Zambia (*12*) have revealed HIV seroprevalence rates above 70% in newly diagnosed tuberculosis patients.

The strong association between HIV infection and tuberculosis is sub-Saharan Africa has led to an upsurge of tuberculosis in many countries in the region. Countries with good tuberculosis surveillance and notification systems, such as Burundi, Malawi, Uganda, the United Republic of Tanzania and Zambia, have seen large increases in notification rates over the last 10 years, particularly for patients notified as suffering from sputum-smear-negative pulmonary tuberculosis (PTB) (*13*). This increase has created considerable operational problems for tuberculosis programmes with regard to correct diagnosis and treatment. An additional negative effect of the HIV–tuberculosis coepidemic is the increasing mortality rates notified during the same period.

Features of smear-negative PTB

In the pre-HIV era, large studies of tuberculosis patients were carried out in Kenya (*14*) and the United Republic of Tanzania (*15*). Of the 8741 patients covered, almost 90% presented with pulmonary disease and, of such patients, 78% had sputum smears positive for acid-fast bacilli (AFB) and 66% had cavitation on chest radiography. There was a strong association between the extent of cavitation and sputum smear positivity. These findings agree with observations from industrialized countries that 98% of tuberculosis patients with cavitations have positive AFB sputum smears (*16*).

For HIV-positive patients, tuberculosis was initially reported as an early manifestation of illness, owing to the relative virulence of *M. tuberculosis* (*17*). In sub-Saharan Africa, however, CD4 lymphocyte counts made at diagnosis of HIV-infected patients with smear-positive PTB found that patients may present across a wide spectrum of immunodeficiency. In Zaire, approximately one third of patients had CD4 lymphocyte counts <200/μl, one third had counts of 200–499/μl and one third had counts ≤500/μl (*18*). In Côte d'Ivoire, 18% of patients had counts ≥500/μl and 43% had counts <200/μl (*19*).

In HIV-positive patients with PTB, the clinical pattern of disease, the results of sputum smear tests and the histological characteristics of the tuberculous lesions correlate with host immune status (*20*). In early HIV infection, with only partially compromised host immunity, the features are characteristic of post-primary tuberculosis and resemble those seen in the pre-HIV/AIDS era. The patient usually has typical symptoms; chest radiography reveals extensive lung destruction, cavitation, and upper lobe involvement; and sputum smears are positive for AFB. The histological appearance is usually that of the classic tuberculous lesion with caseating, giant cell and epithelioid granulomas.

With more advanced HIV infection (reflected by declining CD4 lymphocyte counts and increased B2 microglobulin levels patients usually present with atypical pulmonary disease resembling primary PTB (*20, 21*). Clinical features occurring less frequently are productive cough (probably because there is less cavitation, inflammation and endobronchial irritation) and haemoptysis (which

results from caseous necrosis of the bronchial arteries) (*22–24*). The chest X-ray more frequently shows pulmonary infiltrates with no cavities, lower lobe involvement, intrathoracic lymphadenopathy and sometimes a normal appearance. The sputum smears tend to be negative. Tubercle bacilli do not appear in sputum because of the paucity of pulmonary inflammation and decreased cavitation. The histological appearances are those of necrosis, an almost total absence of granuloma, and large numbers of AFB within macrophages.

Extent of smear-negative PTB in areas with high HIV prevalence

Given the immunopathological spectrum seen in HIV-infected tuberculosis patients, it would be expected that the proportion of patients with smear-negative PTB should increase in areas where the prevalence of HIV is high. Initial impressions were that HIV infection in sub-Saharan Africa was associated with a large and predominant increase in smear-negative PTB (*25*). It is apparent from cross-sectional studies, however, that the majority of HIV-positive PTB patients are smear-positive, although the proportion of smear-negative patients is greater among those infected with HIV than among those who are HIV-negative (*22, 23, 26–28*). A study in Zambia (*29*) of over 100 patients with culture-positive PTB found that 24% of those who were HIV-seronegative had a negative sputum smear, compared with 43% of those who were HIV-seropositive. The occurrence of a low bacillary load in the sputum was related to the absence of radiographic cavitation.

With good routine reporting systems, the national tuberculosis programmes of countries such as Malawi and the United Republic of Tanzania have reported a larger increase in new cases of smear-negative than of smear-positive PTB in the last 10 years (*30*). In the United Republic of Tanzania smear-positive cases still exceed smear-negative cases. In Malawi, however, the number of patients with smear-negative PTB now exceeds that of patients with smear-positive tuberculosis (Malawi National Tuberculosis Programme, unpublished data, 1996). In Malawi, in 1986 there were 2874 smear-positive and 2087 smear-negative cases, while in 1995 there were 6293 smear-positive and 7054 smear-negative cases. It is not clear at present whether these figures reflect the true pattern of PTB or whether there is an overdiagnosis or underdiagnosis of smear-negative cases. Reports from national tuberculosis programmes of the pattern of PTB are influenced by various factors such as the criteria used to diagnose smear-negative PTB, the extent to which these criteria are followed in clinical practice, and the number of other respiratory diseases that can resemble and be misdiagnosed as PTB.

Diagnosis of smear-negative PTB

The diagnostic process

The diagnosis of PTB in adults in most African countries is based on simple techniques such as clinical assessment, sputum smear microscopy and chest radiography. Tuberculin skin testing in adults is not useful for individual diagnosis in populations with a high prevalence of *M. tuberculosis* infection. In addition, for HIV-infected individuals, there is the problem that cutaneous anergy increases as the CD4 lymphocyte count declines. In Zaire, over 50% of HIV-positive PTB patients with a CD4 lymphocyte count <200/μl had a negative tuberculin skin test (*18*). Techniques that are widely available in industrialized countries for obtaining pulmonary specimens (such as induced sputum and fibre-optic bronchoscopy with bronchoalveolar lavage) and for analysing them (such as culture, antigen detection and polymerase chain reaction) are beyond the resources of most hospitals in sub-Saharan Africa.

The usual method of screening tuberculosis suspects in low-income countries with a high prevalence of the disease is by sputum smear microscopy (*31*). A patient with at least two positive sputum smears can be registered and started on treatment, and in most cases a chest X-ray is unnecessary. If only one sputum smear is positive or all sputum smears are negative, a chest X-ray is performed. If the results of the X-ray are compatible with PTB, the patient is registered as having smear-negative PTB and treatment is begun.

Criteria used to diagnose PTB

Clinical. In high-prevalence tuberculosis areas, patients should be considered PTB suspects if they have chronic cough, haemoptysis or acute diffuse pneumonia that has not responded to penicillin. Patients with a cough lasting ≥3 weeks, particularly if this is associated with weight loss, are "tuberculosis suspects" (*31*). Within 3 weeks most upper respiratory tract infections resolve spontaneously and lower respiratory tract infections improve if treated with an appropriate antibiotic. HIV-infected patients may lose weight and are at increased risk of pneumonia, especially that caused by *Streptococcus pneumoniae* (*32, 33*). Thus, failure to respond to a broad-spectrum antibiotic such as amoxycillin or trimethoprim–sulfamethoxazole should be an additional criterion for considering a patient as a "tuberculosis suspect". Physical examination adds little to

the diagnosis in such patients because of the nonspecific nature of the signs.

Haemoptysis is an uncommon symptom, but one that the patient readily reports. It may be caused by several diseases including PTB, lower respiratory tract infection and cardiovascular diseases, particularly rheumatic mitral valve disease. Patients with haemoptysis should be investigated for PTB, but physical examination is important to rule out cardiovascular diseases.

PTB can also present as an acute diffuse pneumonia. In a study in Zimbabwe (*34*), the criteria for diagnosing acute diffuse pneumonia were as follows: radiographic appearance of bilateral pulmonary infiltration with at least three zones involved and no cavitation; negative sputum smears; and no response to intravenous benzylpenicillin. A total of 39% of HIV-positive patients with acute diffuse pneumonia had PTB diagnosed using fibre-optic bronchoscopy with mycobacterial culture of bronchoalveolar lavage fluid.

Sputum smear microscopy. It is usually recommended that PTB suspects submit three sputum specimens for microscopy (*35*). As secretions build up in the airways overnight, it has also been standard practice to examine three early-morning sputum samples. Because this method delays the results, it is now recommended that patients provide an on-the-spot sputum sample followed by an early morning sample and another on-the-spot sample (*31*). On-the-spot specimens are almost as sensitive as early-morning specimens under routine field conditions (*36*), and if performed properly this method allows sputum smears to be made within 24 h of the patient presenting to a health facility. Recent studies have shown that the incremental yield from a third smear examination after two negative examinations is relatively small (*36*, *37*). This suggests that routine microscopical examination of two consecutive sputum specimens can give a yield of cases sufficiently high to form the basis for case-finding in low-income countries, should the workload dictate a reduction in the number of examinations.

Most hospital laboratories screen sputum smears for AFB using light microscopy and the Ziehl–Neelsen stain. Sputum smear microscopy is usually positive when there are $\geq$10 000 organisms per ml of sputum (*35*). Positive smears are graded from 1–9 AFB per 100 high-power fields to >10 AFB per field, thus requiring the laboratory technician to examine 100 fields before a smear can be pronounced negative. A microscopist can expect to examine a maximum of 30–40 Ziehl–Neelsen-stained smears in one day (*35*). Central hospital laboratories that receive many sputum specimens per day may benefit from investing in a fluorescence microscope and phenolic auramine or auramine–rhodamine stains. The advantage of this method is that it is possible to scan smears quickly under low magnification, and a microscopist can examine $\geq$200 smears by fluorescence microscopy during one working day (*35*). The auramine–rhodamine stain is also more sensitive than the Ziehl–Neelsen stain (*35*, *38*). Fluorescence microscopes, however, are expensive and require fairly frequent and expensive bulb changes and a steady source of electricity.

Chest radiography. Although the classical radiographic hallmarks of PTB are cavitation, apical distribution, bilateral distribution, pulmonary fibrosis, shrinkage and calcification, no pattern is absolutely diagnostic of tuberculosis. Patients with HIV infection may have atypical radiographic findings such as infiltrates without cavitation (involving particularly the lower lobes) and hilar lymphadenopathy. The radiographic presentation is related to the CD4 lymphocyte count. A study in Canada (*39*) found that the mean CD4 lymphocyte count in HIV-positive PTB patients was 323 cells per µl when the chest radiograph was "typical" and 69 cells per µl when it was "atypical". Similar findings have been reported from Côte d'Ivoire (*40*) and South Africa (*41*).

HIV testing. The link between HIV infection and tuberculosis is known to many members of the public, and a patient with tuberculosis may therefore be well aware of the possibility that he or she may also be infected with HIV. Counselling and voluntary HIV testing, if available, can be offered to tuberculosis patients. Apart from the fact that patients may wish to know their HIV status, there may be several benefits (*42*), such as better diagnosis and management of other HIV-related illnesses, avoidance of the use of drugs, such as thioacetazone, associated with a high incidence of side-effects, and increased condom use and decreased HIV transmission. Knowledge of HIV serostatus may also help in the diagnosis of difficult cases.

Routine diagnostic practice

Patient selection. There is very little information in sub-Saharan Africa on whether the recommended diagnostic process and the criteria for diagnosing suspected tuberculosis are adhered to in routine clinical practice. Operational research in Malawi (unpublished observations, A.D. Harries, 1997) has shown that the routine diagnostic procedure for outpatients at an urban hospital involves first screening by sputum smear microscopy followed by chest

Table 1: **Causes of a false-negative sputum smear**[a]

Stage	Cause
Sputum collection	Inadequate sputum sample
	Inappropriate sputum container
	Sputum stored too long before microscopic examination
Sputum processing	Faulty sampling of sample for smear
	Faulty smear preparation and staining
Smear examination	Inadequate time spent examining smear
	Inadequate attention to smear
Administration	Misidentification of patient
	Incorrect labelling of sample
	Mistakes in documentation

[a] Adapted from Toman (*35*).

radiography of those who are smear-negative. Nevertheless, many patients who do not fulfil the criteria of suspected tuberculosis (cough >3 weeks, weight loss and no response to an antibiotic (*31*)) are referred for sputum examination, and once in the diagnostic process a number of these patients might be misdiagnosed as having smear-negative PTB.

Sputum smear examination. There is little information on the sensitivity and specificity of sputum smear examination in sub-Saharan Africa. Table 1 shows possible causes of a false-negative sputum smear. In practice, false-negative sputum smear results are probably common for several reasons. Even within good national tuberculosis programmes there are a number of operational difficulties in providing laboratory support. There is often a shortage of laboratory personnel, which may result in the workload being high and of poor quality. Staff may not always examine specimens properly or may look at only one or two of the three specimens submitted for microscopy. Furthermore, in many district laboratories the staff have to perform a wide range of duties, which reduces the time devoted to sputum smear microscopy. There may be shortages of laboratory supplies, particularly slides, sputum containers and stains, and replacement bulbs for microscopes may be difficult to purchase. Because of transport problems, there are often long delays in the delivery of sputum specimens from health centres to district laboratories; many positive AFB sputum specimens become falsely negative if left in a sputum container for over a week (*43*). There is often very little quality control performed, either by the laboratories themselves or by a central reference laboratory.

In many tuberculosis programmes in sub-Saharan Africa, a proportion of patients registered as "smear-negative PTB" will not have had any smears evaluated, the diagnosis having been based on clinical features and chest radiography. Lack of sputum smears may be the result of a dry cough and failure of the patient to expectorate, failure of clinicians to insist on sputum specimens, or sputum specimens being mislaid before they can be analysed. The extent of this problem has not been formally documented. In standardized quarterly reports on case finding, there is no separate category for the patient whose sputum has not been examined, and such a patient will usually be classified as "smear-negative PTB".

Given the large workload imposed on African laboratories by the tuberculosis epidemic, practical solutions to the problem need to be developed and tested and implemented in the field. There are several possible solutions, as outlined below.

- The number of trained microscopists for central and district hospital laboratories could be increased.
- Peripheral health centre staff could be trained to prepare sputum smears to be sent to the district laboratory for reading. This would overcome the problem of positive AFB sputum specimens becoming falsely negative in their containers because of transport delays.
- The sensitivity of microscopical diagnosis could be improved by liquefying sputum with household bleach (sodium hypochlorite solution) and concentrating mycobacteria by centrifugation. In Ethiopia, the sensitivity of sputum smears compared with culture was 31% when smears were prepared directly from sputum and 69% when they were prepared after sodium hypochlorite treatment and centrifugation (*44*).
- The number of smears needed for diagnosis could be reduced, depending on the results of the initial reading (*45*).

Chest radiography. Interpretation of chest X-rays of individuals suspected to have PTB is difficult. In the pre-HIV era, there was considerable inter- and intra-observer variation in chest X-ray interpretation by radiologists and chest physicians (*35*). In sub-Saharan Africa, the problem is compounded because there are few trained radiologists or chest physicians, and in most district hospitals chest X-rays are interpreted by relatively inexperienced medical officers or paramedics. The nonspecific findings of pulmonary infiltrates, in the middle or lower lobes, in HIV-positive PTB patients adds to the difficulties of correct radiographic diagnosis. It is now well recognized in industrialized countries (*46*, *47*) and countries in sub-Saharan Africa (*40*, *48*) that the chest X-ray can appear normal in HIV-positive PTB patients. In one study in the USA, 44% of HIV-positive tuberculosis patients with negative sputum smears

and positive cultures of *M. tuberculosis* had a normal or minimally abnormal chest X-ray (*47*). In health facilities where mycobacterial cultures are not available, such patients will probably not be recognized as having PTB and will therefore not receive antituberculous treatment. In Côte d'Ivoire, 44% of patients diagnosed with HIV wasting syndrome had tuberculosis at autopsy, the diagnosis not having been considered previously (*49*).

Differential diagnosis of smear-negative PTB

There have been a number of research studies in sub-Saharan Africa, using either induced sputum or fibre-optic bronchoscopy with bronchoalveolar lavage and transbronchial biopsy, to determine the range of pulmonary diseases found in patients with respiratory illness and negative AFB sputum smears. The number and proportion of smear-negative PTB patients with bacteriologically confirmed tuberculosis is shown in Table 2 (*34*, *50–53*). In these studies, about one-quarter to one-third of patients were found to have tuberculosis. Other pathogens or diseases identified, and which occurred in about one-third of patients, included *Pneumocystis carinii* pneumonia (PCP), bacterial pneumonia due to a wide range of pathogens, Kaposi's sarcoma, nocardiosis and fungal infections with *Cryptococcus neoformans* and *Aspergillus fumigatus*. In both Zimbabwean studies, no diagnosis was made in 22% of patients with chronic cough (*50*) or in 33% of patients with acute diffuse pneumonia (*34*).

The reported frequency of PCP in sub-Saharan Africa varies considerably. No cases were identified in Zambia (*51*), and the disease was very rare in AIDS patients in Central Africa (*54*). In the United Republic of Tanzania 4% of patients infected with HIV and with respiratory symptoms had PCP (*55*). In studies in Zimbabwe, however, 22–33% of the patients had detectable *P. carinii* cysts (*34*, *50*). Autopsy studies on HIV-positive patients in West Africa identified *P. carinii* in 7–9% of cases (*56*, *57*).

The reasons for the variation in the incidence of PCP in different parts of Africa are not clear. The organism appears to be highly prevalent, with 70% of Gambian children showing serological evidence of infection by the age of 8 years — a rate similar to that for British children of the same age (*58*). Host genetic variation or differences in the virulence of the organism may be partly responsible for some of the geographical differences (*59*). Different patient selection criteria may also provide a partial explanation. Seasonal variations in the presentation of PCP have been described (*60*), suggesting that environmental factors may be relevant. Alternatively, other infections such as tuberculosis or bacterial sepsis may lead to death at an earlier stage of HIV infection, when the risk of PCP is low (>200 CD4 T lymphocytes per μl).

Although it is possible to distinguish PCP from PTB using clinical features and radiographic abnormalities (*42*), it may be difficult to do so for PCP and disseminated PTB. A high respiratory rate, hypoxia and the presence of fine reticulonodular shadowing on the chest X-ray are more indicative of PCP (*34*). Mixed disease is common, however, which adds to the diagnostic difficulties. In the diffuse pneumonia study in Zimbabwe, 6 out of 21 patients (29%) with PCP had tuberculosis, compared with 1 out of 6 (17%) with Kaposi's sarcoma (*34*).

Table 2: **Positive culture of *Mycobacterium tuberculosis* for patients with smear-negative pulmonary tuberculosis in sub-Saharan Africa**

Country	No. of patients	HIV serology	No. of patients infected with *M. tuberculosis*	Ref.
Zimbabwe[a]	36	Positive	12 (33)[b]	*50*
Zambia[c]	27	Positive	11 (41)	*51*
Rwanda[a]	92	Positive	17 (18)	*52*
Malawi[d]	73	Not done	30 (41)	*53*
Zimbabwe[e]	64	Positive	24 (39)	*34*

[a] Patients with cough, weight loss and negative sputum smears; fibre-optic bronchoscopy with bronchoalveolar lavage and transbronchial biopsy.
[b] Figures in parentheses are percentages.
[c] Patients with clinical pneumonia; induced sputum with hypertonic saline.
[d] Clinically suspected PTB with non-productive cough or negative sputum smears; induced sputum with nebulized hypertonic saline.
[e] Patients with diffuse pneumonia and negative sputum smears and unresponsive to benzylpenicillin; fibre-optic bronchoscopy with bronchoalveolar lavage.

Treatment of smear-negative PTB

Standardized treatment regimens for use in developing countries

In industrialized countries, where considerations of cost are relatively minor, newly diagnosed tuberculosis in adults is treated with isoniazid and rifampicin for 6 months plus pyrazinamide for the first 2 months (and also ethambutol or streptomycin in populations with high rates of primary drug resistance). In developing countries with limited resources, current WHO recommendations (*61*), which are endorsed by the International Union against Tuberculosis and Lung Disease (IUATLD), are that tuberculosis patients be categorized according to priority for treatment. In general, patients with new smear-positive PTB and other clinically serious forms of the disease

Table 3: **Treatment regimens currently in use for pulmonary tuberculosis in developing countries**

Patients	Treatment regimen:[a] Initial phase	Continuation phase
New smear-positive PTB	2 SRHZ	4 RH
	2 SRHZ	4 R_3H_3
	2 SRHZ	6 TH
	2 S(E)RHZ	6 EH
New smear-negative PTB	2 RHZ	6 TH
	2 RHZ	6 EH
	2 $R_3H_3Z_3$	6 TH
	2 $R_3H_3Z_3$	6 EH
	1 STH	11 TH
	1 SEH	11 EH
	2 STH	10 TH
	2 SEH	10 EH

[a] The number before the first letter of each phase of the regimen is the duration in months of that phase. The number in subscript after the letters is the number of doses per week in the initial and continuation phase of drug regimens; otherwise, drug treatment is daily. S = streptomycin; H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol; and T = thioacetazone.

are accorded the highest priority and should be treated with "short-course" chemotherapy for either 6 or 8 months. For patients with new smear-negative PTB and less severe forms of extrapulmonary tuberculosis, an 8-month regimen is recommended, and in many cases "standard" chemotherapy is still given for 12 months. Table 3 shows various treatment options for new patients with smear-positive and smear-negative PTB. In practice, a country with an effective national tuberculosis control programme will often choose one regimen for patients with smear-positive PTB and those with clinically serious forms of extrapulmonary tuberculosis and another for patients with smear-negative PTB and those with less severe forms of extrapulmonary tuberculosis.

Rationale for lower priority being given to smear-negative PTB

Pre-chemotherapy mortality. Before chemotherapy became available, about 50% of patients with smear-positive pulmonary tuberculosis died within 5 years of diagnosis (*62*, *63*). Analysis of deaths showed that the "decisive" prognostic indicator was sputum status; patients reported to have paucibacillary sputum had a good chance of survival. In an epidemiological survey in southern India, more than half the patients classified as smear-negative, culture-positive at diagnosis were declared cured at 18 months. Furthermore, the excess death rate was about one-third of that for smear-positive cases (*63*).

Infectivity. Patients with smear-negative PTB are substantially less infectious than those with smear-positive PTB. The risk of contracting disease for household contacts of smear-negative, culture-positive patients is about one-tenth of that for contacts of smear-positive patients (*64*). The risk of infection for 0–14-year-old household contacts of smear-negative PTB patients, whether culture-positive or not, is almost the same as that for children living in tuberculosis-free households under similar sociocultural and economic conditions (*65*).

Results of antituberculous chemotherapy. Controlled trials in the 1960s and 1970s in patients with smear-positive PTB showed that a minimum of 6 months' treatment with multiple potent drugs was required to achieve acceptable cure rates and low relapse rates (*66*). Studies in Hong Kong of smear-negative PTB patients found that, while 2–3 months' therapy with multiple drugs was inadequate and entailed high relapse rates (*67*), a 4-month regimen of isoniazid, rifampicin, pyrazinamide and streptomycin given daily or three times per week resulted in an excellent clinical response and a relapse rate of only 2% (*68*). The question of whether to treat smear-negative patients was addressed in the first set of Hong Kong studies (*67*); of smear-negative patients from whom antituberculous chemotherapy was withheld until active disease had been confirmed, either bacteriologically or radiographically, almost 60% received therapy within 5 years because of disease progression. Based on these studies, WHO recommended that patients with smear-negative PTB be treated, regimens of shorter duration being adequate. In controlled clinical trials in East Africa (*69*) and Rhodesia (*70*), 12-month regimens (thioacetazone and isoniazid daily, plus streptomycin daily for the first 2 months) for PTB patients were also found to be effective and well tolerated, and this led to their widespread use in low-income countries in sub-Saharan Africa, particularly for smear-negative PTB.

Costs of antituberculous chemotherapy. For a long time, the cost of the most expensive antituberculous drugs, rifampicin and pyrazinamide, was considered a major obstacle to the widespread adoption of short-course chemotherapy regimens in low-income countries. According to the 1991 price list issued by UNICEF the basic unit price of the short-course chemotherapy regimen[a] was US$ 43, compared with US$ 10–15 for standard 12-month regimens (*71*). For

[a] Streptomycin, rifampicin, isoniazid and pyrazinamide daily for 2 months, followed by thioacetazone and isoniazid for 6 months.

low-income countries with good national tuberculosis programmes, short-course chemotherapy has therefore been used for high-priority cases, while the cheaper "standard" treatment has been used for low-priority cases such as smear-negative PTB.

The case for improved treatment regimens in smear-negative PTB patients in high-HIV-prevalence areas

Influence of HIV on response to treatment. In sub-Saharan Africa, among smear-positive PTB patients who survive and complete treatment, the clinical response, the clearing of radiographic abnormalities and sputum conversion rates are similar in HIV-positive and HIV-negative patients (*19*, *22*, *24*, *72*). Nevertheless, HIV-positive tuberculosis patients on treatment often develop fever, chest infections, oral candidiasis, diarrhoea and bacteraemia. A cross-sectional study in Kenya showed that bacteraemia (usually with *Salmonella typhimurium* or *S. pneumoniae*) occurred in 18% of HIV-positive tuberculosis patients compared with 6% of HIV-negative patients (*73*). Adverse reactions to antituberculous drugs, particularly thioacetazone, are more frequent in HIV-positive than in HIV-negative patients (*74*). Among HIV-positive patients, drug reactions are more common in those with higher levels of immunosuppression (*74*, *75*).

Recent studies using Kaplan–Meier estimates to calculate the probability of survival have shown consistently poorer survival among HIV-positive compared with HIV-negative tuberculosis patients (*72*, *76*, *77*): 12-month case-fatality rates for HIV-positive patients were 23–34% compared with <10% for HIV-negative patients. A study from the USA which examined survival indicators in HIV-infected tuberculosis patients found that the depletion of the CD4 lymphocyte count at diagnosis was the most important predictor of decreased survival (*78*). In sub-Saharan Africa, more profound clinical immunosuppression is associated with increased risk of death (*76*). In both Côte d'Ivoire and Zaire a low CD4 lymphocyte count at diagnosis for HIV-positive, smear-positive patients has been associated with higher mortality (Table 4).

The type of regimen may be important for survival. In Kenya (*76*), no HIV-positive tuberculosis patients given a regimen containing rifampicin and pyrazinamide died within 6 months, compared with 23% of patients given "standard" chemotherapy containing streptomycin, thioacetazone and isoniazid. In Uganda (*75*), a study examining 1-year survival rates found that the relative risk of death for "standard" chemotherapy was 1.57 compared with rifampicin, isoniazid and pyrazinamide in HIV-positive, smear-positive PTB patients. In Zambia (*77*), smear-negative PTB patients were given standard chemotherapy and smear-positive patients were given short-course chemotherapy. Although these groups were not comparable, the mortality ratio for HIV-positive patients on short-course chemotherapy compared with those on standard chemotherapy was reported to be 0.74. The improved survival of patients receiving short-course regimens (especially during the first 6 months of treatment) may be due to the broad spectrum antibacterial activity of rifampicin in preventing bacterial infections.

Table 4: **Percentage mortality in HIV-positive, smear-positive tuberculosis patients in relation to CD4 lymphocyte counts at start of chemotherapy**

	% mortality for CD4 lymphocytes per μl of:		
Study	<200	200–400	≥500
Côte d'Ivoire			
6-month mortality	10%	4%	3%
Zaire			
24-month mortality	67%	22%	8%

Costs of antituberculous chemotherapy. Since 1992, the price of antituberculous drugs (particularly rifampicin and pyrazinamide) on the international market has fallen considerably, and in 1994 was almost half that in 1992 (*79*). The replacement of thioacetazone with ethambutol, in order to avoid the adverse drug reactions, refutes the argument of using the cost of drugs for prioritizing patients. Some short-course regimens are now cheaper than a 12-month regimen containing streptomycin, isoniazid and ethambutol.

Cost–effectiveness of short-course chemotherapy. Even before the cost of antituberculous drugs was reduced, it was calculated for smear-positive PTB cases in the United Republic of Tanzania that the cost per case cured and the cost per death averted were lower using short-course rather than standard chemotherapy (*80*). An analysis of the cost–effectiveness of chemotherapy for smear-positive PTB was extended to include Malawi and Mozambique (*81*). This showed again that short-course chemotherapy was cheaper than standard 12-month chemotherapy per death averted and per year of life saved, both for hospital and for ambulatory care. Other reasons for preferring short-course over standard therapy are the higher cure rate and the reduced need for expensive retreatment regimens

because of lower relapse rates. Although cost–effectiveness studies have not been reported for smear-negative PTB, it is likely that short-course chemotherapy has similar advantages over standard chemotherapy.

Short-course chemotherapy for smear-negative PTB. The overall objective of tuberculosis control, as endorsed by WHO (*82*), is to reduce mortality, morbidity and transmission until the disease no longer poses a threat to public health. Where HIV prevalence is high, the proportion of PTB patients with smear-negative tuberculosis has significantly increased (*30*, Malawi National Tuberculosis Programme, unpublished data, 1996). A high proportion of smear-negative tuberculosis patients will be HIV-seropositive, and circumstantial evidence strongly indicates that HIV-infected, smear-negative patients are more immunosuppressed than HIV-infected patients with smear-positive disease. Although there are no published studies, the risk of adverse drug reactions and the mortality rate during and after treatment are likely to be increased for HIV-infected smear-negative PTB patients.

National tuberculosis programmes could reduce HIV-related morbidity and avoid premature death from HIV-related disease in tuberculosis patients by employing short-course chemotherapy for those with smear-negative PTB. The choice of the short-course regimen would be based on operational considerations (administration, risk of emergence of drug resistance) rather than the cost of the regimen itself.

Conclusion

It is clear that in sub-Saharan Africa more information is required to help solve some of the problems surrounding the diagnosis and treatment of smear-negative PTB. Clear diagnostic criteria need to be developed and agreed upon, and these may vary from country to country according to the availability of diagnostic facilities. The usefulness of these criteria in routine practice must be evaluated within national tuberculosis programmes, and their diagnostic sensitivity and specificity assessed by good microbiological studies using fibre-optic bronchoscopy and bronchoalveolar lavage. The contribution of false-negative sputum smears to the overall burden of smear-negative PTB and the deficiencies in the system that lead to false-negative results need to be addressed.

In health facilities with no access to facilities for mycobacterial culture, ways need to be found to diagnose PTB in patients with negative sputum smears and a normal chest X-ray. Perhaps in these situations there is place for induced sputum procedures or even serological testing. Unfortunately, while serology appears to have reasonable sensitivity and specificity in smear-positive patients, the weak humoral response in paucibacillary disease (*83*) continues to hamper the diagnostic usefulness of this technique.

To date, no clinical trials have been published that have examined the efficacy of different drug regimens in cases of HIV-positive, smear-negative PTB. In particular, no studies have been published that have addressed the question of whether short-course chemotherapy in these patients is more effective and is associated with reduced mortality compared with "standard" chemotherapy. Clinical trials could answer this question. Now that the cost argument no longer holds, however, it is debatable whether such trials are relevant or even ethically justified. In good national tuberculosis programmes supported by IUATLD, treatment outcomes are assessed and reported only for smear-positive patients (*31*). This might be changed so that tuberculosis officers at least record and report whether smear-negative PTB patients have completed therapy, died, defaulted, or been transferred out of the programme. These data need to be collected and analysed by tuberculosis programmes, and cohort analysis could be carried out to confirm or refute the growing belief that this group of patients has a bad prognosis with the currently recommended "standard" treatments.

There is good evidence that HIV-positive patients with PTB are less infectious than their HIV-negative counterparts (*84*, *85*), and this is partly explained by the lower bacillary load in the sputum. Even though smear-negative PTB patients in high-HIV-prevalence settings do not contribute to the transmission of infection, they do contribute directly and indirectly (by increasing the number of cases, thus compromising the efficiency of a tuberculosis control programme) to overall tuberculosis morbidity and mortality. Short-course regimens seem to reduce HIV-associated morbidity and mortality during chemotherapy. National tuberculosis programmes need seriously to reconsider the advantages of replacing standard regimens with short-course regimens for smear-negative PTB patients.

It is imperative that, in the face of severe resource constraints, national tuberculosis programme policies guarantee the most cost-effective approach to diagnosis and treatment. Promoting the most cost-effective response to the challenge of the considerable morbidity and mortality caused by smear-negative PTB lies in improving the implementation of what is currently recommended but not implemented, and in answering the questions posed by this new dimension of an old epidemic.

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