

W Diagnosis of smear-negative pulmonary tuberculosis in people with HIV infection or AIDS in resource-constrained settings: informing urgent policy changes

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Lancet 2007; 369: 2042-49

Published Online

February 28, 2007

DOI:10.1016/S0140-6736(07)60284-0

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The HIV epidemic has led to large increases in the frequency of smear-negative pulmonary tuberculosis, which has poor treatment outcomes and excessive early mortality compared with smear-positive disease. We used a combination of systematic review, document analysis, and global expert opinion to review the extent of this problem. We also looked at policies of national tuberculosis control programmes for the diagnosis of smear-negative pulmonary tuberculosis to assess their coverage, identify the diagnostic difficulties, and find ways to improve the diagnosis of this type of tuberculosis, with a focus on resource-constrained settings with high HIV infection rates. We propose that the internationally recommended algorithm for the diagnosis of smear-negative pulmonary tuberculosis should be revised to include HIV status, severity of AIDS and tuberculosis, and early use of chest radiography in the decision tree. Increased use of promising methods of diagnosis such as sputum liquefaction and concentration and increased availability of fluorescence microscopy should be explored and encouraged. Culturing of sputum in resource-constrained settings with high HIV infection rates should also be encouraged, existing facilities should be made full use of and upgraded, and effective quality-assurance systems should be used. Innovative ways to address human resources issues involved in addressing the diagnostic difficulties are also needed. The development of rapid, simple, and accurate tuberculosis diagnostic tools with applicability at point of care and remote location is essential. To achieve these goals, greater political commitment, scientific interest, and investment are needed.

The WHO DOTS strategy for tuberculosis control was used to diagnose and treat more than 21 million patients with tuberculosis between 1995 and 2004.¹ This strategy recommends identification of infectious tuberculosis cases by microscopic examination of sputum smears to identify acid-fast bacilli. The HIV epidemic has led to huge rises in incidence of tuberculosis in the worst affected countries, with disproportionate increases in smear-negative pulmonary tuberculosis^{2,3} in children and adults. HIV changes the presentation of smear-negative pulmonary tuberculosis from a slowly progressive disease with low bacterial load and reasonable prognosis, to one with reduced pulmonary cavity formation and sputum bacillary load,⁴ more frequent involvement of the lower

lobes,² and an exceptionally high mortality rate.⁵ The Millennium Development Goals call for halving the prevalence and mortality of tuberculosis by 2015 from the rates in 1990. To achieve these goals, faster and more sensitive diagnostic tools than we have now will be essential, for all forms of tuberculosis, especially in people with HIV infection or AIDS.

We aimed to review the frequency of tuberculosis and HIV/AIDS coinfection and current policies of national tuberculosis control programmes for the diagnosis of smear-negative pulmonary tuberculosis of both adults and children with HIV infection. We also identify difficulties and ways to improve the diagnosis of smear-negative pulmonary tuberculosis, especially in resource-constrained settings with high rates of HIV infection, and propose changes to national and international tuberculosis control policies.

To assess the application of current policies of national tuberculosis control programmes, a convenience sample of 17 countries (that had country-based or subcontinental WHO staff) was used to review the algorithm for the diagnosis of smear-negative pulmonary tuberculosis included in their national tuberculosis control and treatment guidelines. The findings were confirmed and complemented by interviews with managers of these national tuberculosis control programmes and WHO staff based in these countries. We included expert opinions from participants of the consultation on tuberculosis and HIV research⁷ and the core group of the global tuberculosis/HIV working group meetings, which were held in February, 2005, in Geneva, Switzerland, to identify the diagnostic difficulties and ways to improve the diagnosis of smear-negative pulmonary tuberculosis. Expert opinions from the meeting and continuing

Search strategy and selection criteria

We used a combination of systematic review, document analysis, and global expert opinion to prepare this paper. We searched PubMed for combinations of the search terms "tuberculosis" and "HIV" with "pulmonary", "smear negative", and "diagnosis". We included reports of studies published in English, between 1985, and May, 2005. 120 reports were reviewed and assessed by one investigator (HG) for appropriateness for inclusion. Studies were included in the review if they reported on tuberculous disease in people with HIV infection or AIDS and if the disease had been stratified into smear-positive and smear-negative. We reviewed data for smear-negative pulmonary tuberculosis only for patients who were also HIV positive. We describe here the type, purpose, and demographic characteristics of the studies. For studies in which neither mean nor median age of the study population was mentioned, we estimated the median age with IQR from the age-groups presented in that study. We used the WHO definition of a case of smear-negative pulmonary tuberculosis: at least three sputum specimens negative for acid-fast bacilli, abnormalities on radiography consistent with active tuberculosis, no response to broad-spectrum antibiotics, and a decision by a clinician to treat with a full course of antituberculosis chemotherapy.⁶

discussion of the expert group on smear-negative tuberculosis that was convened in September, 2005, to propose changes in the WHO and national tuberculosis control policies, were also included.

Frequency of smear-negative pulmonary tuberculosis

Of the 120 reports reviewed and assessed for inclusion in this review, only 15 studies met the selection criteria. All included studies were institution-based and the purpose of most (11/15) studies was to describe the pattern of HIV prevalence in tuberculosis patients, although one study described the cause of lower-respiratory-tract infections in HIV-positive patients. In the remaining three studies the distribution of type of tuberculosis in HIV-positive patients was obtained from secondary data. Additional

characteristics of the studies are shown in table 1. The studies showed that the proportion of cases of smear-negative pulmonary tuberculosis in HIV-positive tuberculosis patients ranged from 24% to 61%.⁸⁻²² However, these institution-based studies did not aim to investigate the distribution of smear-negative pulmonary tuberculosis and thus could be biased towards smear-positive cases because the identification of such cases is emphasised in these tuberculosis services. Moreover, access to health services and DOTS in most resource-constrained settings with high HIV infection rates is restricted and services reach only a fraction of the population. If the availability of these services were increased, we expect that a much higher frequency of disease would be seen. Negative smears could also be the result of poor quality smear microscopy from inadequate

	Setting, study design, purpose	Number of tuberculosis patients tested for HIV	Male to female ratio	Age (years)	Number of patients with HIV	Proportion of HIV-positive patients with tuberculosis other than SPP		Gold standard used for SNP
						SNP	EP	
Zaire, 1987 ⁸	Hospital, cross-sectional, to assess HIV prevalence in tuberculosis patients	465	1.2	25 (19-34)*	176 (38%)	34%	13%	Culture, chest radiograph, response to antibiotic
Haiti, 1988 ⁹	Hospital, prospective, to describe effect of HIV on sputum smear	289	1.1	12-95†	74 (26%)	32%	NA	Culture
Zambia, 1989 ¹⁰	Hospital, prospective, to describe bacteriological pattern of HIV-positive tuberculosis patients	109	72 (61%)	43%	NA	Culture
Malawi, 1995 ¹¹	Hospital, prospective, to assess outcome of HIV-positive tuberculosis patients	793	..	34 (11)	612 (77%)	26%	29%	Chest radiograph, response to antibiotics
Malawi, 1995 ¹²	Hospital, prospective, to describe pattern of tuberculosis and HIV status	686	1.2	33.8 (10.7)‡	547 (80%)	30%	33%	Chest radiograph
USA, 1996 ¹³	Hospital, prospective, to describe infectivity of SNP	1359	2.4	SNP=47.3 (19.0)‡ SPP=46.7 (17.2)‡	323 (24%)	31%	NA	Culture
Ethiopia, 1996 ¹⁴	Hospital, prospective, to describe HIV prevalence in tuberculosis patients	168	2.3	29 (15-62)	96 (57%)	61%	NA	Culture
Haiti, 1997 ¹⁵	VCT centre, prospective, to describe effect of tuberculosis screening in VCT centres	76	0.8	34¶	50 (66%)	28%	NA	Culture, response to antibiotics
India, 1998 ¹⁶	Multicentre, prospective, to describe HIV prevalence in tuberculosis patients	2361	2.4	35 (23-46)*	111 (5%)	35%	4%	Chest radiograph
Tanzania, 1998 ¹⁷	Institution, cross sectional survey, to describe HIV prevalence in tuberculosis patients	10 612	1.5	29 (22-40)*	4653 (44%)	25%	13%	..
Italy, 1999 ¹⁸	Hospital, retrospective, to describe clinical characteristics of HIV-positive tuberculosis patients	146	3.7	SNP=34 (21-59)§ SPP=35 (21-53)§	146 (n/a)	51%	NA	Culture
Brazil, 2000 ¹⁹	Institution, prospective, to describe pattern of tuberculosis and HIV prevalence	1171	2.0	..	550 (47%)	24%	40%	Culture, PCR
Malawi, 2000 ²⁰	Hospital, prospective, to describe acceptability of VCT for tuberculosis patients	955	1.0	32 (11-82)§	735 (77%)	34%	26%	Chest radiograph
Uganda, 2000 ²¹	Hospital, cross-sectional, describe aetiology of lower-respiratory infections in HIV-positive patients	68	0.8	35 (9.4)‡	68 (n/a)	30%	NA	Culture
Ethiopia, 2002 ²²	Hospital, cross-sectional, to describe HIV prevalence and pattern of tuberculosis	500	1.2	28 (1-73)**	97 (19%)	37%	10%	Chest radiograph, response to antibiotics

SNP=smear-negative pulmonary tuberculosis. SPP=smear-positive pulmonary tuberculosis. EP=extrapulmonary tuberculosis. VCT=voluntary counselling and testing. NA=not applicable. *Estimated median (IQR). †Range. ‡Mean(SD). §Median (range). ¶Median. 50% of patients were aged 15-59 years. **Mean (range).

Table 1: Summary of studies showing distribution of smear-negative pulmonary and extrapulmonary tuberculosis in HIV-positive patients

sputum collection, storage, and staining, reading errors, or poor laboratory services. In children, the diagnosis of pulmonary tuberculosis is especially difficult because the disease is paucibacillary and collection of sufficient sputum for smear microscopy and culture is difficult.²³

HIV-positive patients with smear-negative tuberculosis are more likely to die during or before diagnosis than HIV-negative patients because of their immunosuppression, which leads to further underestimates of the magnitude of the problem. Only one study, in Malawi, included follow-up data (7 years) and reported that patients with smear-negative pulmonary tuberculosis had a significantly higher risk of death than patients with smear-positive tuberculosis, with a hazard ratio of 2.2.¹¹ Autopsy studies of HIV-positive patients identified tuberculosis (including previously undiagnosed disease) as a cause of death in 14–54% of deaths of adults or adolescents with HIV infection or AIDS.^{24–26} Similarly, a postmortem study in Zambia showed that a fifth of children who died from respiratory illness had tuberculosis, of whom 60% were HIV-positive.²⁷

Algorithms for diagnosis

As much as possible, patients should be correctly diagnosed and treated for smear-negative pulmonary tuberculosis, but treatment of those without the disease should be avoided. Many countries adapted the WHO guidelines⁶ and included an algorithm for the diagnosis of smear-negative pulmonary tuberculosis in their national guidelines. Table 2 compares diagnostic algorithms of selected countries. Examination of up to nine sputum smears is recommended before the diagnosis of smear-negative tuberculosis is reached in some of the sampled countries. Clinical peer review, or discussion of the case by a clinical team, was used to establish the diagnosis of smear-negative pulmonary tuberculosis case under routine programme conditions in some countries.²⁸

Treatment with broad-spectrum antibiotics is used to exclude infections other than tuberculosis, and to improve the specificity of the diagnosis.^{29,30} Although the result of antibiotic treatment is not affected by HIV status,³⁰ patients with tuberculosis can lose their respiratory symptoms after a course of antibiotics.³¹ Table 2 shows the range of variation in the recommended number of courses and duration of the antibiotic treatment in the sampled countries. Duration of the antibiotic treatment ranged from 5 days to 28 days.

The use of chest radiography for diagnosis of pulmonary tuberculosis can be compromised by poor film quality, low specificity, and difficulties with interpretation.³² HIV infection further diminishes the reliability of chest radiographs in diagnosis of pulmonary tuberculosis, since the disease commonly presents with an atypical pattern. Furthermore, the chest radiograph was normal in up to 14% of HIV-infected patients with sputum-culture-positive tuberculosis.^{18,33–35} However, chest radiography remains an important component of the diagnostic algorithm for

smear-negative pulmonary tuberculosis. The timing of chest radiography along the decision tree of the diagnostic algorithm varies between countries in their national recommendations. A chest radiograph is recommended after examination of up to nine sputum smears in some countries, whereas others do so after examination of just two to three smears, thereby shortening the total time needed to establish the diagnosis (table 2).

A longer health-service delay in the diagnosis of smear-negative than smear-positive pulmonary tuberculosis has been reported,³⁶ perhaps because the diagnostic algorithm needs 11–34 days to establish the diagnosis of smear-negative pulmonary tuberculosis under the most optimistic scenarios, if applied in a linear fashion (table 2). Such delays in diagnosis could be life-threatening.³⁶ The use of variables such as weight loss and anaemia and the use of clinical predictors with a scoring system have been suggested to improve the diagnostic algorithms.²⁹

Methods of diagnosis

Smear microscopy for acid-fast bacteria

Microscopy for the detection of acid-fast bacilli is rapid, low cost, and specific and detects the most infectious cases of tuberculosis, but needs maintenance of equipment, consistent supply of reagents, and proper training in interpretation of the slides.³⁷ For a smear to be positive, there must be at least 5000–10 000 acid-fast bacilli per mL sputum, but these bacilli could be released only intermittently from cavities. The overall positive rate of a single smear microscopy ranges between 22% and 43%.³² If the sensitivity of smear microscopy could be improved, it would be a valuable instrument for tuberculosis control^{37,38} and would improve the diagnosis of tuberculosis in both adults and children.

Microscopy to detect acid-fast bacilli can be improved by sputum liquefaction and concentration by centrifugation and gravity sedimentation.^{2,29,37–39} Available solvents include sodium hypochlorite (household bleach), sodium hydroxide, N-acetyl-L-cysteine-sodium hydroxide solution, and ammonium sulphate and sodium hydroxide solution.² Liquefaction of sputum with sodium hypochlorite and concentration by either centrifugation or sedimentation is the most widely studied procedure.³⁸ A systematic review of 83 studies⁴⁰ showed that studies that used sputum processing with chemicals including bleach and centrifugation yielded a mean 18% increase in sensitivity and an incremental yield (positives with bleach minus positives with Ziehl-Neelsen stain only) of 9%. Studies using bleach and overnight sedimentation showed a 6% mean increase in incremental yield.⁴⁰ Specificity ranged from 96% to 100% with the bleach method alone and from 95% to 100% with the Ziehl-Neelsen method alone.³⁸ Sodium hypochlorite is mycobactericidal and also kills HIV³⁸ and thus improves safety and acceptability in laboratories.

However, the specific effect of this method in HIV-positive patients has not been adequately investigated because most of the reported studies were done in

hospital or research laboratories, which differ greatly from routine programme settings. One study did show increased sensitivity from 38·5% to 50·0% in HIV-positive patients with the bleach method.³⁹ The main disadvantages of the bleach method are that processing takes longer,² the technique is not standardised, and its advantages over other sputum concentration methods are not clear. Issues for consideration in standardisation of this method include the concentration of sodium hypochlorite in the solution, the volume to mix with sputum, and use of distilled or tap water.

Fluorescence microscopy increases the probability of detecting acid-fast bacilli, especially if the sputum contains few bacteria, and hence improves the sensitivity of microscopy in HIV-positive patients. The use of fluorescence microscopy in resource-constrained settings is limited by high investment and maintenance costs: fluorescence microscopy is four to five times more expensive than light microscopy and the lightbulbs must be replaced after 200 h of use. Therefore for economic reasons,⁴¹ fluorescence microscopy is currently recommended only in district laboratories that process more than 30 smears per day² or in regional laboratories where more than 100 smears are examined per day.⁴² Other difficulties are the need for a reliable electricity supply² and the presence of naturally fluorescent particles in sputum that can be confused with acid-fast bacilli.³²

In many settings with high rates of HIV infection, staff spend less than the recommended time examining smears because of the high laboratory workload;⁴³ however, fluorescence microscopy can greatly reduce the time needed for examination of smears. About 15 times as many fields of view can be scanned by fluorescence microscopy as by conventional microscopy in the same period.³² A systematic review⁴⁴ of 43 studies that used fluorescence microscopy showed that on average, in comparison with Ziehl-Neelsen microscopy, fluorescence microscopy showed a 10% increase in sensitivity and 9% incremental yield, and this improvement was not affected by HIV status.⁴¹ The methods had similar specificity, but fluorescence microscopy done on one or two specimens was more cost effective than the Ziehl-Neelsen method used on three sputum specimens.⁴¹ Expanded use of fluorescence microscopy could also improve the diagnosis of other opportunistic infections that are common in people with HIV infection or AIDS such as *Pneumocystis jirovecii* pneumonia.⁴⁵

Sputum and blood cultures

Sputum culture is the gold standard for the diagnosis of tuberculosis and is recommended for that purpose in all developed countries. A positive result in solid or liquid medium needs 10–100 viable bacteria per mL of sputum.² In resource-poor settings, culture is recommended selectively and is mainly used for surveillance of drug sensitivity, to confirm treatment failure and relapse, and in pulmonary tuberculosis patients with repeated negative

	Smear samples: acid-fast bacilli before antibiotic treatment	Courses of antibiotics*	Smear samples: acid-fast bacilli after unsuccessful antibiotic treatment	Chest radiograph after unsuccessful antibiotic treatment	Clinical assessment after successful antibiotic treatment	Estimated time until diagnosis of SNP (days)†
Cambodia, (2003)	3x (1 set) 3 specimens	2 (1–2 weeks)	3x (1 set) 3 specimens	Yes	Yes	20
Côte d'Ivoire, (2003)	3x (1 set) 3 specimens	2 (7–10 days)	3x (1 set) 3 specimens	Yes	Yes	16
Ethiopia, (2002)	3x (1 set), 2x (1 set) 5 specimens	1 (7–10 days)	3x (1 set) 3 specimens	Yes	Yes	18
India (2005)	3x (1 set) 3 specimens	1 (10–14 days)	3x (1 set) 3 specimens	Yes	No	20
Kenya (2003)	3x (1 set) 3 specimens	1 (5–7 days)	3x (1 set) 3 specimens	Yes‡	No	11
Laos, (2004)	3x (1 set) 3 specimens	1 (2 weeks)	3x (1 set) 3 specimens	Yes	No	25
Lesotho (2005)	3x (1 set) 3 specimens	1 (10–14 days)	3x (1 set) 3 specimens	Yes	No	20
Mozambique, (2004)	2x (1 set) 2 specimens	2 (7–15 days)	2x (1 set) 2 specimens	No§	Yes	21
Malawi, (2002)	2x (1 set) 2 specimens	1 (1 week)	None¶	Yes	No	11
Sri Lanka (2005)	3x (1 set) 3 specimens	1 (1–2 weeks)	3x (1 set) 3 specimens	Yes	Yes	20
Sudan, (2000)	3x (1 set) 3 specimens	1 (1 week)	3x (1 set) 3 specimens	Yes	No	13
Swaziland (2004)	3x (1 set) 3 specimens	1 (1 week)
Tajikistan, (2003)	3x (1 set) 3 specimens	1 (7–14 days)	3x (1 set) 3 specimens	Yes	Yes	20
Tanzania, (2003)	3x (2 sets) 6 specimens	1 (14 days)	3x (1 set) 3 specimens	Yes	No	22
Uganda, (2002)	3x (1 set) 3 specimens	1 (1 week)	3x (1 set) 3 specimens	Yes	No	13
Zambia, (2001)	3x (1 set) 3 specimens	2 (3–4 weeks)	3x (1 set) 3 specimens	Yes	Yes	34
Zimbabwe, (1999)	3x (1 set) 3 specimens	2	3x (1 set) 3 specimens	Yes
WHO (2003)	3x (1 set) 3 specimens	1 (..)	3x (1 set) 3 specimens	Yes	Yes	13

SNP=smear-negative pulmonary tuberculosis. Best scenario assumption: 2 days to obtain one set (2–3 samples) sputum examination result, 2 days to obtain chest radiograph, 2 days for clinical peer review, plus the maximum duration for the antibiotic course specified. Sputum examinations, chest radiograph, and clinical consultations done in the same facility. *Duration of each treatment. †This scenario assumes the activities to be done sequentially, which might not always be the case. ‡Timed with repeat smear samples. §Before antibiotic treatment. ¶Direct to chest radiograph. ||Not specified, but for sufficient period.

Table 2: National tuberculosis control programme recommendations of selected countries for diagnosis of smear-negative pulmonary tuberculosis

smear results.^{6,42} In a study of HIV-positive tuberculosis patients in Khayelitsha, South Africa, 49% of patients on tuberculosis treatment had negative smears on direct microscopy but their sputum cultures were positive.⁴⁶

Mycobacteria are slow-growing organisms, therefore culture takes 6–8 weeks and needs reasonably sophisticated facilities and technical expertise.⁴² Thus its usefulness is restricted, especially in resource-constrained settings that

have high HIV infection rates. Sputum culture of HIV-infected patients needed more incubation time than that of patients without HIV infection,⁴⁷ which is consistent with the lower bacillary load seen in the sputum of HIV-infected patients.⁴⁸ The specificity of culture is also affected by contamination since manipulations in the laboratory can result in transfer of bacteria from positive to negative samples. Even in microbiology laboratories with the best anticontamination procedures, 1–4% of positive cultures might be false-positives.³² Moreover, 15–20% of adults with pulmonary tuberculosis whose diagnosis has been based on clinical, radiographic, and histopathological findings and response to anti-tuberculosis treatment have negative sputum cultures.⁴⁹

Conventional culture that uses a growth medium made from egg or agar is five to ten times more costly per sample than smear microscopy.³² Modern liquid media and accurate growth detection systems improve the sensitivity and greatly shorten the time needed for growth to be seen. The mycobacteria growth incubator tube (MGIT) is one of the most studied new culture methods.⁵⁰ The mean time for detection of growth of mycobacteria in MGIT was short and ranged from 8 days to 16 days, including in HIV-infected tuberculosis patients, as compared with 20 days to 26 days in conventional culture (Lowenstein-Jensen) media.^{51–53} The detection time in smear-negative cases was slightly longer than the mean detection time of all specimens.⁵¹ Moreover, the same infrastructure and technical expertise are needed as for the conventional culture method, and the MGIT is costly to install,³² which restricts its use, especially in peripheral facilities of resource-constrained settings. Studies on the contamination rate with MGIT compared with conventional culture have had contrasting results. A few studies showed lower contamination rates with MGIT (8 vs 21% and 10 vs 17%)⁵² than with conventional culture media. Other studies showed contamination rates in MGIT (4–15%) that exceeded those in solid media (1–10%).⁵¹ These doubts about accuracy have hindered the uptake of this new culture method.⁵¹

Mycobacteraemia is detected in many patients with HIV infection and active tuberculosis⁵⁴ including children,²³ and has also been noted as an important cause of fever among patients in hospital in settings with high HIV infection rates.^{55,56} Hence, blood culture was suggested as a tool to assist the diagnosis of tuberculosis in HIV-positive patients⁵⁴ especially those with disseminated disease,⁵⁷ and in locations where atypical mycobacteria are common.⁵⁸ Liquid culture technique^{59,60} can shorten the recovery time of the mycobacteria by 15 days compared with the standard Lowenstein-Jensen medium.⁵⁹ PCR has also been used by several investigators to detect mycobacteraemia.⁶¹ However, most tuberculosis cases can be diagnosed by routine methods and protocols, and in one study identification of the presence of mycobacteraemia did not improve outcome.⁵⁶ Moreover, mycobacterial blood culture was not

cost-effective⁶² in resource-constrained settings. Several studies also showed that the detection of mycobacteraemia among people with HIV infection or AIDS varies widely between 19% and 96%.^{54,63–66}

Rapid diagnostic methods

New methods for rapid identification of *Mycobacterium tuberculosis* have been under development, especially in the past decade.³⁷ These methods include gene amplification assays that can identify mycobacterial isolates from culture or directly from clinical specimens, and serological assays against various mycobacterial antigens. FASTPlaque TB (Biotec Laboratories) is a test that uses phage amplification technology, and has been well tested, including in settings with high rates of HIV infection, but has produced contradictory results.^{67,68} Antigen-specific assays that measure interferon gamma released from T cells through ELISA (QuantiFERON-TB) and enzyme-linked immunospot (ELISPOT) have been developed.⁶⁹ Although ELISPOT was used to detect active tuberculosis disease in HIV-infected adults⁷⁰ and children,⁷¹ these tests are generally known for their inability to distinguish between active disease and latent infection.⁷² Moreover, these tests need advanced and sophisticated infrastructure, so they are almost exclusively used in more developed countries. Even in such countries some of the methods have little use.³⁷

What needs to be done?

There is an urgent need to develop rapid, simple, and accurate tuberculosis diagnostic tools. Although such tests are under development and validation, policy and clinical practice should be modified to improve the diagnosis and management of smear-negative pulmonary tuberculosis. Rapid diagnosis and treatment of smear-negative pulmonary tuberculosis in settings with high HIV prevalence are important⁷³ because the HIV epidemic is driving a large increase in the proportion of patients with smear-negative pulmonary and extrapulmonary tuberculosis who have inferior treatment outcomes. Such outcomes include excessive early mortality compared with HIV-positive, smear-positive pulmonary tuberculosis patients.⁴ Furthermore, an increasing trend of mycobacteraemia was seen in HIV-positive adults admitted to hospital in a setting with high HIV infection rates, who had not been diagnosed with tuberculosis.⁵⁵ Therefore, existing evidence, even if incomplete, and diagnostic methods that proved effective under difficult conditions should be assessed and implemented if proven useful. Existing tools should be improved while the relevant research issues are addressed, with both approaches having equal priority.

Recording and reporting needs to be improved. The main aim of national tuberculosis control programmes is to detect, treat, and cure infectious cases of tuberculosis for sound public-health reasons. Thus, less attention is given to documentation of treatment outcomes of patients with smear-negative and extrapulmonary tuberculosis, although the programmes providing the diagnosis and treatment of

such patients. For example, WHO guidelines recommend the inclusion and reporting of tuberculosis cases without smear results as cases of smear-negative pulmonary tuberculosis.⁶ This policy has to be urgently revisited and countries should be encouraged to generate sound case notification and treatment outcome data for cases of smear-negative pulmonary tuberculosis. Such data should be used to inform policy makers and boost programme performance both nationally and globally.

The internationally recommended diagnostic algorithm should be revised to shorten the recommended time to establish a diagnosis of smear-negative pulmonary tuberculosis, and also to include procedures for children. For application in resource-constrained settings with high HIV prevalence, the revision should include HIV status, severity of both tuberculosis and AIDS disease, earlier use of chest radiography in the decision tree of the algorithm, and if possible, prompt discussion of the case by a clinical team.

Other approaches to be explored include improvement of the quality of chest radiographs, and interpretation by clinical practitioners, including nurses, through specialised training and encouragement of participatory peer review by clinicians. Strengthening of referral systems from peripheral services to higher institutions with radiographic facilities is essential to prevent patients from repeatedly undergoing the same routine diagnostic process. The maximum numbers of sputum smears examined and courses of antibiotics prescribed in the decision tree of the diagnosis should depend on the clinical status of the patient. The revised diagnostic algorithms should be promptly validated and assessed for feasibility and cost-effectiveness.

Sputum concentration methods that show potential to improve sputum microscopy need to be encouraged. Careful standardisation of the concentration methods (eg, the bleach method) by use of existing evidence and through multicentre randomised controlled trials is also essential. Operational studies to assess the efficiency, feasibility, and cost-effectiveness of these methods under routine programme conditions are urgently needed.

Additionally, the decentralised use of fluorescence microscopy in settings with high HIV rates should be explored and encouraged. Resources available to countries through funding mechanisms such as The Global Fund to fight AIDS, Tuberculosis, and Malaria should be used to ensure the expanded use of fluorescence microscopy as a routine activity of tuberculosis-control programmes. Careful assessment of the effectiveness of this strategy (including cost) and improvement of its performance through quality assurance and external review are important.

Culture in resource-constrained settings with high HIV infection rates should be encouraged as part of routine tuberculosis control activities with an effective quality assurance system. Routine sputum culture

needs a reasonably efficient health system and adequate laboratory and programme staff. Therefore, emphasis should first be on making full use of and upgrading existing facilities. Country-specific models that enable effective and rapid decentralisation of culture services need to be sought. Establishment of effective integrated district transportation systems in coordination with other services (eg, WHO's Expanded Immunization Programme) is also helpful for transfer of sputum specimens to facilities with culture services.

Tuberculosis control services in resource-constrained settings with high HIV prevalence emphasise identification and cure of patients with tuberculosis who present to health facilities. However, these facilities generally have weak capacity to detect tuberculosis. Early detection is affected by a range of factors such as patients' motivation and degree of diagnostic suspicion by health workers. Specific detection of active tuberculosis cases in patients with HIV infection or AIDS is feasible and improves the rate of early diagnosis and successful treatment of tuberculosis.¹⁵ Intensified tuberculosis case finding should be encouraged in patients with HIV infection or AIDS and those presenting to the general outpatient services.⁷⁴ The role of community members in identification and referral of people suspected to have tuberculosis should be encouraged.⁷⁵

Conclusion

Extensive basic research to develop rapid, simple, and accurate tuberculosis diagnostic tools that can be used in laboratories and remote locations is essential. Increased political commitment, greater scientific interest, and massive investment are needed. At the same time, innovative means need to be sought to address the human resources issues in the diagnosis problem, such as strategic efforts to train adequate and efficient laboratory staff at all levels. Strong advocacy and activism should be promoted to push for research and development to yield feasible and robust technologies such as solar-powered fluorescence microscopy or culture facilities, which would be useful for resource-constrained settings with no electricity and could be implemented with little technical expertise. Price negotiation with manufacturers of products such as rapid culture technologies and portable chest radiography machines could also be useful. Urgent actions are needed from national HIV and tuberculosis control authorities and service providers in HIV prevalent and resource-constrained settings to implement the revised WHO recommendations, including case definitions to improve and expedite the diagnosis and treatment of tuberculosis in people with HIV infection or AIDS.⁷⁶

Conflict of interest statement

Rick O'Brien is an employee of the Foundation for Innovative New Diagnostics (FIND), which has a formal agreement with Becton Dickinson Diagnostics to undertake demonstration studies to

determine the feasibility and effect of its mycobacteria growth indicator tube MGIT culture system. FIND also has an agreement with Biotec to assist in the further development of Biotec's phage-based FASTPlaque technology.

Acknowledgments

We thank the members of the core group of the TB/HIV Working Group of the Stop TB Partnership, participants of the TB/HIV research priority and informal expert consultation on smear-negative tuberculosis diagnosis meetings which were held in Geneva, Switzerland, in February and September, 2005, respectively. We also thank Getachew Aderaye, Charlie Gilks, Tony Harries, Malgorzata Grzemska, Dermot Maher, Mario Raviglione, and Bertie Squire for their reviews and comments on this paper.

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