

**Improving the
diagnosis and
treatment of
smear-negative
pulmonary and
extrapulmonary
tuberculosis
among adults and
adolescents**

Recommendations
for HIV-prevalent and
resource-constrained
settings



World Health
Organization

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STOP TB DEPARTMENT
DEPARTMENT OF HIV/AIDS



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Acknowledgements

Prepared by

Members of the WHO Expert Group on Smear-Negative TB: Getachew Aderaye (Addis Ababa University, Ethiopia), Ludwig Apers (Institute of Tropical Medicine, Antwerp, Belgium), Leopold Blanc (World Health Organization, Switzerland), Amy Bloom (United States Agency for International Development, United States of America), Jermiah Chakaya (Ministry of Health, Kenya), Liz Corbett (London School of Tropical Medicine and Hygiene, United Kingdom), Haileyesus Getahun (World Health Organization, Switzerland), Charlie Gilks (World Health Organization, Switzerland), Jeroen van Gorkom (KNCV Tuberculosis Foundation, the Netherlands), Mark Harrington (Treatment Action Group, United States of America), Pierre-Yves Norval (World Health Organization, Switzerland), Paul Nunn (World Health Organization, Switzerland), Rick O'Brien (Foundation for Innovative and New Diagnostics, Switzerland), T. Santha (Ministry of Health, India) and Jay Varma (United States Centers for Disease Control and Prevention, Thailand).

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Overall coordination

Haileyesus Getahun.

Abbreviations

AFB	acid-fast bacillus
CPT	co-trimoxazole preventive therapy
CXR	chest X-ray
ETB	extrapulmonary tuberculosis
HIV	human immunodeficiency virus
IRIS	immune reconstitution inflammatory syndrome
PCP	Pneumocystis carinii pneumonia
WHO	World Health Organization

PART I

Improving the diagnosis and treatment of smear- negative tuberculosis

Background

Rates of smear-negative pulmonary and extrapulmonary tuberculosis have been rising in countries with HIV epidemics. The mortality rate among HIV-infected tuberculosis patients is higher than that of noninfected tuberculosis patients, particularly for those with smear-negative pulmonary and extrapulmonary tuberculosis. Delayed diagnosis may be an important cause of excess mortality in people living with HIV who have smear-negative pulmonary and extrapulmonary tuberculosis. In the absence of rapid, simple, and accurate diagnostic tools for smear-negative pulmonary and extrapulmonary tuberculosis, diagnostic algorithms have been recommended. Earlier algorithms and recommendations have been developed through consensus and expert opinion, without a firm evidence base. These algorithms extend a patient's evaluation over a period of time, during which HIV-infected patients may die from undiagnosed tuberculosis or from advanced HIV complications. The Stop TB Strategy now emphasizes the timely diagnosis and treatment of all cases of tuberculosis, including smear-negative pulmonary and extrapulmonary tuberculosis.

The existing guidelines for diagnosis of smear-negative pulmonary tuberculosis were published by WHO in 2003 (1) and codified in 2006 in the *International standards for tuberculosis care* (2), a publication of organizations, including WHO, which are members of the Stop TB Partnership. The *International standards* generally maintained the 2003 WHO recommendations, but recognize the importance of "flexibility" when applying these guidelines to smear-negative patients who are seriously ill, such as patients with HIV infection. It also highlights the absence of evidence showing how well these guidelines perform in HIV-infected patients.

Target audience

This document is intended for those dealing with tuberculosis and HIV at all levels in HIV-prevalent and resource-constrained settings. It is intended to assist development of national policies to improve the diagnosis and

management of smear-negative pulmonary and extrapulmonary tuberculosis. The recommendations and algorithms are designed for use by national tuberculosis and HIV/AIDS control programmes and service providers. HIV-prevalent settings are defined as countries, subnational administration units (e.g. districts, counties) or selected facilities (e.g. referral hospitals, drug rehabilitation centres) where the adult HIV prevalence rate among pregnant women is $\geq 1\%$ or HIV prevalence among tuberculosis patients is $\geq 5\%$. In those countries where national HIV prevalence is below 1%, national tuberculosis and HIV control authorities should identify and define HIV-prevalent settings (subnational administrative units or facilities) based on the epidemiology of the HIV epidemic and the magnitude of HIV-associated tuberculosis, and develop appropriate guidance for the implementation of these recommendations. The recommendations and revised algorithms are intended for immediate implementation in sub-Saharan Africa and other HIV-prevalent settings, as defined by national tuberculosis and HIV control authorities, to guide the expedited diagnosis and management of tuberculosis.

Process of formulation

In September 2005, WHO convened an expert group to review currently recommended approaches to the diagnosis of smear-negative tuberculosis in HIV-prevalent settings and to propose revisions to existing WHO guidelines. The Expert Group has reviewed existing evidence in each of the relevant areas and made recommendations and has revised the existing diagnostic algorithms. The recommendations and revised diagnostic algorithms were then posted on the WHO Stop TB Department's web site for an open consultation. Feedback was obtained from national programme managers, researchers, clinicians and other health workers throughout the world, and from all the leading international organizations working on tuberculosis. The Expert Group subsequently revised the recommendations and algorithms in the light of the feedback from the global consultation and from presentations at various international scientific meetings. The Strategic and Technical

Advisory Group for Tuberculosis (STAG-TB) and the Strategic and Advisory Committee for HIV (STAC-HIV), the two independent bodies that advise WHO on tuberculosis and HIV respectively, endorsed the recommendations.

Strength of the recommendations

The recommendations contained in these guidelines are based on evidence from randomized clinical trials, high-quality scientific studies, observational cohort data and, where sufficient evidence is not available, on expert opinion (see Table 1). When appropriate, the level of evidence used to formulate the recommendations is included in the text of the document and shown in Table 1. The strength of each recommendation is stated when appropriate, along with the level of evidence, to provide a general indication of the extent to which regional and country programmes should consider implementing the recommendations.

For example, a recommendation marked as A II is a recommendation that should be followed and is based on evidence from at least one high-quality study or several adequate studies with clinical, laboratory or programmatic endpoints. Those recommendations which are based on well established clinical practice are presented as such, without any indication of the level of evidence. For example, the recommendation that calls for an increased level of clinical awareness and competence in managing extrapulmonary tuberculosis at first-level health facilities is not linked with a particular level of evidence. The recommendations do not explicitly consider

cost-effectiveness, although the realities of burden of disease, human resources, health system infrastructure and socioeconomic issues need to be taken into account when adapting these recommendations to regional and country programmes.

Implementation and evaluation

In the absence of complete evidence, the recommendations were built on consensus and iterative global expert opinion. It is believed that they will provide a reasonable response to the catastrophe posed by the dual tuberculosis and HIV epidemics. These recommendations should, therefore, be implemented in HIV-prevalent settings in order to improve and expedite the diagnosis of tuberculosis among people living with HIV. The implementation of the recommendations requires a reasonably efficient health system, including quality assurance for laboratories and effective supply management and training for programme staff. Moreover, depending on country-specific-factors, it may require revision of national guidelines, logistical and technical arrangements including human resources, training and infrastructure development. While the recommendations are being implemented, it is essential to build up the evidence base required to assess their effectiveness and feasibility. Careful evaluations by national authorities, research groups and interested parties are needed to assess the likely benefits and responsiveness of the recommendations for the dual tuberculosis and HIV epidemics. The findings of these evaluations will inform policy

Table 1. Grading of recommendations and levels of evidence

Strength of the recommendations	Level of evidence available for the recommendations
A. Recommended – should be followed	I. At least one randomized controlled trial with clinical, laboratory or programmatic endpoints
B. Consider – applicable in most situations	II. At least one high-quality study or several adequate studies with clinical, laboratory or programmatic endpoints
C. Optional	III. Observational cohort data, one or more case-controlled or analytical studies adequately conducted IV. Expert opinion based on evaluation of other evidence

Sources: adapted from (3), (4), (5), (6).

change designed to improve programme performance both globally and nationally. A protocol that provides generic guidance on evaluation of the recommendations to improve the diagnosis of tuberculosis in HIV-prevalent settings is annexed to this document.

Recommendations

Revised case definitions

The following are suggested case definitions for use in HIV-prevalent settings:

Smear-positive pulmonary tuberculosis

- One sputum smear examination positive for acid-fast bacilli (AFB) **and**
- Laboratory confirmation of HIV infection **or**
- Strong clinical evidence of HIV infection.¹

Smear-negative pulmonary tuberculosis

- At least two sputum specimens negative for AFB **and**
- Radiographical abnormalities consistent with active tuberculosis **and**
- Laboratory confirmation of HIV infection **or**
- Strong clinical evidence of HIV infection¹ **and**
- Decision by a clinician to treat with a full course of antituberculosis chemotherapy

OR

- A patient with AFB smear-negative sputum which is culture-positive for *Mycobacterium tuberculosis*.

Extrapulmonary tuberculosis

- One specimen from an extrapulmonary site culture-positive for *Mycobacterium tuberculosis* or smear-positive for AFB

OR

- Histological or strong clinical evidence consistent with active extrapulmonary tuberculosis **and**

¹ Depending on clinical assessment and national and/or local policy, a person of unknown HIV status may be classified as HIV-positive for the purposes of diagnosis and management.

- Laboratory confirmation of HIV infection **or**
- Strong clinical evidence of HIV infection¹ **and**
- A decision by a clinician to treat with a full course of antituberculosis chemotherapy.

Strength of recommendation: A

Antibiotics trial

Context: There is limited evidence for the use of empirical antibiotic treatment to rule out tuberculosis as a cause of cough in HIV-infected persons. Although non-response to antibiotics increases the likelihood of tuberculosis, the converse is not true; response to antibiotics does not exclude tuberculosis in tuberculosis suspects living in HIV-prevalent settings. Inappropriate use of broad-spectrum antibiotics may also lead to drug resistance, treatment delay and death of patients because of prolonged symptoms.

Recommendations:

- The primary role of antibiotics should not be as a diagnostic aid; they should be used to treat concomitant bacterial infection in people living with HIV/AIDS with cough or serious illness (**Strength: A–IV**).
- Antibiotic treatment is appropriate for HIV-infected patients with cough, because bacterial infections are common both with and without tuberculosis (**Strength: A–II**).
- Seriously ill patients with symptoms suggestive of tuberculosis should be treated empirically with broad-spectrum antibiotics because the benefits outweigh the risks (**Strength: A–II**).
- When indicated, one course of broad-spectrum antibiotics, including coverage for typical and atypical causes of community-acquired pneumonia, should be used to reduce the time delay for tuberculosis diagnosis (**Strength: A–IV**). In such circumstances, fluoroquinolones should be avoided, as they may cause undue delay in the diagnosis of tuberculosis (**Strength: A–II**).
- More research about the effectiveness and use of an antibiotic trial in the diagnostic algorithm and the choice of antibiotics, par-

ticularly for people living with HIV is needed (**Strength: A**).

Chest radiograph

Context: Although chest X-ray abnormalities are common in HIV-infected persons without tuberculosis, the chest X-ray plays an important role in the diagnosis of tuberculosis among people living with HIV. The chest X-ray can also be an important entry point to diagnosing non-tubercular chest diseases, which are common among people living with HIV.

Recommendations:

- Chest X-ray presentations of tuberculosis in HIV patients are now well characterized and should no longer be considered “atypical” for tuberculosis in HIV-prevalent settings (**Strength: A–IV**).
- Chest X-rays play a significant role in shortening delays in diagnosis and should be performed early in the course of investigation of a tuberculosis suspect (**Strength: A–II**).
- Sound clinical judgement is needed to put a seriously ill patient with negative sputum smear results on antituberculosis treatment using only suggestive radiographical findings. In such circumstances, the clinical response of the patient has to be monitored and tuberculosis diagnosis should be confirmed at least by clinical response to antituberculosis treatment and preferably by culture (**Strength: B–II**).
- The limitations that exist on the wider use of chest X-rays, such as nonavailability at peripheral health facilities and the difficulty of interpreting results, even by trained physicians, need to be addressed, including through training (**Strength: A**).
- Research is needed to identify innovative ways to enhance the ability of clinicians, including nonphysicians, to interpret chest X-rays accurately, to assess the feasibility and added value of peer reviewing of chest X-rays and to evaluate novel imaging techniques that might replace conventional radiography (**Strength: A**).

Sputum culture

Context: Sputum culture is the gold standard for the diagnosis of tuberculosis. However, Mycobacteria are slow-growing organisms and culture takes several weeks and requires relatively sophisticated facilities and technical expertise. Sputum culture of HIV-infected individuals requires more incubation time than for non-HIV-infected patients, although it is still of value. There are major challenges to ensuring access to high-quality sputum culture in HIV-prevalent and resource-constrained settings.

Recommendations:

- Careful feasibility studies are needed, particularly for liquid culture systems that are more sensitive and rapid than solid culture, and have the potential for expanded use, including in HIV-prevalent and resource-limited settings (**Strength: A–II**).
- In patients with negative sputum smears, sputum culture should be encouraged as part of the diagnostic procedure for people living with HIV who are being evaluated for AFB smear-negative tuberculosis, since it will improve the quality of care and assist the confirmation of the diagnosis (**Strength: A–I**).
- Existing capacity for the use of conventional culture systems in countries should be explored, encouraged and strengthened. Decentralization of sputum culture services with an efficient quality assurance system is essential. Establishment of an effective transport system for sputum is also essential (**Strength: A**).

Immune reconstitution inflammatory syndrome (IRIS) and tuberculosis diagnosis

Context: Immune recovery usually occurs rapidly in HIV-infected adults who are started on antiretroviral treatment (ART). Occasionally, recovery of the immune system leads to clinical signs and symptoms of active tuberculosis. This may be because patients had subclinical tuberculosis before the antiretroviral treatment began, or because a latent tuberculosis infection has been reactivated. The condition, which is

known as immune reconstitution inflammatory syndrome (IRIS), usually occurs within three months of initiation of antiretroviral treatment. It can also appear as exacerbation of tuberculosis when initiating antiretroviral treatment in HIV-infected tuberculosis patients who are already undergoing tuberculosis treatment, similar to the well documented paradoxical reactions seen in some patients without underlying HIV infection. IRIS is commonly associated with tuberculosis, although it can also occur with other pathogens.

Recommendations:

- Tuberculosis should be diagnosed and treated before initiation of antiretroviral treatment and whenever there is clinical suspicion of IRIS (**Strength: A–IV**).
- IRIS is not a reason to switch patients on to second-line antiretroviral treatment, although adjustment to the treatment regimen may be needed to ensure compatibility with tuberculosis treatment (**Strength: A–IV**).
- Health care workers should be aware of paradoxical worsening of tuberculosis on starting antiretroviral treatment and both antiretroviral and antituberculosis treatments should be continued (**Strength: A–IV**).

Diagnosis of extrapulmonary tuberculosis

Context: Extrapulmonary tuberculosis is more strongly HIV-related than pulmonary tuberculosis, with a combination of the two being especially suggestive of underlying HIV-infection. HIV-related extrapulmonary tuberculosis is a WHO clinical stage 4 (advanced AIDS) diagnosis, and patients with HIV-related extrapulmonary tuberculosis often have disseminated disease and are at high risk of rapid clinical deterioration and death. The accurate diagnosis of extrapulmonary tuberculosis is complex and difficult, particularly in peripheral health facilities with limited support and diagnostic infrastructure. Simplified, standardized clinical management guidelines for most common and serious forms of extrapulmonary tuberculosis are included in this document to assist health care workers at the district hospital level in HIV-prevalent settings (see Part II below).

Recommendations:

- There should be an increased level of clinical awareness and competence in managing extrapulmonary tuberculosis at first-level health facilities, including earlier referral of patients when appropriate (**Strength: A**).
- In peripheral health facilities in HIV-prevalent settings, health care workers should initiate empirical tuberculosis treatment early in patients with serious illness thought to be due to extrapulmonary tuberculosis. Every effort should then be made to confirm the diagnosis of tuberculosis, including monitoring the clinical response of the patient, to ensure that the patient's illness is being managed appropriately. If additional diagnostic tests are unavailable, and if referral to a higher level facility for confirmation of the diagnosis is not possible, tuberculosis treatment should be continued and completed (**Strength: B–IV**).
- Empirical trials of treatment with incomplete regimens of antituberculosis drugs should not be performed (**Strength: A–I**).
- If a patient is treated with empirical antituberculosis drugs, treatment should be with standardized, first-line regimens, which should be used for the entire duration of tuberculosis treatment. Empirical treatment should only be stopped if there is bacteriological, histological or strong clinical evidence of an alternative diagnosis (**Strength: A**).

Recording and reporting

Context: The recording and reporting of smear-negative pulmonary and extrapulmonary tuberculosis by national tuberculosis control programmes needs strengthening. Information from case-reporting should increasingly be used to inform changes in programme performance.

Recommendations:

- The 2003 recommendation that cases without smear results should be reported as smear-negative pulmonary cases should be revised (**Strength: A**).
- The revised standard tuberculosis recording and reporting formats should be used to gen-

erate sound case-notification and treatment outcome data for smear-negative pulmonary and extrapulmonary cases. This should inform policy and programme performance both nationally and globally (**Strength: A**).

Algorithms for the diagnosis of smear-negative tuberculosis

In the absence of rapid and simple tools to diagnose tuberculosis, the main aim of these algorithms is to assist clinical decision-making in HIV-prevalent and resource-constrained settings, to expedite the diagnostic process and minimize incorrect diagnosis and mortality. The algorithms will have significant implications for both tuberculosis and HIV/AIDS service providers in these settings, and will catalyse the integration of HIV and tuberculosis interventions at the point of service delivery. The algorithms are aimed at adult and adolescent patients presenting with cough of 2–3 weeks' duration and differ according to the clinical condition of the patient (ambulatory or seriously ill).

Guiding principles

Target group: The newly revised algorithms (Figures 1 and 2) are targeted at adults living with HIV/AIDS and those considered to be at high risk of HIV infection on clinical and epidemiological grounds, as laid down in national and/or local policy. The diagnostic procedure for HIV-negative patients and those who are less likely to be HIV-infected should follow the codified algorithm (based on WHO's 2003 recommendations) included in the *International standards for tuberculosis care*, 2006 (2) (Figure 3).

Danger signs: The adult patient will be classified as seriously ill if one or more of the following danger signs are present:

- unable to walk unaided
- respiratory rate over 30 per minute
- fever of more than 39 °C
- pulse rate of over 120 per minute.

AFB microscopy: At least two sputum specimens should be taken and examined for AFB. One of the specimens should be early-morning

sputum produced after an overnight sleep. One positive AFB smear will be sufficient to classify a patient as a smear-positive case if the patient is HIV-infected or if there is strong clinical suspicion of HIV infection.

HIV testing: HIV testing should be routinely offered along with sputum examination for AFB in HIV-prevalent settings for patients presenting with cough of 2–3 weeks' duration. A person with unknown HIV status (e.g. because of unavailability of HIV test kits or refusal to be tested) can be classified as HIV-positive if there is strong clinical evidence of HIV infection.

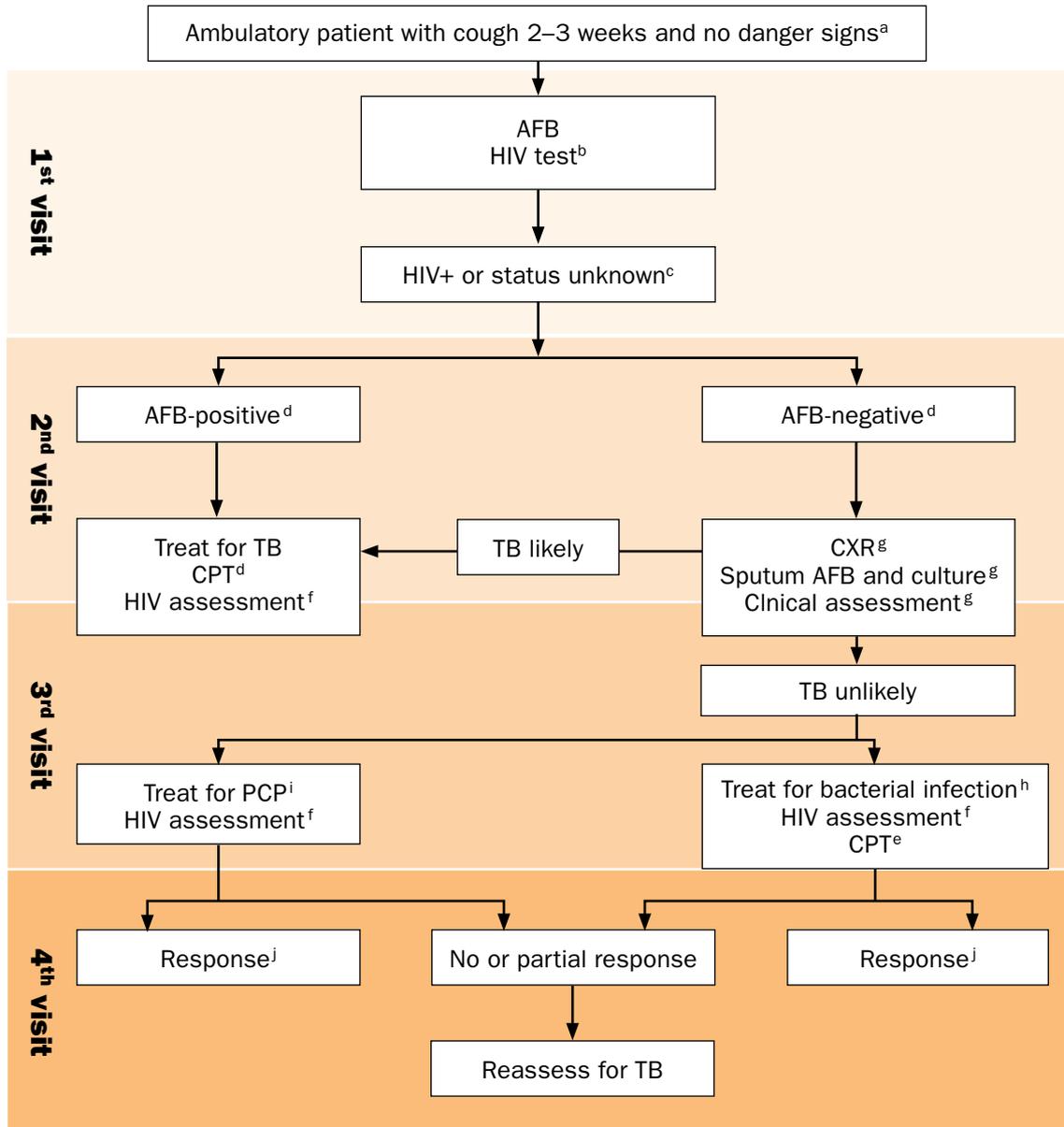
HIV assessment: This includes clinical staging of HIV infection (see Table 2), immunological staging (CD4 count), referral for HIV care including antiretroviral treatment, long-term follow-up and chronic management, including co-trimoxazole preventive therapy. The clinical staging is important, as some patients with pulmonary tuberculosis may also have concurrent stage IV disease requiring more rapid initiation of antiretroviral treatment.

Clinical assessment: This is a critical step in the diagnostic process, particularly in the absence of any bacteriological confirmation of tuberculosis. It must be based, as far as possible, on supportive investigations and sound clinical judgement in order to arrive at a correct diagnosis without undue delay and prevent excess mortality from undiagnosed tuberculosis. It is also useful for the diagnosis and management of nontubercular conditions during all evaluations of the patient. Sound clinical judgement will be essential for: classifying the patient as ambulatory or seriously ill on the basis of danger signs; classifying the patient of unknown HIV status as HIV-positive or negative; starting the patient on broad-spectrum antibiotics or antituberculosis drugs on the basis of his/her clinical condition and presentation; assessing, managing and/or referring the patient for treatment for other diseases. Because performing these activities is part of basic clinical practice, it is not possible to be more instructive in these recommendations.

Clinical response: For patients in whom tuberculosis is less likely and who are treated empirically for bacterial pneumonia or *Pneumocystis carinii* pneumonia (PCP), clinical response

FIGURE 1

Algorithm for the diagnosis of tuberculosis in ambulatory HIV-positive patient



^a The danger signs include any one of: respiratory rate > 30/minute, fever > 39 °C, pulse rate > 120/min and unable to walk unaided.

^b For countries with adult HIV prevalence rate \geq 1% or prevalence rate of HIV among tuberculosis patients \geq 5%.

^c In the absence of HIV testing, classifying HIV status unknown as HIV-positive depends on clinical assessment or national and/or local policy.

^d AFB-positive is defined as at least one positive and AFB-negative as two or more negative smears.

^e CPT = Co-trimoxazole preventive therapy.

^f HIV assessment includes HIV clinical staging, determination of CD₄ count if available and referral for HIV care.

^g The investigations within the box should be done at the same time wherever possible in order to decrease the number of visits and speed up the diagnosis.

^h Antibiotics (except fluoroquinolones) to cover both typical and atypical bacteria should be considered.

ⁱ PCP: *Pneumocystis carinii* pneumonia, also known as *Pneumocystis jirovecii* pneumonia.

^j Advise to return for reassessment if symptoms recur.

should not automatically exclude the diagnosis of tuberculosis. Acute bacterial pneumonia or PCP may occur in patients with underlying tuberculosis and patients should, therefore, be re-evaluated for tuberculosis, particularly if respiratory symptoms persist after treatment. Follow-up assessment of these patients can take place under either tuberculosis services or HIV services, according to country-specific guidance and practice.

Algorithm for the ambulatory patient

This algorithm is used for a tuberculosis suspect without the danger signs defined above (an ambulatory patient). The diagnostic process should be expedited if the patient is HIV-positive, or likely to be so. The total number of visits for separate evaluations from the time of initial presentation to a health facility to the time of diagnosis should not exceed four. The number of days involved between evaluations will vary depending on several country-specific factors, and appropriate measures should be instituted by national and local tuberculosis and HIV authorities to minimize the time and the number of visits required to establish the diagnosis. Shortening the turnaround time for sputum smear examinations is crucial.

The following principles should be followed when applying the algorithms for the ambulatory patient in order to expedite the diagnosis of smear-negative pulmonary tuberculosis.

- **First visit:** HIV testing should be offered and AFB sputum examination should be performed. If AFB test is positive, treat for tuberculosis.
- **Second visit:** If the AFB examination is negative, the patient should be provided with all available investigations during the second visit. The second visit should ideally take place on the second day following first presentation at the health facility. The investigations include: repeated sputum AFB, sputum culture and chest X-ray. Clinical assessment is also important for deciding whether it is worth putting the patient on antituberculosis treatment at this stage. HIV assessment should also be performed and co-trimoxazole

preventive therapy provided according to national guidelines.

- **Third visit:** Results of the second-visit investigations (except culture) should be available during the patient's third visit. Patients suspected of having tuberculosis after these investigations (e.g. compatible radiograph plus symptoms) should be treated for tuberculosis. Patients who are not treated for tuberculosis should receive either a broad-based antibiotic (not a fluoroquinolone) to treat bacterial infection or treatment for PCP. HIV assessment should also be performed and co-trimoxazole preventive therapy provided according to national guidelines.
- **Fourth visit:** The patient's response is assessed and a clinical follow-up mechanism is established (in either the tuberculosis or the HIV services). For patients with immediate response to PCP or antibiotic treatment, continued vigilance is necessary to exclude superimposed tuberculosis. Those patients with an unsatisfactory response to treatment for PCP or bacterial pneumonia should be reassessed both clinically and bacteriologically for tuberculosis.

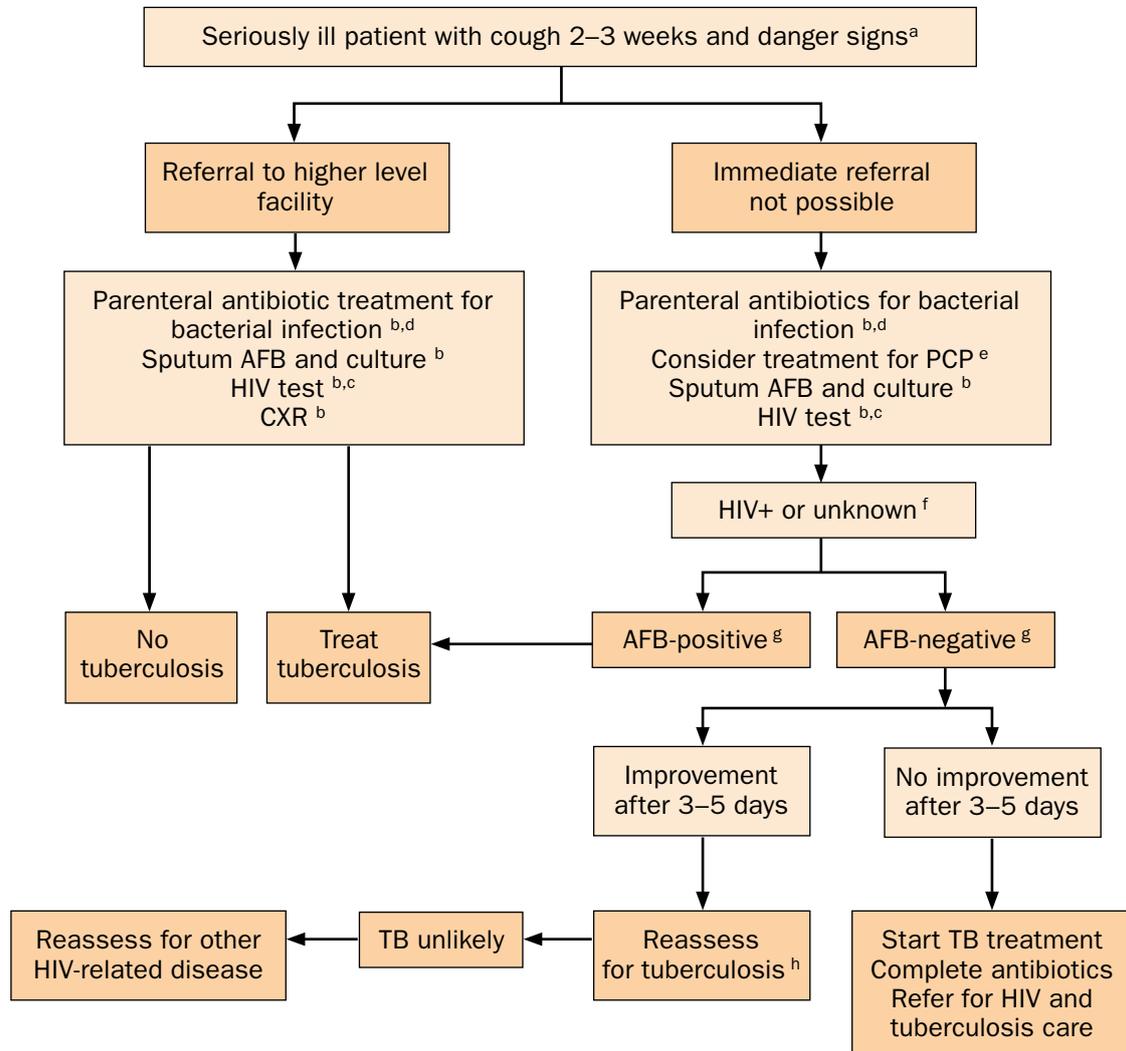
Algorithm for seriously ill patient

A seriously ill patient with one of the danger signs should be immediately referred to a higher-level health facility. When immediate referral is not possible, the following measures should be undertaken in the peripheral health facility.

- Immediately start with broad-spectrum parenteral antibiotics for bacterial infection and perform HIV test and sputum AFB examination. Safe injection practices should be strictly followed. If the indications laid down in national guidelines are present, PCP treatment should be considered. If the HIV test is negative or there is less clinical suspicion of HIV infection, or if the national or local guidelines do not classify the area as HIV-prevalent, continue management of the HIV-negative patient according to national practice and guidelines. If the HIV test is positive, or there is high clinical suspicion of HIV infection, follow the algorithm.

FIGURE 2

Algorithm for the diagnosis of tuberculosis in seriously ill HIV-positive patient



^a The danger signs include any one of: respiratory rate > 30/min, fever > 39 °C, pulse rate > 120/min and unable to walk unaided.

^b The investigations within the box should be done at the same time wherever possible in order to decrease the number of visits and speed up the diagnosis.

^c For countries with adult HIV prevalence rate \geq 1% or prevalence rate of HIV among tuberculosis patients \geq 5%.

^d Antibiotics (except fluoroquinolones) to cover both typical and atypical bacteria should be considered.

^e PCP: *Pneumocystis carinii* pneumonia, also known as *Pneumocystis jirovecii* pneumonia.

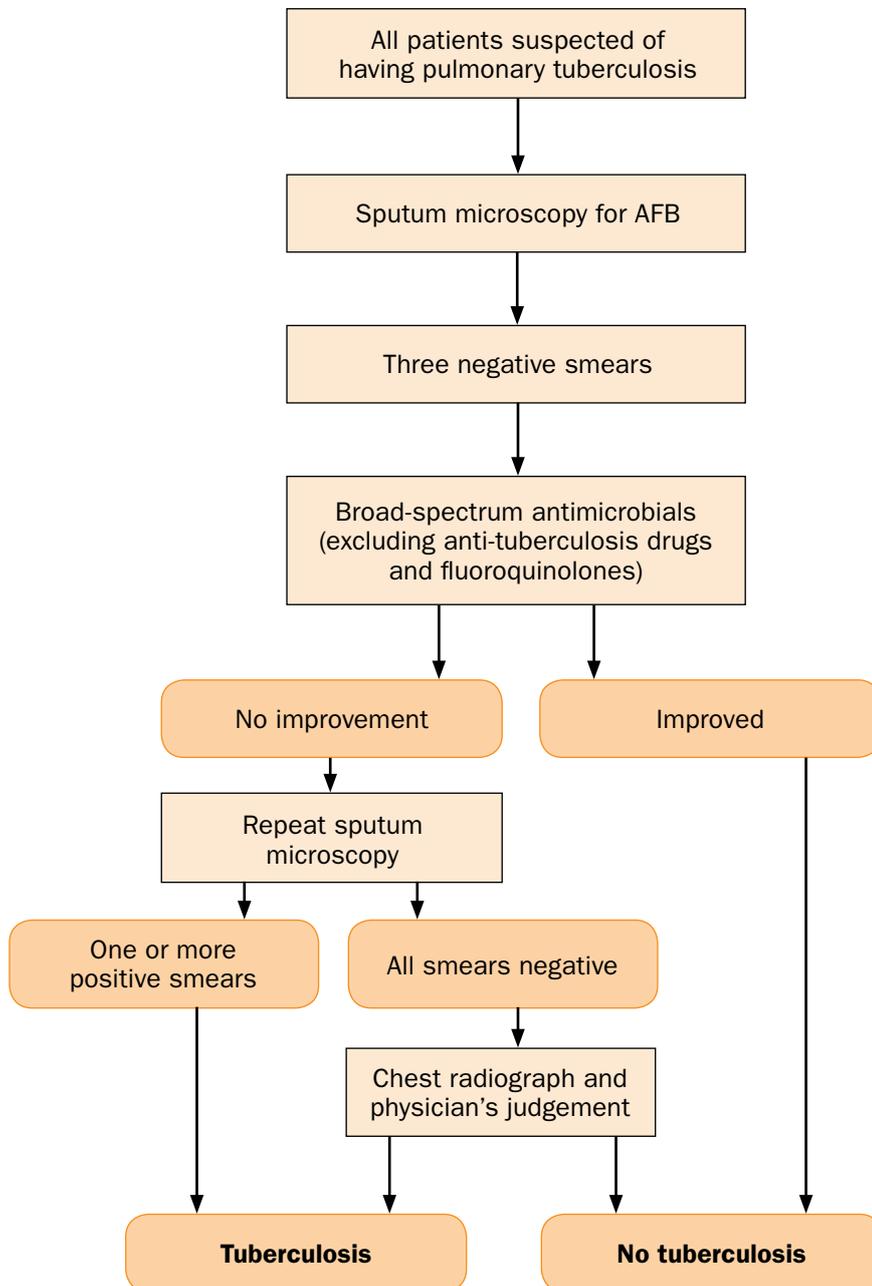
^f In the absence of HIV testing, classify HIV status unknown into HIV-positive depends on clinical assessment or national and/or local policy.

^g AFB-positive is defined as at least one positive and AFB-negative as two or more negative smears.

^h Reassessment for tuberculosis includes AFB examination and clinical assessment.

FIGURE 3

Algorithm for the diagnosis of tuberculosis in HIV-negative patients
(International standards for tuberculosis care, 2006)



Source: Adapted from (1)

Table 2. Revised WHO clinical staging of HIV/AIDS for adults and adolescents with confirmed HIV infection

CLINICAL STAGE 1	Asymptomatic Persistent generalized lymphadenopathy
CLINICAL STAGE 2	Moderate unexplained ^a weight loss (< 10% of presumed or measured body weight) ^b Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruptions Seborrhoeic dermatitis Fungal nail infections
CLINICAL STAGE 3	Unexplained ^a severe weight loss (> 10% of presumed or measured body weight) ^b Unexplained ^a chronic diarrhoea for longer than one month Unexplained ^a persistent fever (above 37.5 °C intermittent or constant for longer than one month) Persistent oral candidiasis Oral hairy leukoplakia Pulmonary tuberculosis Severe bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia) Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis Unexplained anaemia (< 8 g/dl), neutropenia (< 0.5 x 10 ⁹ /L) and or chronic thrombocytopenia (< 50 X 10 ⁹ /L ³)
CLINICAL STAGE 4^c	HIV wasting syndrome <i>Pneumocystis</i> pneumonia Recurrent severe bacterial pneumonia Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site) Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) Extrapulmonary tuberculosis Kaposi's sarcoma Cytomegalovirus infection (retinitis or infection of other organs) Central nervous system toxoplasmosis Extrapulmonary cryptococcosis including meningitis Disseminated nontuberculous mycobacteria infection Progressive multifocal leukoencephalopathy Chronic cryptosporidiosis Chronic isosporiasis Disseminated mycosis (extrapulmonary histoplasmosis, coccidiomycosis) Recurrent septicaemia (including nontyphoidal <i>Salmonella</i>) Lymphoma (cerebral or B cell nonHodgkin) Invasive cervical carcinoma Atypical disseminated leishmaniasis Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy

Source: Adapted from (7).

- Unexplained indicates that the condition is not explained by any other condition.
- Assessment of body weight in pregnant women needs to take into account the expected weight gain of pregnancy.
- Some additional specific conditions can also be included in regional classifications (e.g. reactivation of American trypanosomiasis (meningoencephalitis and/or myocarditis) in the WHO Region of the Americas and penicilliosis in Asia).

- If the diagnosis of tuberculosis is confirmed by AFB smear examination, start tuberculosis treatment. The antibiotic treatment should be continued and completed.
- If the AFB smear is negative, response to parenteral antibiotics should be assessed 3–5 days into treatment, and, if there is no improvement, tuberculosis treatment should be initiated. The initial antibiotic course should be continued and completed. HIV assessment and clinical staging should be performed. Patients should be referred to the next level of care to confirm the diagnosis of tuberculosis and for HIV care. If referral is not possible, tuberculosis treatment should be completed.
- If referral to a higher-level facility is possible, the patient should be managed as an emergency and all available investigations, including HIV testing, should be performed at one time for the diagnosis of tuberculosis.

PART II

Simplified and standardized clinical management guidelines for extrapulmonary tuberculosis

Background

One in five registered tuberculosis patients has extrapulmonary tuberculosis (8, 9, 10). The commonest forms include lymph node (especially in the neck or under the arms), pleural (usually one-sided pleural effusion) and disseminated tuberculosis (disease that is not limited to one site in the body). Pericardial and meningeal tuberculosis are less frequent forms of extrapulmonary tuberculosis that are also covered in these guidelines. About one-third of deaths in HIV-positive Africans are due to disseminated tuberculosis (11, 12, 13) but only about half of HIV-positive patients who die from disseminated tuberculosis are diagnosed before death (12, 13, 14). With the exception of lymph node tuberculosis, which can usually be confirmed through aspiration of affected lymph nodes, most patients with extrapulmonary tuberculosis are managed without bacteriological or histological confirmation (15). Therefore, it is important for health care workers to have simplified, standardized guidelines for the prompt diagnosis and management of extrapulmonary tuberculosis.

Target audience

These guidelines are intended to assist the prompt diagnosis and management of extrapulmonary tuberculosis by physicians and other clinicians working in district hospitals of HIV-prevalent and resource-constrained settings as part of national tuberculosis control programme activities.

Diagnosis and management

The indications for suspected extrapulmonary tuberculosis and the key signs to look for in the commonest forms of the disease are summarized in Figure 4. Table 3 summarizes the essential investigations required for diagnosis and key steps for immediate management of suspected extrapulmonary tuberculosis cases. For a patient with suspected extrapulmonary tuberculosis who is started on antituberculosis treatment without bacteriological or histological confirmation, the clinical response to treat-

ment should be assessed after one month. If there is no improvement, a clinical reassessment should be performed and an alternative diagnosis sought.

HIV testing should be offered to all patients suspected of extrapulmonary tuberculosis. This is because HIV-related extrapulmonary tuberculosis is an indication for early commencement of antiretroviral treatment (clinical stage 4 of HIV disease). For HIV-related extrapulmonary tuberculosis, the following interventions should be carried out:

- refer for HIV care or start antiretroviral treatment according to national guidelines
- start co-trimoxazole preventive therapy
- remain vigilant for clinical deterioration of extrapulmonary tuberculosis after the start of antiretroviral treatment (immune reconstitution inflammatory syndrome – IRIS) and take appropriate measures.

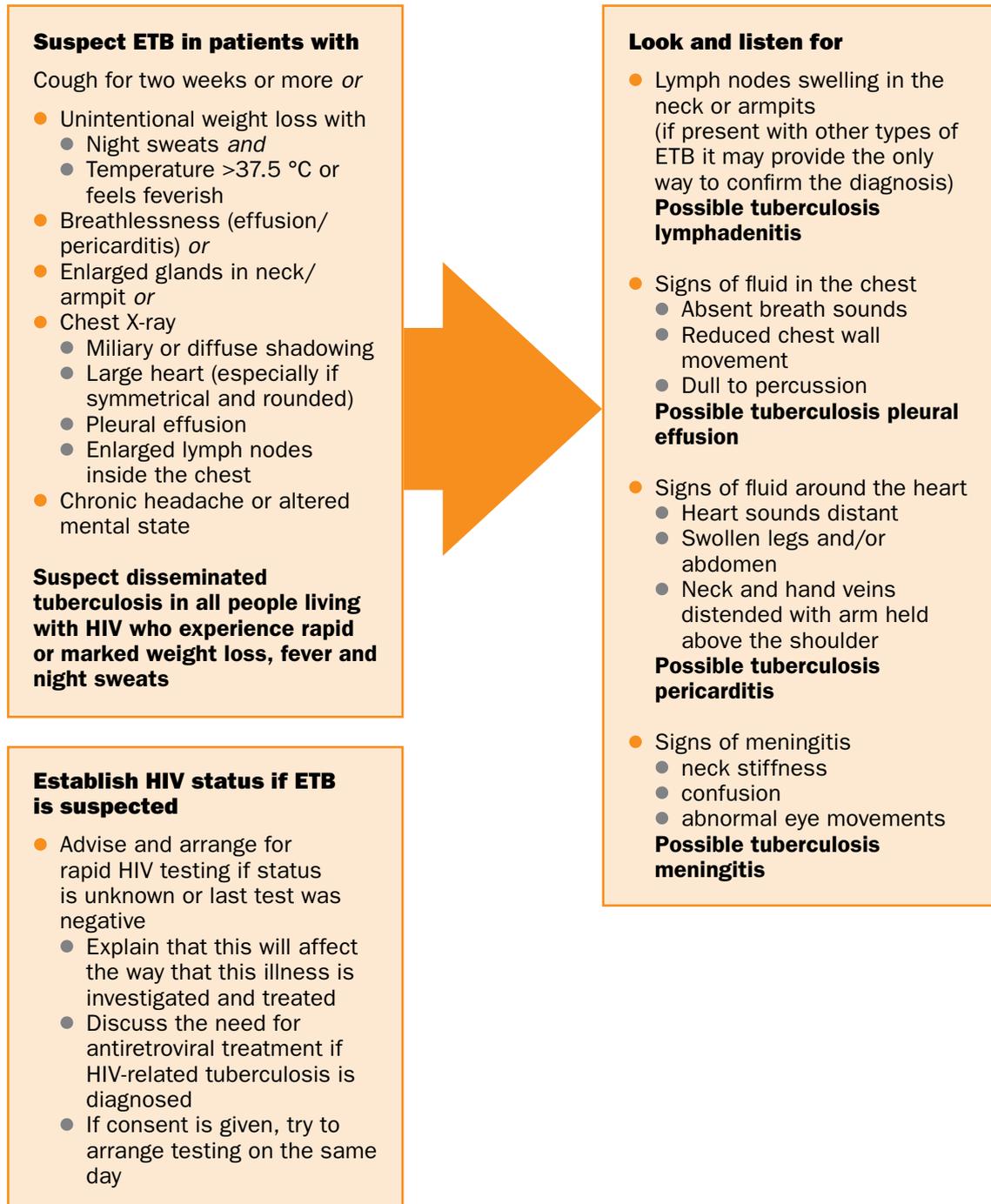
Tuberculous lymphadenitis

Tuberculous lymphadenitis should be suspected in any patient with enlarged lymph nodes that are firm, asymmetrical, more than 2 cm in diameter, or where a node has become fluctuant or developed a fistula over several months. It most commonly affects the nodes in the neck (cervical region) and is difficult to distinguish clinically from other causes of enlarged nodes, such as reactive and/or HIV-related lymphadenopathy, malignancies and other lymph node infections, which are also common. Therefore, needle aspiration using recommended techniques (see box “Guidelines for lymph node aspiration” below) should be carried out at the first outpatient visit for all patients.

Needle aspiration with cytology and tuberculosis microscopy of aspirated material has a high diagnostic yield, with confirmation of over 85% of patients with tuberculous lymphadenitis in some (16, 17, 18, 19) but not all (20) reports, suggesting that the technique may be important. If a fistula has formed, then microscopy of discharging pus is likely to show AFB. Cytology, if available, can identify most other important causes of enlarged lymph nodes, including

FIGURE 4

Suggested clinical characteristics to assist the diagnosis of extrapulmonary tuberculosis (ETB)



malignancies and other infections. Follow-up to receive the results should be within seven days. If the aspirate does not yield a diagnosis, then excision biopsy for gross examination, Ziehl-Neelsen microscopy, mycobacterial culture and, if available, histological examination can be considered.

However, tuberculosis treatment should be started immediately if:

- the patient is HIV-infected and has clinical features of disseminated tuberculosis (such as marked weight loss, rapid clinical deterioration or multiple sites of suspected tuberculosis) **or**
- tuberculous lymphadenitis is considered the most likely clinical diagnosis, but logistical or economic barriers are likely to delay excision biopsy for two weeks or longer.

Pleural effusion

Tuberculosis is the likely cause of unilateral pleural effusion in countries with a high tuberculosis burden. It was the diagnosis reached in 95% of patients in two recent case-series from Uganda and Zimbabwe (21, 22). Pleural effusion is the most common form of HIV-related extrapulmonary tuberculosis, with high mortality (over 20%) in the first two months of tuberculosis treatment (21, 22).

The following key steps should be undertaken.

- The management of tuberculous pleural effusion should aim at starting tuberculosis treatment and identifying underlying HIV infection without delay. Pleural biopsy has a high diagnostic yield (21, 22), but is **not** recommended because it is unnecessarily invasive and has the potential to introduce diagnostic delay.
- Suspected pleural effusion should be confirmed by chest radiography and immediate aspiration of fluid whenever possible (see Table 3), placing aliquots of the aspirate into one plain and two anticoagulated tubes.
- Treatment with broad-spectrum antibiotics is not required before tuberculosis treatment in patients with unilateral effusions if the pleural fluid is clear and clots on standing,

Guidelines for lymph node aspiration

Equipment needed: topical antiseptic, gloves, 5 ml syringe and 18 to 21 gauge needle,* 3 glass microscopy slides, cytological fixative (e.g. absolute alcohol or methanol) if cytology available

Steps

1. Prepare the microscopy slides with the patient's name and identification number.
2. Apply a topical antiseptic to the skin overlying the enlarged lymph node.
3. Attach the needle and expel all air from the syringe.
4. With the nondominant hand, take the gland between the thumb and the index finger to make it stand out and hold it steady.
5. Taking the syringe in the dominant hand, insert the needle through healthy skin into the centre of the node or at the point of maximum fluctuance, and pull back on the syringe piston. If no aspirate is obtained, move the needle in and out of the centre of the node while pulling back on the syringe piston. Gently compress the node with the nondominant hand and revolve the needle in both directions. Small amounts of lymph node tissue will collect in the needle and needle hub, even if there is no visible aspirate inside the syringe.
6. Withdraw the needle and syringe and spread aspirate onto each slide. It may be necessary to disconnect the syringe and introduce a small amount of air in order to expel the contents. A separate aspirate may be needed for each slide.
7. Allow slides to air-dry. If pus is obtained, send one slide for Gram stain and one for tuberculosis microscopy. If no pus is obtained, then send both slides for tuberculosis microscopy.
8. If available, spray the remaining slide with cytological fixative, and send for cytology when dry.

* Reported yields are better with larger needle sizes (18 or 19G: wide-needle aspiration), but fine-needle aspiration with a standard phlebotomy (21G) needle can be used if that is all that is available. Lymph node needle-core biopsy is an acceptable alternative for facilities with appropriate equipment.

unless there is clinical concern about bacterial pneumonia.

- Patients with unusual findings, such as bilateral effusions, cloudy or bloody aspirates should undergo the additional investigations detailed in Table 3. If visible clots form in

Table 3. Diagnosis and immediate management of suspected extrapulmonary tuberculosis

LYMPH NODE TUBERCULOSIS (PERIPHERAL)	PLEURAL EFFUSION	DISSEMINATED TUBERCULOSIS	PERICARDIAL EFFUSION	TUBERCULOUS MENINGITIS
<p>Essential investigations</p> <ul style="list-style-type: none"> HIV test (rapid if possible) CXR Sputum smears if coughing Aspirate & inspect fluid^b Differential white blood cell count and protein determination (if possible) of aspirate <p>High suspicion of tuberculosis if:</p> <ul style="list-style-type: none"> 2 cm or more in size Asymmetrical/localized Painless swelling Firm/fluctuant/fistulated lymph node location Weight loss, night sweats, fever <p>Findings that suggest a non-tuberculosis diagnosis</p> <ul style="list-style-type: none"> KS^a in skin or mouth (probable KS nodes) Symmetrical (probable lymphoma or HIV lymphadenopathy) Tender, inflamed, purulent (bacterial or fungal) Site other than cervical <p>Immediate management</p> <ul style="list-style-type: none"> Aspirate for cytology and AFB microscopy Excision biopsy if aspirate non-diagnostic unless <ul style="list-style-type: none"> HIV+ with possible disseminated tuberculosis (e.g. rapid clinical deterioration) Tuberculosis considered the most likely clinical diagnosis, and biopsy not available within 2 weeks 	<p>Essential investigations</p> <ul style="list-style-type: none"> HIV test (rapid if possible) CXR Sputum smears if coughing Aspirate & inspect fluid^b Differential white blood cell count and protein determination (if possible) of aspirate <p>High suspicion of tuberculosis if:</p> <ul style="list-style-type: none"> Unilateral effusion Aspirate of fluid^b is: <ul style="list-style-type: none"> Clear and straw coloured and Clots on standing in a tube without anticoagulants Weight loss, night sweats, fever Evidence for tuberculosis elsewhere <p>Findings that suggest a non-tuberculosis diagnosis</p> <ul style="list-style-type: none"> Bilateral effusion (possible heart failure or pneumonia) Clinical KS^a/other malignancy Aspirate of fluid is: <ul style="list-style-type: none"> Cloudy/pus (probable empyema) Fails to clot (does not exclude tuberculosis, but send fluid for protein and differential cell count, and consider heart failure) <p>Immediate management</p> <ul style="list-style-type: none"> Start tuberculosis treatment <p>Features of tuberculosis only</p> <ul style="list-style-type: none"> Send aspirate for differential cell count, protein and, if available, cytology: ≥ 50% lymphocytes and protein > 30 g/L suggests tuberculosis Treat for tuberculosis if the only unusual feature is failure of aspirate to clot, or no other diagnosis by 7 days 	<p>Essential investigations</p> <ul style="list-style-type: none"> HIV test (rapid if possible) CXR Malaria blood film Sputum smears, if coughing Blood cultures, full blood count and cryptococcal antigen <p>High suspicion of tuberculosis if:</p> <ul style="list-style-type: none"> Weight loss, fever and cough Abnormal CXR (which can include miliary pattern) Large spleen/liver Night sweats Anaemia <p>Findings that suggest a non-tuberculosis diagnosis if HIV+ consider Salmonella, Cryptococcus</p> <ul style="list-style-type: none"> Rigors Very breathless (respiratory rate > 30/min) Severe diarrhoea Blood in stool Positive cryptococcal antigen, malaria smear or likely pathogen isolated from blood culture <p>Immediate management</p> <ul style="list-style-type: none"> Start tuberculosis treatment (add antibiotics if critically ill) <p>Features of non-tuberculosis diagnosis</p> <ul style="list-style-type: none"> Investigate other causes Start both tuberculosis treatment and antibiotics if critically ill 	<p>Essential investigations</p> <ul style="list-style-type: none"> HIV test (rapid if possible) CXR Sputum smears if coughing Cardiac ultrasound (ideally) Electrocardiogram if ultrasound not available <p>High suspicion of tuberculosis if:</p> <ul style="list-style-type: none"> Lung fields clear (but may have bilateral pleural effusion) Weight loss, night sweats, fever Evidence of tuberculosis elsewhere <p>Findings that suggest a non-tuberculosis diagnosis</p> <ul style="list-style-type: none"> Streaky shadowing of lung fields and/or heart shape not symmetrical (probable heart failure) High blood pressure Electrocardiogram suggests another cause for enlarged heart (e.g. high blood pressure, valve disease, dilated cardiomyopathy) Murmur (probable valvular disease) Rigors (probable bacterial pericarditis) <p>Immediate management</p> <ul style="list-style-type: none"> Start tuberculosis treatment Refer for urgent aspiration if very breathless/unwell <p>Features of non-tuberculosis diagnosis</p> <ul style="list-style-type: none"> Investigate other causes (urea and cardiac ultrasound) Treat for tuberculosis if ultrasound confirms effusion and no other diagnosis made by 7 days 	<p>Essential investigations</p> <ul style="list-style-type: none"> HIV test (rapid if possible) Lumbar puncture Microscopy (Gram stain and AFB)/protein/glucose in cerebrospinal fluid Cryptococcal antigen/stain Sputum smears if coughing <p>High suspicion of tuberculosis if:</p> <ul style="list-style-type: none"> Weight loss, night sweats, fever Cerebrospinal fluid clear with high protein, low glucose and lymphocytes Cryptococcal antigen (or India ink and fungal culture) –ve in cerebrospinal fluid Evidence of tuberculosis elsewhere <p>Findings that suggest a non-tuberculosis diagnosis</p> <ul style="list-style-type: none"> HIV test +ve (cryptococcal disease more likely than tuberculosis) Cerebrospinal fluid cloudy or neutrophils on microscopy (probably bacterial) Cryptococcal tests +ve Rapid onset Very high cerebrospinal fluid pressure (probably cryptococcal) <p>Immediate management</p> <ul style="list-style-type: none"> Start tuberculosis treatment Admit <p>Features of tuberculosis only</p> <ul style="list-style-type: none"> Admit <p>Features of non-tuberculosis diagnosis</p> <ul style="list-style-type: none"> Treat for cryptococcal disease if crypto tests +ve or if HIV+ and no other diagnosis made

^a KS-Kaposi's sarcoma

^b The aspirate should be put in a plain tube (with no anticoagulant) in order to observe its appearance and clotting. A second aliquot should be placed into an anticoagulated tube, so that a differential white blood cell count and protein determination can be requested if there are any findings to suggest a non-tuberculosis diagnosis.

the aspirate within a few minutes of its being placed into a plain tube (no anticoagulant), then this confirms the high protein content of the fluid, which indicates tuberculosis. No further investigations are needed if the aspirate is clear and straw-coloured and there are no other features suggestive of a diagnosis other than tuberculosis.

- Failure of the aspirate to clot does not exclude tuberculosis, and such patients can still be started on tuberculosis treatment immediately if there are no other unusual findings (Table 3), but laboratory analysis of fluid is needed to determine the protein content (expect ≥ 30 g/L in patients with a tuberculous effusion, but it can be lower in very wasted patients) and differential cell count (expect $\geq 50\%$ lymphocytes in a tuberculous effusion). The aim should be to start tuberculosis treatment within seven days unless another diagnosis has been made.
- If thoracentesis is not available, tuberculosis treatment should be started immediately, particularly if the patient is HIV-infected, unless there are clinical or radiological features suggestive of a diagnosis other than tuberculosis.

Other forms of extrapulmonary tuberculosis

Most patients with other forms of extrapulmonary tuberculosis present in a sufficiently characteristic way to allow tuberculosis treatment to be started without attempting to confirm the disease bacteriologically or histologically. Although extrapulmonary tuberculosis can be confirmed in the majority of patients through invasive biopsy and/or multiple cultures, these investigations are not routinely recommended, as they are expensive and may result in lengthy diagnostic delays that can reduce the chances of a good treatment response (19).

Taking specimens for culture increases the chances that tuberculosis will be confirmed, but treatment should not generally be delayed until culture results are available. Instead, tuberculosis treatment should be started promptly, if indicated after the essential investigations and

assessments shown in Table 3. The attending health care worker should carefully consider the need for additional investigations and treatment (such as antibiotics) if a diagnosis other than tuberculosis is suspected. However, it is not necessary to give broad-spectrum antibiotics routinely before considering tuberculosis treatment.

Tuberculosis treatment should be started as soon as other common conditions that can cause a similar clinical picture have been excluded (see Table 3 for essential investigations) in patients presenting with the following conditions.

- Pericardial effusion: tuberculosis is the cause of about 90% of HIV-related pericardial effusion, but a lower percentage (50% to 70%) of pericardial effusions in HIV-negative individuals (23, 24, 25).
- Meningitis with features of the cerebrospinal fluid suggestive of tuberculosis (see Table 3).
- Suspected disseminated tuberculosis in febrile patients presenting with HIV wasting syndrome. High rates of undiagnosed disseminated tuberculosis have been consistently identified in febrile, HIV-positive inpatients and in postmortem series from several countries (11, 12, 13, 14, 26, 27, 28, 29, 30).

Patients with clinical features or investigation results that suggest a diagnosis other than extrapulmonary tuberculosis (listed in Table 3) need more extensive investigation before tuberculosis treatment is considered, but with the aim of keeping diagnostic delays to a minimum.

Adjuvant corticosteroids

Corticosteroids started at the time of tuberculosis diagnosis and given for the first two months of treatment significantly improve survival from tuberculous meningitis in HIV-negative patients, and are now recommended for such patients (31). For other forms of extrapulmonary tuberculosis and for HIV-related tuberculous meningitis, the effects of steroids are still uncertain. The results of small trials on tuberculous pericarditis are promising (32). There appears to be no benefit in adding steroids to

the treatment of tuberculous pleural effusion, with some suggestion of possible harm to HIV-positive patients (33). Recommendations may change when the results of larger randomized clinical trials become available within the next few years.

Further reading

- *Antiretroviral therapy for HIV infection in adults and adolescents in resource-limited settings: towards universal access. Recommendations for a public health approach.* Geneva, World Health Organization, 2006. <http://www.who.int/hiv/pub/guidelines/adult/en/index.html> (accessed 29 October 2006).
- *Guidance for national tuberculosis programmes on the management of tuberculosis in children* (WHO/HTM/TB/2006.371/WHO/FCH/CAH/2006.7). Geneva, World Health Organization, 2006.
- *Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults in resource-limited settings. Recommendations for a public health approach.* Geneva, World Health Organization, 2006. <http://www.who.int/hiv/pub/guidelines/ctx/en/index.html> (accessed 29 October 2006).
- *Interim policy on collaborative TB/HIV activities* (document WHO/HTM/TB/2004.330/WHO/HTM/HIV/2004.1). Geneva, World Health Organization, 2004. <http://www.who.int/hiv/pub/tb/tbhiv/en/> (accessed 29 October 2006).
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- *WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children.* Geneva, World Health Organization, 2006. <http://www.who.int/hiv/pub/guidelines/hivstaging/en/index.html> (accessed 29 October 2006).

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ANNEX

Protocol for operational
evaluation of the revised
recommendations and
algorithms for improving the
diagnosis of tuberculosis in
HIV-prevalent settings

Background

In 1991, WHO first published guidelines for national tuberculosis control programmes which included criteria for the diagnosis of smear-positive and smear-negative pulmonary and extrapulmonary tuberculosis. These were subsequently revised in 1997 and 2003. In response to concerns that the 2003 guidelines (1) did not adequately reflect the diagnostic and treatment challenges of HIV-associated tuberculosis, WHO has revised its recommendations for the diagnosis of tuberculosis in HIV-prevalent settings.

Major changes between the revised recommendations presented in this document, and the previous guidelines (2003) are as follows.

1. The revised 2006 guidelines apply only to:
 - (a) patients suspected of having tuberculosis and living in settings (geographical area or health facility) with an HIV prevalence > 1% in pregnant women or an HIV-prevalence \geq 5% in tuberculosis patients.
 - (b) patient's age > 15 (guidelines for childhood tuberculosis are separate).
 - (c) note that, for all other populations, the existing guidelines laid down in the *International standards for tuberculosis care* (2) should be followed.
2. All tuberculosis **suspects** should be routinely offered HIV counselling and testing. This differs from the existing WHO recommendation that these should be offered only to tuberculosis **patients**.
3. A "trial" of antibiotics is not required to diagnose smear-negative pulmonary tuberculosis.
4. **Two** sputum specimens, with one collected in the morning, are sufficient for the initial diagnostic evaluation of tuberculosis in HIV patients. This differs from the 2003 WHO recommendation that "at least" three specimens should be AFB-negative before diagnosing smear-negative pulmonary tuberculosis.
5. A patient is considered to have smear-positive tuberculosis if at least one specimen is positive for AFB.

6. Sputum culture for *Mycobacterium tuberculosis* should be performed in patients who are sputum smear-negative to confirm the diagnosis of tuberculosis and improve the quality of care.

In the absence of complete evidence, the recommendations are based on consensus and iterative global expert opinion in order to respond to the catastrophe posed by the HIV epidemic. They should, therefore, be implemented in HIV-prevalent settings. However, it is equally important to build up the evidence base simultaneously, in settings where this is possible, in order to assess the effectiveness and feasibility of the guidelines and thus inform changes in policy and practice.

Objectives of the evaluation

The primary intent of the evaluation is to measure the performance of tuberculosis programmes that implement the revised recommendations and generate knowledge for improving those specific programmes. The evaluation involves measuring different indicators of input, process, output, outcome and impact in settings that implement the revised recommendations and comparing them with settings that have not implemented the recommendations. The evaluation provides information for international and national health policy-makers and public health officials about the strengths and weaknesses of the revised guidelines in order to inform changes in international and national policy and practice. Therefore, the evaluations should be conducted in close collaboration with national tuberculosis and HIV control programmes in the countries concerned.

Purpose of the protocol

This protocol provides generic guidance on conducting evaluations of the revised recommendations to improve the diagnosis of tuberculosis in HIV-prevalent settings. It is intended to standardize the minimum information that needs to be generated by the evaluation in order to inform changes in policy at both national and global levels. The protocol will also provide a flexible platform for research groups and inter-

ested stakeholders to evaluate these recommendations and, at the same time, enable them to contribute to changes in policy and improvements in programme performance both globally and nationally.

Hypotheses

Compared with settings implementing the 2003 guidelines (existing practice), settings implementing the revised guidelines of 2006 are expected to display the following characteristics.

1. A larger proportion of tuberculosis suspects diagnosed with smear-negative tuberculosis.
2. A smaller proportion of smear-negative pulmonary and extrapulmonary tuberculosis patients who die before treatment is completed.
3. A smaller proportion of tuberculosis suspects who die before completion of the diagnostic evaluation or within two months of initial contact with health services for tuberculosis diagnosis.
4. A shorter time-lag between onset of cough and treatment for tuberculosis, and between date of initial contact with health services for tuberculosis diagnosis and beginning of tuberculosis treatment.
5. A larger proportion of patients and providers satisfied with the speed and quality of diagnostic services.
6. A larger proportion of patients with a complete diagnostic evaluation, including two sputum smears, chest radiography and sputum culture.

Study design and procedure

The highest-quality evidence would come from a randomized clinical trial in which individual patients would be enrolled and then randomly assigned to either the revised or the existing recommendations and algorithms. However, even if such a trial was technically and financially feasible, it would be extremely difficult to justify ethically, as it would involve failing to perform chest radiography, sputum culture or HIV

testing, or withholding the results of those tests from patients and clinicians. Therefore, a more practical, ethically acceptable approach to validating the revised guidelines is to measure only operational performance, rather than diagnostic test performance, and randomize only facilities or populations, not individuals.

Depending on country-specific factors, implementation of the revised guidelines may require revision of national guidelines and new logistical and technical arrangements, including human resources and infrastructure development. Therefore, in many countries, the revised recommendations will probably be implemented in stages. This will facilitate evaluation by interested parties and stakeholders and help to define intervention and nonintervention settings within a country as part of the scale-up process.

Overall design

The suggested overall design for the study is a prospective, observational study. The justification for this approach is as follows.

1. Prospective: Historical data, such as medical chart reviews, could be used to compare outcomes, but such data may lack the detail required to answer important public health questions about patient and provider satisfaction or to compare costs. Similarly, in many countries, rapid advances are occurring in HIV care and treatment, which could affect the frequency of diagnosis of tuberculosis, the types of disease diagnosed and the outcomes of patients treated for tuberculosis. Conducting this study prospectively will help control for these factors.
2. Observational: The study will involve no experimental diagnostic tests or medicines. Clinical care will be implemented according to existing national guidelines. Even if a country wanted to implement the revised guidelines nationwide, implementation would be likely to occur in stages. The observational study design therefore allows for both implementation of guidelines and a quasi-experimental assessment of impact. For the reasons described above, a randomized clinical trial

is not an ethically appropriate design. Involving multiple centres will both be useful and allow for comparison of the impact on programmes.

Study description

A “setting” denotes either an individual health facility or an administrative area (e.g. district) that contains multiple health facilities. Settings will only be included in the study if they are already following the WHO-recommended Stop TB strategy, which includes standardized recording and reporting of tuberculosis cases, and if they are implementing either the existing (2003) or the revised (2006) recommendations. The settings implementing the revised recommendations should also be required to implement the revised recording and reporting formats according to national guidelines. (The relevant documents are available from the WHO website: <http://www.who.int/tb/err/en/index.html>). Ideally, settings will be allocated in a concealed, randomized process; but because the study is being conducted in a programme context, other factors may need to be considered when selecting sites, including availability of personnel, infrastructure and budget. For example, the availability of necessary tests and services (e.g. HIV testing, chest X-ray, sputum culture etc.) would affect the selection of an intervention site.

Likewise, it may not be possible to select non-intervention sites randomly. There may be substantial variations in practice across and within settings that need to be considered for the selection. In those countries that have already adopted the revised guidelines as their national guidelines, those settings which have not implemented the revised guidelines for the duration of the evaluation may be selected as nonintervention sites. The ideal nonintervention site will have a standardized approach to tuberculosis diagnosis: its practice should be consistent with national guidelines and, if possible, with the 2003 WHO guidelines.

Before data collection begins, both intervention sites and nonintervention sites should undergo training in conducting the evaluation of the revised guidelines. For intervention sites (i.e.

sites implementing the revised guidelines), all clinicians (physicians, clinical officers, nurses and other clinical staff) will receive training on the revised guidelines, basic diagnosis and management of tuberculosis and HIV, and completion of study documents. Supplies and equipment necessary for the implementation of the revised guidelines will be installed and relevant staff trained in their use. To reduce the potential bias in study outcomes which may be associated with such training, nonintervention sites will undergo similar training focusing on the 2003 guidelines.

Suggested studies

Within each setting (intervention and non-intervention), a number of evaluations will be conducted to measure input, process, output, outcome and impact of the revised guidelines. These suggested studies can be conducted either as independent studies or as part of a larger study, depending on the local context and the interests of research groups. Table A1 below describes the types of study and the indicators they will measure.

Study 1: assessment of costs

A standardized instrument to measure costs should be developed. The purpose of this instrument should be to measure the cost of the human resources development and infrastructure required to implement the revised guidelines. As far as possible, identical information will be obtained from the sites implementing the 2003 guidelines, in order to permit an estimate of costs associated with routine practice. The study instrument will be also used, if necessary, to abstract data from financial records.

Minimum cost components to be measured in this instrument should include costs related to: training, study materials, personnel time (including health care workers and trainers), transportation of persons and specimens, construction, equipment, supplies, reagents and consumables, standard diagnostic procedures (e.g. microscopy, radiography, culture, HIV testing), antituberculosis treatment, antibiotics prescribed for bacterial infection.

Table A1. Study tools to be used during evaluation, populations to be studied, and indicators to be measured

Study no.	Tool	Study population	Indicator type	Indicators measured
1	Questionnaire	Public health officers implementing study; clerks maintaining financial records	Input	Cost of human resources development to implement guidelines (e.g. training, staffing, materials)
			Input	Cost of infrastructure needed to implement guidelines (e.g. equipment, supplies, construction, transportation)
2	Questionnaire	Tuberculosis suspects attending health facilities	Process	Satisfaction of patients with speed and quality of services, as measured through patient survey
3	Questionnaire	Health care providers working at health facilities	Process	Satisfaction of providers with clinical practice guidelines, as measured through provider survey
4	Case-report form	Tuberculosis suspects attending health facilities	Output	Proportion of pulmonary tuberculosis suspects with at least two sputum smears collected, a chest radiograph performed, a sputum culture performed
			Output	Proportion of pulmonary tuberculosis suspects who complete diagnostic evaluation
			Output	Proportion of pulmonary tuberculosis suspects (a) who die before diagnostic evaluation completed; (b) before beginning tuberculosis treatment; (c) within two months of initial contact with health services for tuberculosis diagnosis
			Output	Proportion of pulmonary tuberculosis suspects with known HIV status
			Output	Proportion of pulmonary tuberculosis suspects given a diagnosis other than tuberculosis
			Output	Proportion of pulmonary tuberculosis suspects who complete diagnostic evaluation
5	Case-report form	Tuberculosis patients treated in health facilities	Outcome	Proportion of pulmonary tuberculosis cases diagnosed as smear-negative
			Outcome	Proportion of pulmonary tuberculosis cases with known HIV status
			Outcome	Days between onset of cough and treatment for tuberculosis; days between initial contact with health services for tuberculosis diagnosis and initiation of tuberculosis treatment
			Impact	Proportion of pulmonary tuberculosis cases who have died two months into treatment and six months into treatment (or at end of treatment), stratified by smear status
			Impact	Proportion of pulmonary tuberculosis cases who complete treatment, stratified by smear status
			Impact	Proportion of pulmonary tuberculosis cases who complete diagnostic evaluation

No statistical sampling will be performed for this study. No informed consent will be obtained, because no personal, sensitive or health-related information will be collected.

Study 2: patient satisfaction survey

A survey of tuberculosis suspects will be conducted to determine their satisfaction with the diagnostic process in facilities implementing the revised guidelines, compared with those implementing the 2003 guidelines.

Case definition: A pulmonary tuberculosis suspect will be defined as any person not currently receiving tuberculosis treatment and without a current diagnosis of tuberculosis, with cough > 2 weeks duration or sputum collected for AFB smear microscopy at the request of a clinician.

Inclusion criteria: All persons meeting the case definition who seek health care at a participating facility during the enrolment period, who agree to be contacted one month after their first diagnostic evaluation as a tuberculosis suspect.

Exclusion criteria: Persons not meeting the case definition and inclusion criteria, or persons meeting both the case definition and inclusion criteria who are aged < 15 years, cannot be contacted or refuse to participate, or who die before they can be interviewed.

Estimated number of participants and sampling: At least 200 persons in total will be interviewed, 100 from intervention and 100 from nonintervention sites over a six-month period. This sample size and study period are suggested for convenience and practicality. However, more accurate sample-size estimations and study periods may be employed, based on the local tuberculosis and HIV epidemiology. If the estimated number of suspects is > 200, an appropriate and uniform method for sampling the population will be chosen for both intervention and nonintervention sites.

Enrolment procedure:

1. Persons presenting at the health care facility will be identified as tuberculosis suspects using routine criteria for that facility, and a register will be maintained of all tuberculosis suspects (see below).

2. Study staff will present tuberculosis suspects with a consent card or form, informing them that a survey is being conducted about patient satisfaction. Staff will explain to patients that they will be asked to provide contact information so that they can be contacted in one month to determine how satisfied they were with their tuberculosis evaluation. Patient consent or refusal to participate in the survey will be recorded in the register.

3. After two months, study staff will review the list of consenting patients and, according to the established sampling criteria, attempt to contact tuberculosis suspects who were evaluated during the first month of the study. Subsequent reviews of the list will occur every month.

4. Study staff will attempt to contact patients to perform the survey. The survey may be administered by telephone or in person, depending on the logistics at each site. If a patient cannot be contacted, patients will continue to be selected from the list of consenting tuberculosis suspects, following the same selection procedure. If that procedure cannot be followed, an alternative procedure for randomly selecting patients will be identified; that procedure will be documented.

Consent: Patients will be asked to consent to participating in the survey. They have to be assured that consenting or refusing to participate in the survey will have no effect on the treatment they receive. Consent will be verbal and brief, because no sensitive health care information is being collected and such surveys are part of routine health care practice in many settings. Contact information for tuberculosis suspects, such as address or telephone, may already be collected routinely for financial, administrative or public health reasons. In that situation, individual sites will decide whether it is ethically appropriate to use that information for selecting tuberculosis suspects for the satisfaction survey.

Study instruments: A study instrument will be developed to meet the needs of the site concerned. Minimum data elements to be included are patient ratings of: speed of service; comprehensiveness of service; affordability of service; perception of attention to individual needs; overall satisfaction with service.

Study 3: health care provider survey

A survey of health care providers will be conducted to determine their satisfaction with the clinical practice guidelines.

Case definition: a health care provider will be defined as any person employed by a health care facility and involved in the clinical care of tuberculosis patients.

Inclusion criteria: all health care providers, including nurses, clinical officers, physicians or other care providers, who work in facilities participating in this study during the study period and are involved in the diagnosis or treatment of tuberculosis.

Estimated number of participants and statistical sampling: the number of participants will vary depending on the size of the participating facilities. If possible, all health care providers will be studied and there will be no statistical sampling.

Enrolment procedure:

1. A supervisor at the health care facility will prepare a list of all health care providers meeting the inclusion criteria.
2. At the beginning of the study period, the questionnaire will be sent to all health care providers.
3. At the end of the study period (i.e. after six months) the same questionnaire will be readministered.

Consent: health care providers will be asked to consent to participating in the survey. Consent will be written. It will be brief, because no sensitive information is being collected.

Study instruments: A study instrument will be developed. Minimum data elements will include: basic questions about tuberculosis knowledge, attitudes and practices; basic questions about HIV knowledge, attitudes and practices; ranked measurement of availability and quality of smear microscopy and chest radiography; patient perception of the diagnostic process; availability, speed, quality; individual perception of current guidelines in the facility for smear-negative tuberculosis diagnosis; feasibility, speed, quality, overall satisfaction; open-ended questions

about satisfaction with the process for diagnosis of tuberculosis in HIV-infected patients.

Study 4: tuberculosis suspect outcome review

Case-report forms will be completed for all tuberculosis suspects to measure programme outputs from implementation of the clinical practice guidelines. Depending on existing practices at participating health facilities, it is possible that no new data collection instruments or procedures, other than those already used routinely, will be needed for this component of the study.

Case definition: The definition of a tuberculosis suspect is given in the section “Patient satisfaction survey” above.

Inclusion criteria: All persons meeting the case definition who seek health care at a participating facility during the enrolment period.

Exclusion criteria: None.

Estimated number of participants and statistical sampling: The number of participants will vary depending on the size of participating facilities. The minimum sample size needed to demonstrate a difference between facilities implementing the 2003 guidelines (i.e. existing practice) and the 2006 guidelines will be calculated on the basis of the epidemiological situation and baseline programme performance in participating sites.

Enrolment procedure:

1. Persons presenting at the health care facility will be identified as tuberculosis suspects using routine criteria for that facility and a register will be maintained of all tuberculosis suspects.
2. Patients will be informed generally by written signs or posters that the clinic is participating in a study, but individual patients will not be asked to provide informed consent (see justification below).
3. Case-report forms will be collected for all tuberculosis suspects, using a separate study form or a modification of existing clinical records (see below).

4. For patients who do not complete the diagnostic evaluation, health care facilities will use existing contact information (e.g. telephone number, address, treatment supporters) to contact patients two months after their initial contact with health services for tuberculosis diagnosis to determine whether they are still alive and, if they have died, when death occurred.

Consent: Tuberculosis programmes routinely collect and review the medical records of tuberculosis suspects to assess programme performance, e.g. measuring the number of sputum specimens collected. This process does not involve informed consent, because no patient identifiers are collected and data are used specifically to evaluate and improve programme performance. Although the number of data components being reviewed is likely to be greater than usual, the process and intent are similar.

Study instruments: Health care facilities routinely collect standard data about patients. The extent of such routine data collection varies depending on the facility and provider practice. For this evaluation, health care forms will be modified (or nationally revised recording and reporting formats will be used) to include the following minimum data elements, or a separate study-specific form will be used, depending on each site's preference: unique tuberculosis suspect identifying number; age; sex; district; date when first presented at clinic; cough; date when cough began; other symptoms; HIV diagnosis (status: positive/negative/unknown and date of HIV diagnosis); sputum smear (date, results); sputum culture (date, result); chest radiograph (date, findings); antibiotics taken before visit and after initial visit (prescribed/self-procured/ name of antibiotic and dosage); date of tuberculosis diagnosis; final diagnosis (if not diagnosed with tuberculosis) and date of last evaluation in clinic.

Study 5: tuberculosis patient outcome review

Case-report forms will be completed for all tuberculosis patients to measure programme outcome and impact of implementation of the

clinical practice guidelines. Depending on existing practices at participating health facilities, it is possible that no new data collection instruments or procedures, other than those already used routinely, will be needed for this component of the study.

Case definition: A tuberculosis patient will be defined as any person diagnosed with tuberculosis and advised to begin antituberculosis medication. The definitions of smear-positive vs. smear-negative tuberculosis will depend on the guidelines being implemented at the study site (the 2003 guidelines – i.e. existing practice – or the 2006 guidelines).

Inclusion criteria: All persons meeting the case definition who are diagnosed with tuberculosis at a participating facility during the enrolment period.

Exclusion criteria: Patients will be excluded if they are registered as “transfer in”, “treatment after default”, “treatment after failure” or “chronic”.

Estimated number of participants and statistical sampling: The number of participants will vary depending on the size of participating facilities. The minimum sample size needed to demonstrate a difference between facilities implementing the 2003 guidelines (i.e. existing practice) and the 2006 guidelines will be calculated on the basis of the epidemiological situation and baseline programme performance in participating sites.

Enrolment procedure:

1. Patients will be registered and begin tuberculosis treatment following the routine practice at the health care facility concerned.
2. Patients will be informed generally by written signs or posters that the clinic is participating in a study, but individual patients will not be asked to provide informed consent (see justification below).
3. Data from the tuberculosis register and patient records will be abstracted during the course of the study. No specific procedures will be used for enrolment or withdrawal from the study, since patients will be treated according to routine practice.

Consent: see section on “Consent” under Study 4 above.

Study instruments: Health care facilities routinely collect standard data about patients. The extent of such routine data collection varies depending on the facility and provider practice. If necessary, health care forms will be modified to include the following minimum data elements, or a separate study-specific form will be used, depending on each site’s preference: unique, random tuberculosis suspect identifying number, tuberculosis patient registration identifying number; tuberculosis registration date; HIV clinical stage; CD4 count; dates and dosage of co-trimoxazole prescribed; dates, dosage and regimen of antiretroviral treatment; tuberculosis treatment regimen; presence or absence of adverse events during tuberculosis treatment; sputum conversion result (if smear-positive at the beginning of treatment); treatment outcome and date of treatment outcome.

Study timeline

The exact duration of the study will depend on the number of settings involved, the total volume of patients in each setting and local formalities (such as ethical clearance) of the stakeholders carrying out the evaluation. Expedited implementation of the evaluation is highly recommended and desirable.

Reimbursements and incentives

Participants will receive no formal reimbursements or incentives as part of this study, although sites are permitted to provide modest incentives, such as food, for patients who attend follow-up visits, if such incentives are part of routine care.

Data handling and analysis

Statistical methodology, data collection, planned tables and figures may vary depending on the investigators conducting the evaluation. Public health programmes related to tuberculosis and HIV are changing rapidly throughout the world. The study is designed as an observational study to evaluate the impact of implement-

ing the revised recommendations, but other changes may occur in the health system at the same time, e.g. wider availability of antiretroviral treatment or active case-finding for HIV or tuberculosis that identifies patients at an earlier stage of either disease. Such events will need to be considered when interpreting findings from the studies.

Identifying, managing and reporting adverse events

Adverse events are common during treatment of HIV-associated tuberculosis, including adverse drug reactions, hospitalization and death. As part of routine public health practice, tuberculosis control programmes maintain direct communication with patients throughout the course of treatment. During this observational study, such events will be handled according to routine public health and clinical practice. Participating study sites are all public facilities to which the patients have access because they have been registered for tuberculosis treatment. Otherwise, patients will not be exposed to any physical or psychological risks beyond those normally encountered during routine clinical care.

References

- *Treatment of tuberculosis: guidelines for national programmes*, 3rd ed. Geneva, World Health Organization, 2003. http://www.who.int/tb/publications/cds_tb_2003_313/en/index.html (accessed 29 October 2006).
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**Stop TB Department
HIV/AIDS, Tuberculosis and Malaria**

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**WORLD HEALTH ORGANIZATION
20 Av. Appia, CH-1211 Geneva 27, Switzerland
Website: <http://www.who.int/gtb>**

**For further information about tuberculosis
or other communicable diseases, please contact:**

**Information Resource Centre
Communicable Diseases, World Health Organization
20 Av. Appia, CH-1211 Geneva 27, Switzerland**

Fax +41 22 791 4285

E-mail: cdsdoc@who.int

For further information about HIV/AIDS, please contact:

**Information Resource Centre
HIV/AIDS Department, World Health Organization
20 av. Appia, CH-1211 Geneva 27, Switzerland**

Fax +41 22 791 4834

E-mail: hiv-aids@who.int