

**Recommendations to improve the diagnosis of
smear negative pulmonary and extrapulmonary
TB among adults and adolescents in HIV prevalent
and resource constrained settings.**

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1. Background: Rates of smear-negative pulmonary and extrapulmonary TB have been rising in countries with HIV epidemics. The mortality rate for HIV-infected TB patients is higher than HIV-uninfected TB patients, particularly for those with smear-negative pulmonary and extrapulmonary TB. Delayed TB diagnosis may be an important cause of excess mortality in People Living with HIV (PLWH) with smear-negative pulmonary and extrapulmonary TB. In the absence of rapid, simple, and accurate TB diagnostic tools for smear-negative pulmonary and extrapulmonary TB, diagnostic algorithms have been recommended. Prior algorithms and recommendations have been developed through consensus and expert opinion without a firm evidence base. Most existing algorithms extend a patient's evaluation over a period of time, during which HIV-infected patients may die from undiagnosed TB or from advanced HIV complications. The Stop TB Strategy now emphasises the timely diagnosis and treatment of all TB cases, including smear-negative pulmonary and extrapulmonary TB.

The existing guidelines for diagnosis of smear-negative pulmonary TB were published by WHO in 2003 and codified in 2006 in the International Standards for TB Care, a publication of organisations including WHO, which are members of the Stop TB Partnership. The International Standards of TB Care largely maintained the 2003 WHO recommendations, but recognize, however, 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 for how well these guidelines perform in HIV-infected patients.

2. Target audience: This document is intended for those dealing with tuberculosis and HIV at all levels in HIV prevalent and resource constrained settings to assist development of national policies to improve the diagnosis and management of smear negative pulmonary and extrapulmonary TB. The recommendations and the algorithms are designed for use by National TB and HIV/AIDS Control Programmes and service providers. HIV prevalent settings are defined as countries, sub-national 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 in which the HIV prevalence among TB patients is $\geq 5\%$. In those countries where the national HIV prevalence rate is below 1%, national TB and HIV Control Authorities should identify and define HIV prevalent settings (sub-national administrative units or facilities) based on the epidemiology of the HIV epidemic and the magnitude of HIV-associated TB, and develop appropriate guidance for the implementation of these recommendations. The recommendations and the revised algorithms are intended for immediate implementation in sub-Saharan Africa and other high HIV prevalent settings as defined by National TB and HIV Control Authorities, to guide the expedited diagnosis and management of TB.

3. Process of formulation: In September 2005, WHO convened an expert group to review currently recommended approaches to the diagnosis of smear-negative TB in HIV-prevalent settings and propose revisions to existing WHO guidelines. The Expert Group has reviewed existing evidence in each of the relevant areas and made recommendations and revised the existing diagnostic algorithms to improve the diagnosis of smear-negative pulmonary and extrapulmonary TB in HIV prevalent settings. The recommendations and the revised diagnostic algorithms then were posted on the World Health Organization Stop TB Department's website for an open consultation. Feedback was obtained from national programme managers, researchers, clinicians and other health workers throughout the world. All leading international organisations working on TB have provided their feedback. The Expert Group subsequently revised the recommendations and the algorithms based on the feedback from this global consultation. The recommendations were further enriched from feedback from presentations in different international scientific meetings. The Strategic and Technical Advisory Group for TB and the Strategic Technical Advisory Committee for HIV, the two independent bodies that advise WHO on TB and HIV respectively, endorsed the recommendations.

4. 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 (Table 1). When appropriate, the level of evidence that help in the formulation of the recommendations is included in the text of the document according to table 1. The strength is given for each recommendation when appropriate, along with the level of evidence, to generally guide the degree to which regional and country programmes should consider the recommendations for implementation.

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 BHIVA Writing Committee on behalf of the BHIVA Executive Committee. *The British HIV Association (BHIVA) treatment guidelines for 2005*. London, British HIV Association, 2005 (<http://www.bhiva.org/guidelines/2005/BHIVA-guidelines>, accessed 16 June 2006); Developing an evidence-based guide to community preventive services – methods. Task Force on Community Preventive Services. *American Journal of Preventive Medicine*, 2000, 18(1 Suppl):35–43; WHO Health Evidence Network. *What is the evidence for the effectiveness of interventions to reduce hepatitis co-infection and the associated morbidity?* Copenhagen, WHO Regional Office for Europe, 2005 (http://www.euro.who.int/HEN/Syntheses/hepatitisC/20050412_1, accessed 16 June 2006); EBM guidelines: evidence-based medicine [online database]. New York, Wiley (<http://ebmg.wiley.com/ebmg/ltk.koti>, accessed 16 June 2006).

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 indication of the level of evidence. For example, the recommendation that calls for increased level of clinical awareness and competence in managing extrapulmonary TB at first-level health facilities is not linked with 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.

5. Implementation and evaluation

In the absence of complete evidence, the recommendations were built on consensus and iterative global expert opinion and it is believed that they will be responsive to the catastrophe posed by the dual TB and HIV epidemics. Therefore, these recommendations should be implemented in HIV prevalent settings in order to improve and expedite the diagnosis of TB among PLWH. The implementation of these recommendations requires reasonably efficient health system including quality assurance for laboratories and effective supply management and training of 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. Concomitant with their implementation it is essential to build the evidence base to assess their effectiveness and feasibility. Careful evaluations by national authorities, research groups, and interested parties are critical to assess the likely benefits and the responsiveness of the recommendations for the dual TB and HIV epidemics. The findings of these evaluations will inform evolving policy changes to improve programme performance both globally and nationally. A protocol that provides generic guidance on how to evaluate the recommendations to improve the diagnosis of TB in HIV prevalent settings is annexed to this document (Annex I).

6. Recommendations

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

6.1.1. Smear positive pulmonary TB:

- *One sputum smear examination positive for AFB and;*
- *Laboratory confirmation of HIV infection or;*
- *Strong clinical evidence of HIV infection¹.*

6.1.2. Smear negative pulmonary TB:

- *At least two negative sputum specimens for AFB and;*
- *Radiographic abnormalities consistent with active TB 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 anti-TB chemotherapy;*

¹ Depending on clinical assessment and national and/or local policy guidance a person with unknown HIV status can be classified as HIV positive for the diagnosis and management.

OR

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

6.1.3. Extrapulmonary TB

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

OR

- *Histological or strong clinical evidence consistent with active extrapulmonary TB and;*
- *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 anti-TB chemotherapy.*

Strength of recommendation: A

6. 2. Antibiotics trial

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

Recommendations:

- *The primary role of antibiotics should not be as a diagnostic aid, but rather to treat concomitant bacterial infection in PLWHA with cough or serious illness. (Strength: A-IV)*
- *Antibiotic treatment is appropriate for HIV-infected patients with cough, because bacterial infections are common in both those with and without TB. (Strength: A-II)*
- *Seriously ill patients with symptoms suggestive of TB 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 to TB diagnosis. (Strength: A-IV) Under such circumstances Fluoroquinolones should be avoided to prevent undue delay in the diagnosis of TB. (Strength: A-II)*
- *More research about the effectiveness and use of an antibiotic trial in the diagnostic algorithm, and the choice of antibiotics particularly for PLWH is needed. (Strength: A)*

6.3. Chest Radiograph

Context: Although chest radiographic (CXR) abnormalities are common in HIV-infected persons without TB, the CXR plays an important role in the diagnosis of TB among PLWH. CXR can also be an important entry point to diagnosing non-TB chest diseases, which are common among PLWH.

Recommendations:

- *CXR presentations of TB in HIV patients are now well characterised and should no longer be considered 'atypical' for TB in HIV-prevalent settings. (Strength: A-IV)*
- *CXR plays a significant role in shortening the delay of diagnosis and should be done early in the course of investigation of a TB suspect. (Strength: A-II)*
- *Sound clinical judgement is needed to put a seriously ill patient with negative sputum smear results on anti-TB treatment using only suggestive radiographic findings. Under such circumstances the clinical response of the patient has to be monitored and TB diagnosis should be confirmed at least by clinical response to anti-TB treatment and preferably by culture. (Strength: B-II).*
- *The limitations that exist for the wider use of CXR such as non-availability at peripheral health facilities and difficulty of interpreting results, even by trained physicians, need to be addressed, including through trainings. (Strength: A)*
- *Research is needed to identify innovative ways to enhance the ability of clinicians, including non-physicians, to interpret CXRs accurately, to assess the feasibility and added value of peer reviewing of CXRs and to evaluate novel imaging techniques that might replace conventional radiography. (Strength: A)*

6.4. Sputum culture

Context: Sputum culture is the gold standard for the diagnosis of TB. However, *Mycobacteria* are slow growing organisms and culture takes several weeks and needs relatively sophisticated facilities and technical expertise. Sputum culture of HIV infected individuals requires more incubation time than for non-HIV infected patients. Nonetheless, it is useful to diagnose smear negative pulmonary TB among HIV infected individuals. There are major challenges to insuring 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 in PLWH who are being evaluated for AFB smear-negative TB. This is because 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. Decentralisation of sputum culture services with efficient quality assurance system is essential. Establishment of an effective transport system for sputum is also essential. (Strength: A)*

6.5. Immune reconstitution inflammatory syndrome (IRIS) and TB 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 TB. This is because before the initiation of the ART such patients may have had either sub-clinical TB disease or were started to reactivate latent TB infection. This condition, which is known as Immune reconstitution inflammatory syndrome (IRIS), usually occurs within three months of ART initiation. It can also appear as exacerbation of the TB disease when initiating ART in HIV infected TB patients, who are already taking TB treatment similar to the well documented paradoxical reactions seen in some patients without underlying HIV infection. IRIS is commonly associated with TB, although can occur with other pathogens.

Recommendations:

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

6.6. Diagnosis of extrapulmonary TB

Context: Extrapulmonary TB is more strongly HIV-related than pulmonary TB, with combined extrapulmonary and pulmonary TB being especially suggestive of underlying HIV-infection. HIV-related extrapulmonary TB is a WHO Clinical Stage 4 (advanced AIDS) diagnosis, and patients with HIV-related extrapulmonary TB often have disseminated disease and are at high risk of rapid clinical deterioration and death. The accurate diagnosis of extrapulmonary TB is complex and difficult, particularly in peripheral health facilities with limited support and diagnostic infrastructure. Simplified, standardised clinical management guidelines for most common and serious forms of extrapulmonary TB are included in this document to assist healthcare workers at the district hospital level of HIV prevalent settings (page 18).

Recommendations:

- *There should be increased level of clinical awareness and competence in managing extrapulmonary TB at first-level health facilities, including earlier referral of patients when appropriate. (Strength: A)*
- *In peripheral health facilities of HIV-prevalent settings, health care workers should initiate empiric TB treatment early in patients with serious illness thought to be due to extrapulmonary TB. After empiric TB treatment has been initiated, every attempt should be made to confirm the diagnosis of TB, including through 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, TB treatment should be continued and completed. (Strength: B-IV)*
- *Empiric trials of treatment with incomplete regimens of anti-TB drugs should not be performed. (Strength: A-I)*
- *If a patient is treated with empiric anti-TB drugs, treatment should be with standardized, first-line regimens, and it should be used for the entire duration of TB treatment. Empiric treatment should only be stopped if there is bacteriological, histological, or strong clinical evidence of an alternative diagnosis. (Strength: A)*

6.7. Recording and reporting

Context: The recording and reporting of smear-negative pulmonary and extrapulmonary TB by National TB Control Programmes needs strengthening and information from case reporting should increasingly be used to inform changes in programme performance.

Recommendations:

- *The current recommendation of reporting of those cases with out smear results as smear negative pulmonary cases should be revised. (Strength: A)*
- *The revised standard TB recording and reporting formats should used generate 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)*

7. Algorithms for the diagnosis of smear negative pulmonary TB

In the absence of rapid and simple tools to diagnose TB, 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 minimise incorrect diagnosis and mortality from TB. The algorithms will have significant implications for both TB and HIV/AIDS service providers in these settings and will catalyse the integration of HIV and TB interventions at the point of service delivery. The algorithms are targeted for adult and adolescent patients presenting with cough of 2-3 weeks duration and are tailored according to the clinical condition of the patient (ambulatory or seriously ill).

7.1. Guiding principles

Target group: The newly revised algorithms (Figure 1 and 2) are targeted for adult PLWHA and those considered being at high risk of HIV infection based on clinical and epidemiologic grounds following national and/or local policy guidance. 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 2003 recommendations) included in the International Standards for Tuberculosis Care, 2006 (Figure 3).

Danger signs: The clinical condition of 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 more than 30 per minute
- Fever of more than 39 °C
- Pulse rate of more than 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 (for e.g. due to lack 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, (Table 1), immunological staging (CD₄ count), and referral for HIV care including ART, long term follow-up and chronic management, including co-trimoxazole preventive therapy. The clinical staging is important as some patients with pulmonary TB may also have concurrent stage IV disease requiring more rapid initiation of ART.

Clinical assessment: This is a critical step in the diagnosis process, particularly in the absence of a bacteriological confirmation for TB. It must be based, as much as possible, on supportive investigations and include sound judgement to arrive at a correct diagnosis without undue delay so as to prevent mortality from undiagnosed TB. It is also useful for the diagnosis and management of non-TB clinical conditions during all evaluations of the patient. Sound clinical judgement will be essential to: classify the patient as ambulatory or seriously ill based on the danger signs; classify the patient with unknown HIV status as HIV positive or negative; to begin the patient on broad spectrum antibiotics or anti-TB drugs based on the clinical condition

and presentation; to assess, manage, and/or refer the patient 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 TB is less likely and who are treated empirically for bacterial pneumonia or *Pneumocystis carinii pneumonia* (PCP), clinical response should not automatically exclude the diagnosis of TB. Acute bacterial pneumonia or PCP may occur in patients with underlying TB and, therefore, patients should be re-evaluated for TB particularly if respiratory symptoms persist after treatment. Follow up assessment of these patients can be either within the TB services or HIV services according to country specific guidance and practice.

7.2. Algorithm for ambulatory patient: This algorithm is used for a TB suspect without the danger signs defined above (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 TB and HIV authorities to minimise the time and the number of visits required to establish the diagnosis. Shortening the turn around time for sputum smear examinations is crucial.

The following principles should be followed while applying the algorithms for ambulatory patient to expedite the diagnosis of smear negative pulmonary TB:

- **First visit:** HIV testing should be offered and AFB sputum examination should be performed. If AFB is positive, treat for TB.
- **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 be the second day after first presentation at the health facility. The investigations include: repeated sputum AFB, sputum culture and Chest X ray. Clinical assessment is also important to decide whether it is worth to put the patient on anti TB treatment at this stage. HIV assessment should also be done and co-trimoxazole preventive therapy (CPT) provided according to national guidelines.
- **Third visit:** Results of the second visit investigations (except culture) should be available during the third visit of the patient. Patients suspected of having TB after these investigations (e.g., compatible radiograph plus symptoms) should be treated for TB. For patients who are not treated for TB, either a broad based antibiotic (except Fluoroquinolones) to treat bacterial infection or treatment for PCP should be initiated.

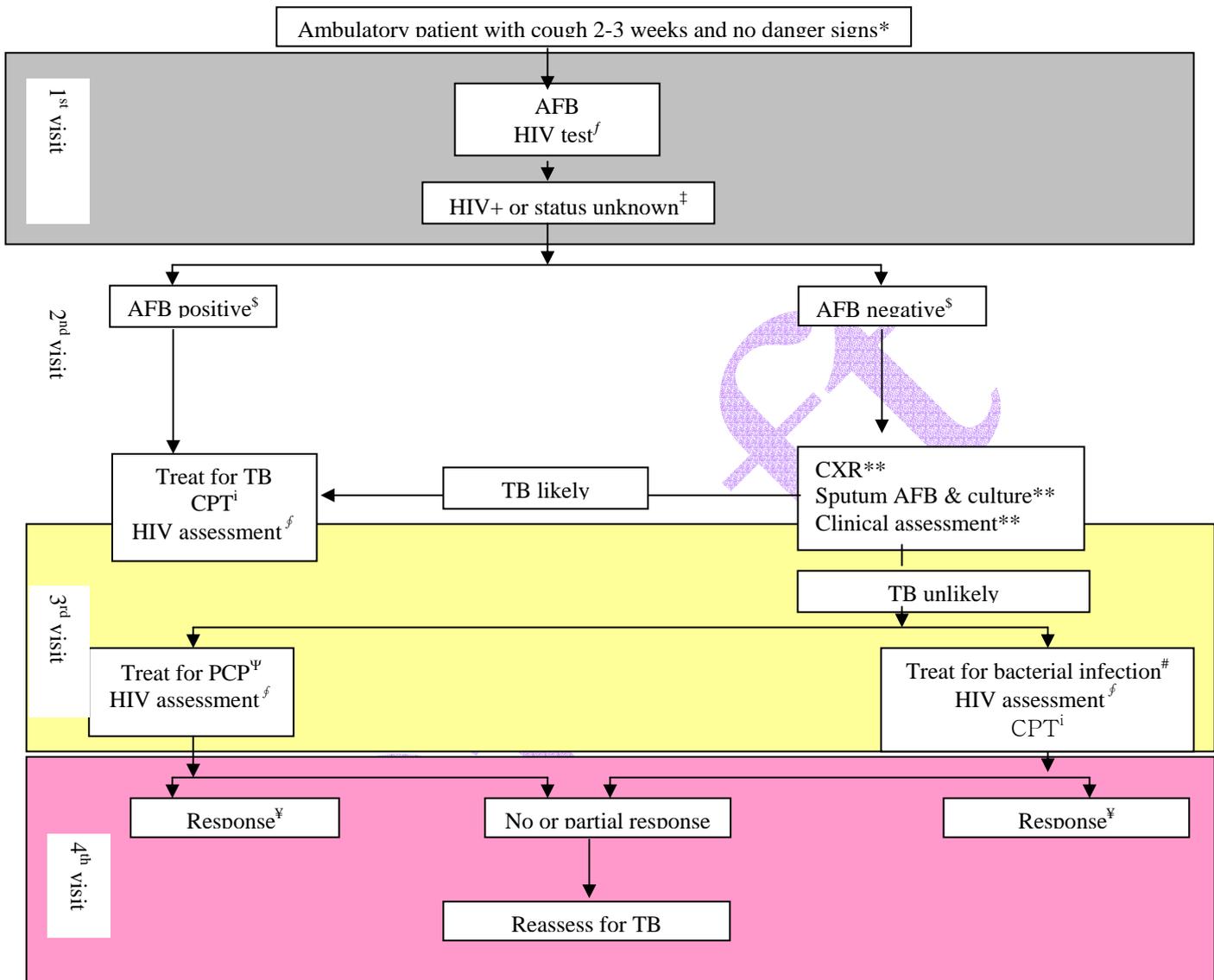
HIV assessment should also be done and co-trimoxazole preventive therapy (CPT) provided according to national guidelines.

- **Fourth visit:** This is a step where patients' response is assessed and a clinical follow-up mechanism is established (either in the TB or HIV services). For patients with immediate response to the PCP or antibiotic treatment, continued vigilance is necessary to exclude superimposed TB disease. Those patients with an unsatisfactory response to treatment for PCP or bacterial pneumonia should be reassessed both clinically and bacteriologically for TB disease.

7.3. 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 testing and sputum AFB examination. Principles of safe injection practice should be strictly followed. If there are indications according to national guidelines, 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.
- If TB diagnosis is confirmed by AFB smear examination, start TB treatment. The antibiotic treatment should be continued and completed.
- If AFB is negative, response to parenteral antibiotics should be assessed between 3-5 days into treatment, and, if there is no improvement, TB treatment should be initiated. The initial antibiotic course should be continued and completed. HIV assessment and clinical staging should be done. Patients should be referred to the next higher level to confirm the diagnosis of TB and for HIV care. If referral is not possible, TB treatment should be continued for the whole duration.
- 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 all at one time for the diagnosis of TB.

Figure 1. Algorithm for the diagnosis of TB in ambulatory HIV positive patient



* The danger signs include any one of respiratory rate >30/minute, fever >39⁰ C, pulse rate > 120/mt and unable to walk unaided.

^f For countries with adult HIV prevalence rate ≥1% or prevalence rate of HIV among TB patients ≥5%

[‡] In the absence of HIV test, classifying HIV status unknown into HIV positive depends on clinical assessment or national and/or local policy guidance

[§] AFB positive is defined at least one positive and AFB negative defined when two or more smears are negative.

ⁱ CPT= Co-trimoxazole preventive therapy

[§] HIV assessment include HIV clinical staging , determination of CD₄ count if available and referral for HIV care.

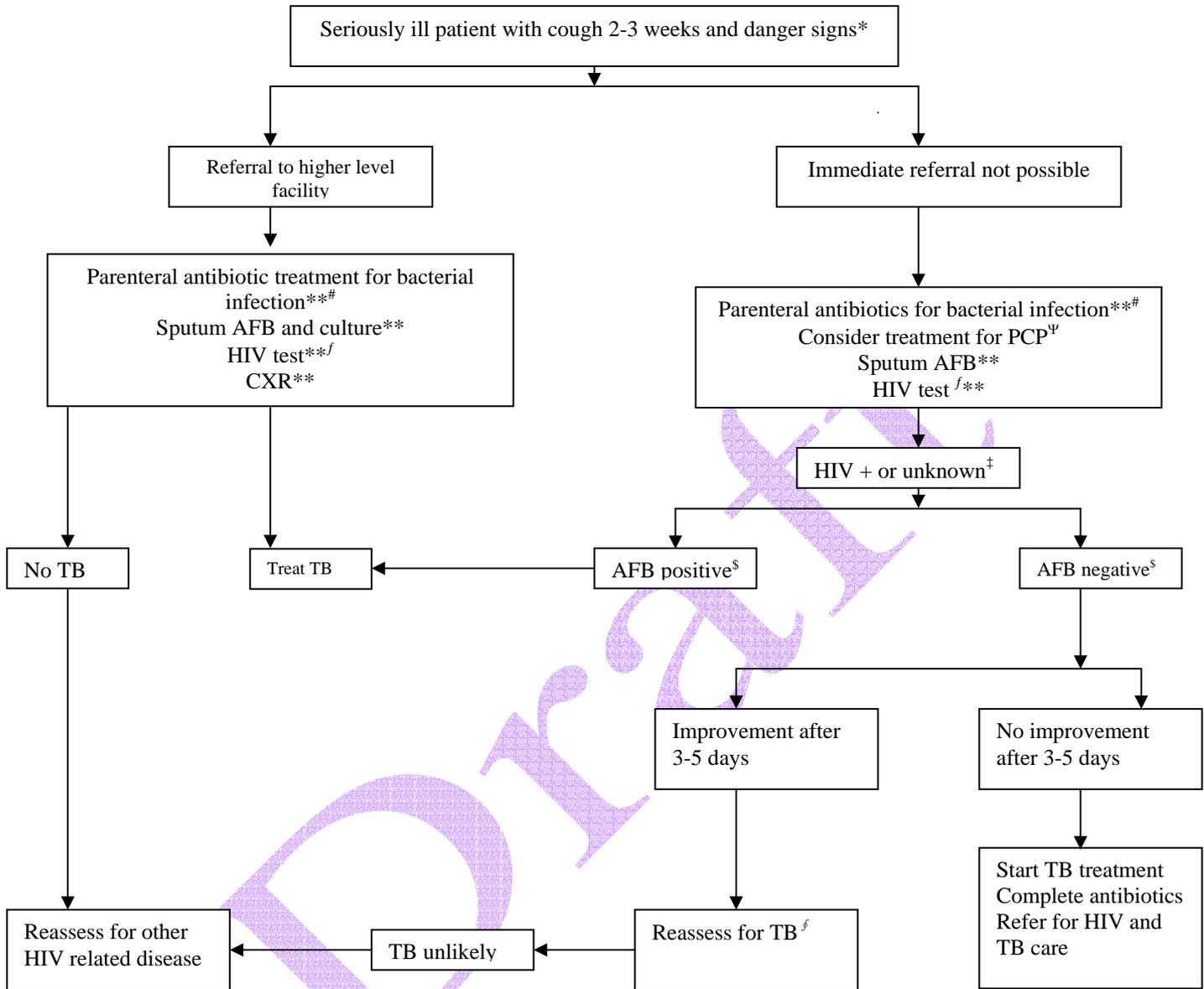
** The investigations within the box should be done all at a time, wherever it is possible in order to decrease the number of visits and speed up the diagnosis.

Antibiotics (except Fluoroquinolones) to cover both typical and atypical bacteria should be considered.

^ψ PCP: *Pneumocystis carinii pneumonia* also known as *Pneumocystis jirovecii pneumonia*

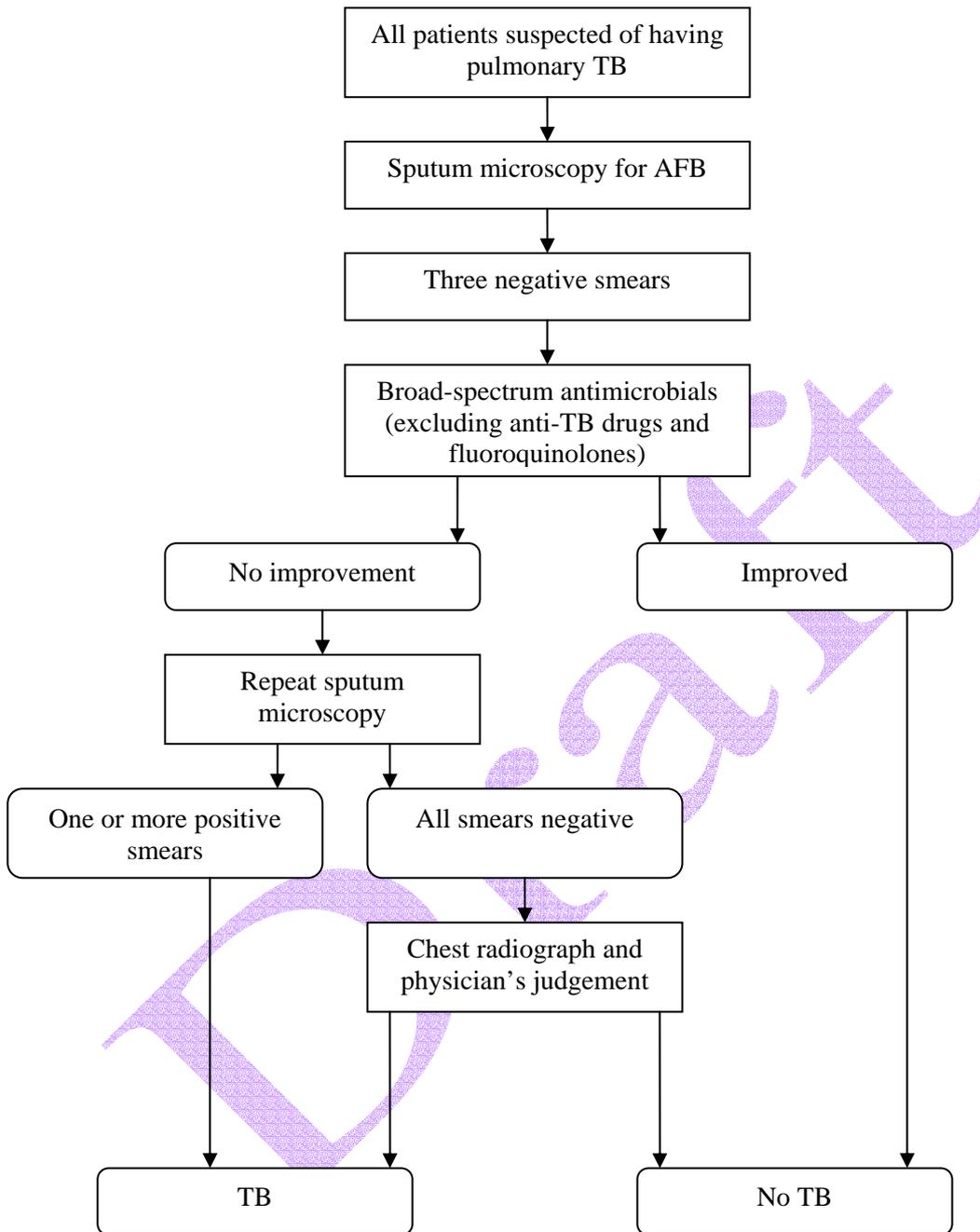
[¥] Advise to return for reassessment if symptoms recur

Figure 2. Algorithm for the diagnosis of TB in seriously ill HIV positive patient



- * The danger signs include respiratory rate >30/minute, fever >39⁰ C, pulse rate>120/mt and unable to walk unaided.
- f For countries with adult HIV prevalence rate ≥1% or prevalence rate of HIV among TB patients ≥5%
- ** The investigations within the box should be done all at a time, wherever it is possible in order to decrease the number of visits and speed up the diagnosis.
- † In the absence of HIV test, classifying HIV status unknown into HIV positive depends on clinical assessment or national and/or local policy guidance
- § AFB positive is defined at least one positive and AFB negative defined when two or more smears are negative.
- # Antibiotics (except Fluoroquinolones) to cover both typical and atypical bacteria should be considered.
- ψ PCP: *Pneumocystis carinii pneumonia* also known as *Pneumocystis jirovecii pneumonia*
- f Reassessment for TB includes AFB exam and clinical assessment.

Figure 3. Algorithm for the diagnosis of HIV negative patients (ISTC , 2006)



Source: Modified from WHO, 2003

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
Unexplained moderate weight loss (<10% of presumed or measured body weight) ¹ 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 ² severe weight loss (>10% of presumed or measured body weight) ⁸ Unexplained chronic diarrhoea for longer than one month Unexplained 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 4³
HIV wasting syndrome Pneumocystis 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 HIV encephalopathy Extrapulmonary cryptococcosis including meningitis Disseminated non-tuberculous mycobacteria infection Progressive multifocal leukoencephalopathy Chronic cryptosporidiosis Chronic isosporiasis Disseminated mycosis (extrapulmonary histoplasmosis, coccidiomycosis) Recurrent septicaemia (including non-typhoidal salmonella) Lymphoma (cerebral or B cell non-Hodgkin) Invasive cervical carcinoma Atypical disseminated leishmaniasis Symptomatic HIV associated nephropathy or Symptomatic HIV associated cardiomyopathy

¹ Assessment of body weight in pregnant woman needs to consider expected weight gain of pregnancy.

² Unexplained refers to where the condition is not explained by other conditions.

³ Some additional specific conditions can also be included in regional classifications (e.g. reactivation of American trypanosomiasis (meningoencephalitis and/or myocarditis) in Americas region, Penicilliosis in Asia).

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**Part II: Simplified and standardised clinical management guidelines for
extrapulmonary TB for HIV prevalent and resource-limited settings**

Draft

1. Background: One out of five registered TB patients have extrapulmonary TB¹⁻³. Commonest forms include lymph node (especially in the neck or under the arms), pleural (usually one-sided pleural effusion) and disseminated TB (disease that is not limited to one site of the body). Pericardial and meningeal TB are less frequent forms of extrapulmonary TB that are also covered in these guidelines. About a third of deaths in HIV-positive Africans are due to disseminated TB⁵⁻⁷; but only about half of HIV-positive patients who die from disseminated TB are diagnosed before death⁶⁻⁸. With the exception of lymph node TB, which can usually be confirmed through aspiration of affected lymph nodes, most patients with extrapulmonary TB are managed without bacteriological or histological confirmation.⁴ Therefore, it is important for healthcare workers to have simplified, standardised guidelines for the prompt diagnosis and management of extrapulmonary TB.

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

3. Diagnosis and management: The indications when to suspect extrapulmonary TB in a patient and the key signs to look for the commonest forms are summarised in Figure 5. Similarly, Table 3 summarises the essential investigations to the diagnosis, and key steps for immediate management of suspected extrapulmonary TB case. For a patient with suspected extrapulmonary TB and started on anti-TB treatment without bacteriological or histological confirmation, the clinical response to treatment should be assessed after one month. If there is no improvement, clinical re-assessment should be done to look for an alternative diagnosis.

HIV testing should be offered to all patients suspected of extrapulmonary TB. This is because HIV related extrapulmonary TB is an indication for early commencement of antiretroviral treatment (Stage IV of HIV disease). For HIV related extrapulmonary TB the following interventions should be carried out:

- Refer for HIV care or start ART according to National guidelines
- Start cotrimoxazole prophylaxis
- Be vigilant of clinical deterioration of extrapulmonary TB after the start of ART (Immune reconstitution inflammatory syndrome: IRIS) and take appropriate measures.

3.1. TB Lymphadenitis

TB lymphadenitis should be suspected in any patient with enlarged lymph-nodes that are firm, asymmetrical, more than 2cm in diameter, or where a node has become fluctuant or developed a fistula over several months. TB lymphadenitis 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 Table 4) should be carried out on the first out-patient visit for all patients

Needle aspiration with cytology and TB microscopy of aspirated material has a high diagnostic yield, with confirmation of over 85% of patients with TB lymphadenitis in some⁹⁻¹² but not all¹³ reports, suggesting that 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 malignancies and other infections. Follow-up to receive the results should be within 7 days. If the aspirate is non-diagnostic, then excision biopsy for gross examination, ZN microscopy, mycobacterial culture, and, if available, histological examination can be considered.

However, TB treatment should be started immediately if:-

- The patient is HIV-infected and has clinical features of disseminated TB (such as marked weight loss, rapid clinical deterioration, or multiple sites of suspected TB) *or*
- TB lymphadenitis is considered the most likely clinical diagnosis but logistical or economic barriers are likely to delay excision biopsy for 2 weeks or longer.

3.2. Pleural effusion

TB is the likely cause of unilateral pleural effusion in countries with high TB burden, being the diagnosis made in 95% of patients in two recent case series from Uganda and Zimbabwe.^{14, 15} Pleural effusion is the most common form of HIV-related extrapulmonary TB with high mortality in the first 2 months of TB treatment (over 20%).^{14, 15}

The following key steps that should be followed:

- The management of TB pleural effusion should aim at starting TB treatment and identify underlying HIV infection without delay. Pleural biopsy has a high diagnostic yield^{14,15}, but is **not** recommended because of being unnecessarily invasive and with the potential to introduce diagnostic delay.
- Suspected pleural effusions should be confirmed by chest radiography and immediate aspiration of fluid whenever possible (Table 1), and placing aliquots of the aspirate into one plain and two anticoagulated tubes.
- Treatment with broad-spectrum antibiotics is not required before TB treatment in patients with unilateral effusions if the pleural fluid is clear and clots on standing, unless there is clinical concern for bacterial pneumonia.
- Patients with unusual findings, such as bilateral effusions, cloudy or bloody aspirates should have the additional investigations detailed in Table 1. If visible clots form in the aspirate within a few minutes of being placed into a plain (no anticoagulant) tube, then this confirms a high protein content of the fluid. No further investigations are needed if the aspirate is clear and straw-coloured and there are no other features suggestive of a non-TB diagnosis.

- Failure of the aspirate to clot does not exclude TB, and such patients can still be started on TB treatment immediately if there are no other unusual findings (Table 1), but laboratory analysis of fluid is needed for protein content (expect ≥ 30 g/l in patients with a tuberculous effusion, but 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 TB treatment within 7 days unless another diagnosis has been made.
- If thoracentesis is not available, TB treatment should be started immediately, particularly if the patient is HIV infected, unless there are clinical or radiological features suggestive of a non-TB diagnosis.

3.3. Other forms of Extrapulmonary TB

Most patients with other forms of extrapulmonary TB present in a sufficiently characteristic way to allow TB treatment to be started without attempting to confirm TB bacteriologically or histologically. Although extrapulmonary TB 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 response¹².

Taking specimens for TB culture increases the chances that TB can be confirmed, but treatment should not generally be delayed until culture results are available. Instead, TB treatment should be started promptly if indicated after carrying out the essential investigations and assessments shown in Table 1. The attending healthcare worker should carefully consider the need for additional investigations and treatment (such as antibiotics) not shown in Table 1 if a non-TB diagnosis is suspected. However, it is not necessary to routinely give broad-spectrum antibiotics before considering TB treatment.

TB treatment should be started as soon as other common conditions that can cause a similar clinical picture have been excluded (see Table 1 for essential investigations) in patients presenting with: -

- Pericardial effusion: TB 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.^{16;17;18}
- Meningitis with CSF features suggestive of TB (see Table 1)
- Suspected disseminated TB in febrile patients presenting with HIV wasting syndrome. High rates of undiagnosed disseminated TB have been consistently identified in febrile in-patient PLWH and in post mortem series from several countries.^{5-8;19-23}

Patients with clinical features or investigation results that suggest a diagnosis other than extrapulmonary TB (listed in Table 1) need more extensive investigation before TB treatment is considered, but with the aim of keeping diagnostic delays to a minimum.

3.4. Adjuvant corticosteroids

Corticosteroids started at the time of TB diagnosis and given for the first two months of TB treatment significantly improved survival of TB meningitis in HIV-negative patients, and are now recommended for such patients²⁴. For other forms of extrapulmonary and, and for HIV-related TB meningitis, the effects of steroids are still uncertain. Results of small trials are promising for TB pericarditis.²⁵ There appears to be no benefit of adding steroids to the treatment of TB pleural effusions, with some suggestion of possible harm among HIV-positive patients.²⁶ Recommendations may change when results of larger randomized clinical trials become available within the next few years.

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Figure 5: Suggested clinical characteristics to assist the diagnosis of extrapulmonary TB

Suspect ETB in patients with

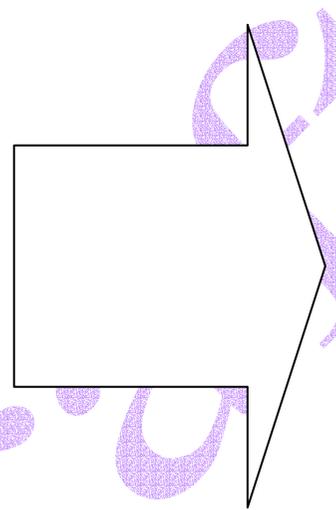
Cough for 2 weeks or more *or*

- Unintentional weight loss with
 - Night sweats *and*
 - Temperature > 37.5 or feels feverish
- Breathlessness (effusion/pericarditis) *or*
- Enlarged glands in neck/armpit *or*
- Chest x-ray
 - Miliary or diffuse shadowing
 - Large heart (especially if symmetrical and rounded)
 - Pleural effusion
 - Enlarged lymph nodes inside the chest
- Chronic headache or altered mental state

Suspect disseminated TB in all PLWH with rapid or marked weight loss, fever and night sweats

Establish HIV status if ETB is suspected

- Advise and arrange for rapid HIV testing if status is unknown or last test was negative
 - Explain that this will affect the way that this illness is investigated and treated
 - Discuss the need for ART if HIV-related TB is diagnosed
 - If consent is given, try to arrange testing on the same day



Look and listen for

- Lymph nodes swelling in the neck or armpits (if present with other types of ETB it may provide the only way to confirm the diagnosis)
Possible TB lymphadenitis
- Signs of fluid in the chest
 - Absent breath sounds
 - Reduced chest wall movement
 - Dull to percussion**Possible TB pleural effusion**
- Signs of fluid around the heart
 - Heart sounds distant
 - Swollen legs and/or abdomen
 - Neck and hand veins distended with arm held above the shoulder**Possible TB pericarditis**
- Signs of meningitis
 - neck stiffness
 - confusion
 - abnormal eye movements**Possible TB meningitis**

Table 3: Diagnosis and immediate management of suspected ETB

Lymph node TB (Peripheral)	Pleural effusion	Disseminated TB	Pericardial effusion	TB Meningitis
<p>Essential investigations</p> <ul style="list-style-type: none"> ➤ HIV test (rapid if possible) ➤ Sputum smears if coughing ➤ Needle aspirate for AFB (wide bore needle 18 to 21 gauge) <p>High suspicion of TB if:</p> <ul style="list-style-type: none"> ➤ 2cm or more in size ➤ Asymmetrical /localised ➤ Painless swelling ➤ Firm / fluctuant / fistulated ➤ Cervical location ➤ Wt loss, night sweats, fever <p>Findings that suggest a non-TB diagnosis</p> <ul style="list-style-type: none"> ➤ KS[‡] 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 +ve with possible disseminated TB (eg rapid clinical deterioration) ○ TB 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[§] ➤ Differential WBC count and protein determination (if possible) of aspirate <p>High suspicion of TB if:</p> <ul style="list-style-type: none"> ➤ Unilateral effusion ➤ Aspirate of fluid[§] is:- <ul style="list-style-type: none"> ○ Clear and straw coloured <i>and</i> ○ Clots on standing in a tube without anticoagulants ➤ Wt loss, night sweats, fever ➤ Evidence for TB elsewhere <p>Findings that suggest a non-TB diagnosis</p> <ul style="list-style-type: none"> ➤ Bilateral effusion (possible heart failure or pneumonia) ➤ Clinical KS[‡] /other malignancy ➤ Aspirate of fluid is:- <ul style="list-style-type: none"> ○ Cloudy / pus (probable empyema) ○ Fails to clot (does not exclude TB, but send fluid for protein and differential cell count, and consider heart failure) <p>Immediate Management</p> <p>Features of TB only</p> <ul style="list-style-type: none"> ➤ Start TB treatment <p>Features of non-TB diagnosis</p> <ul style="list-style-type: none"> ➤ Send aspirate for differential cell count, protein and, if available, cytology: ≥ 50% lymphocytes and protein > 30g per L suggests TB ➤ Treat for TB 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, FBC & cryptococcal antigen <p>High suspicion of TB if:</p> <ul style="list-style-type: none"> ➤ Wt loss, fever and cough ➤ Abnormal CXR (which can include miliary pattern) ➤ Large spleen/liver ➤ Night sweats ➤ Anaemia <p>Findings that suggest a non-TB diagnosis</p> <p><i>if HIV+ consider salmonella, pneumococcus, malaria, Cryptococcus</i></p> <ul style="list-style-type: none"> ➤ Rigors ➤ Very breathless (RR>30/mt) ➤ Severe diarrhoea ➤ Blood in stool ➤ Positive cryptococcal antigen, malaria smear or likely pathogen isolated from blood culture <p>Immediate Management</p> <p>Features of TB only</p> <ul style="list-style-type: none"> ➤ Start TB treatment (add antibiotics if critically ill) <p>Features of non-TB diagnosis</p> <ul style="list-style-type: none"> ➤ Investigate other causes ➤ Start both TB 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) ➤ ECG if ultrasound not available <p>High suspicion of TB if:</p> <ul style="list-style-type: none"> ➤ Lung fields clear (but may have bilateral pleural effusion) ➤ Wt loss, night sweats, fever ➤ Evidence of TB elsewhere <p>Findings that suggest a non-TB 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 ➤ ECG suggests another cause for enlarged heart (eg high BP, valve disease, dilated cardiomyopathy) ➤ Murmur (probable valvular disease) ➤ Rigors (probable bacterial pericarditis) <p>Immediate Management</p> <p>Features of TB only</p> <ul style="list-style-type: none"> ➤ Start TB treatment ➤ Refer for urgent aspirate if very breathless / unwell <p>Features of non-TB diagnosis</p> <ul style="list-style-type: none"> ➤ Investigate other causes (Urea and cardiac ultrasound) ➤ Treat for TB 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 on CSF ➤ Cryptococcal antigen / stain ➤ Sputum smears if coughing <p>High suspicion of TB if:</p> <ul style="list-style-type: none"> ➤ Wt loss, night sweats, fever ➤ CSF clear with high protein, low glucose and lymphocytes ➤ Cryptococcal antigen (or India ink and fungal culture) –ve on CSF ➤ Evidence of TB elsewhere <p>Findings that suggest a non-TB diagnosis</p> <ul style="list-style-type: none"> ➤ HIV test +ve (cryptococcal disease more likely than TB) ➤ CSF cloudy or neutrophils on microscopy (probable bacterial) ➤ Cyptococcal tests +ve ➤ Rapid onset ➤ Very high CSF pressure (probable cryptococcal) <p>Immediate Management</p> <p>Features of TB only</p> <ul style="list-style-type: none"> ➤ Start TB treatment ➤ Admit <p>Features of non-TB diagnosis</p> <ul style="list-style-type: none"> ➤ Treat for cryptococcal disease if crypto tests +ve or if HIV+ve and no other diagnosis made

[‡] KS-Kaposis sarcoma

[§] 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 differential WBC count and protein determination can be requested if there are any findings to suggest a non-TB diagnosis.

Table 4: Guidelines for fine needle lymph-node aspiration

Equipment needed: topical antiseptic, gloves, 5mls syringe and an 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 non-dominant 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 non-left 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 2 slide to air-dry. If pus is obtained, send one slide for Gram stain and one for TB microscopy. If no pus is obtained, then send both slides for TB 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.²⁷

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**Annex: Protocol for operational evaluation of the revised
recommendations and algorithms for improving the diagnosis of
TB in HIV prevalent settings**

1. Background

In 1991, WHO first published guidelines for National TB Control Programmes which include criteria for the diagnosis of smear positive and negative pulmonary and extrapulmonary TB, and subsequently revised these in 1997 and 2003. In response to concerns that the 2003 guidelines did not adequately reflect the diagnostic and treatment challenges of HIV-associated TB, WHO has revised its recommendations for the diagnosis of TB for HIV prevalent settings, which is included in this document.

Major changes between the revised guidelines (2006) and the previous guidelines (2003) are that:

- (1) The revised 2006 guidelines apply only to:
 - a. Patients suspected of having TB and living in settings (geographic area or health facility) with an HIV prevalence $> 1\%$ in pregnant women or an HIV-prevalence $\geq 5\%$ in TB patients.
 - b. Patients age ≥ 15 (guidelines for childhood TB are being developed separately).
 - c. Note that for all other populations, the existing guidelines from the International Standards for TB Care should be followed.
- (2) All TB **suspects** should be routinely offered HIV counselling and testing. This is different from the existing WHO recommendation that only TB **patients** offered HIV counselling and testing.
- (3) A “trial” of antibiotics is not required to diagnose smear-negative TB.
- (4) Two sputum specimens, with one collected in the morning, are sufficient for the initial diagnostic evaluation of TB in HIV patients. This is different from the 2003 WHO recommendation that “at least” three specimens be AFB negative before diagnosing smear-negative TB.
- (5) A patient is considered to have smear-positive TB if at least one specimen is positive for AFB.
- (6) Sputum culture for MTB should be performed in patients who are sputum smear-negative to confirm the diagnosis of TB and improve the quality of care.

In the absence of complete evidence, the recommendations were built on consensus and iterative global expert opinion in order to respond to the catastrophe posed by the HIV epidemic. Therefore, the revised recommendations should be implemented in HIV prevalent settings. However, it is

equally important to build the evidence-base concomitantly, particularly in the settings in which it is possible, to look for their effectiveness and feasibility so as to inform changes in policy and practice.

2. Objectives of the evaluation

The primary intent of the evaluation is to measure the performance of TB programs that implement the revised recommendations and then to generate knowledge for improving those specific programs. The evaluation involves measuring different indicators of input, process, output, outcome, and impact in the settings that implement the revised recommendations compared with settings not implementing the recommendations. The evaluation provides information for international and national health policy makers and public health officials about the strengths and weaknesses of these revised guidelines to inform changes in international and national policy and practice. Therefore, the evaluations should be conducted in close collaboration with National TB and HIV Control Programmes of the respective countries.

3. Purpose of the protocol

This protocol is a document that provides generic guidance on the conduct of the evaluation of the revised recommendations to improve the diagnosis of TB in HIV prevalent settings. It intends to standardize the minimum information that needs to be generated from the evaluation in order to inform changes in the policy both at national and global levels. The protocol will also provide a flexible platform for research groups and interested stakeholders to evaluate these recommendations, at the same time enabling them contribute towards informing changes in policy and improving programme performance both globally and nationally.

4. Hypotheses

Compared with settings implementing the 2003 guidelines (existing practice), settings implementing the revised guidelines of 2006 will have:

- (1) A larger proportion of TB suspects diagnosed with smear-negative TB;
- (2) A smaller proportion of smear-negative pulmonary and extrapulmonary TB patients that die before treatment completion.
- (3) A smaller proportion of TB suspects that die before completion of the diagnostic evaluation and two months after initial contact with health services for TB diagnosis;
- (4) A shorter time lag between onset of cough and treatment for TB and date of initial contact with health services for TB diagnosis and beginning of TB 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;

5. Study design and procedure

The highest quality evidence would come from a randomized clinical trial (RCT) in which individual patients would be enrolled and then randomly assigned to the revised and the existing recommendations and algorithms. However, assuming it was technically and financially feasible, a RCT comparing the guidelines would be extremely difficult to justify ethically as it will involve failing to perform, or withholding results of chest radiography, sputum culture, or HIV testing from patients and clinicians. Therefore, a more practical, ethically-acceptable approach to validating the revised guidelines would be to measure only operational performance, rather than diagnostic test performance, and randomize only facilities or populations, not individuals.

Depending on country specific factors, the implementation of the revised guidelines requires revision of national guidelines, logistic and technical arrangements, including human resources and infrastructure development. Therefore, the implementation of the revised recommendations would probably be in a phased manner in many countries. This will facilitate the evaluation by interested parties and stakeholders and help to define intervention and non-intervention settings within a country through the scale-up process.

5.1 General Design

The suggested general design for the study is prospective, observational study. The justification for this approach is:

- (1) **Prospective:** Historical data, such as medical chart review, could be used to compare outcomes, but such data may lack sufficient detail to answer the important public health questions about patient and provider satisfaction, as well as to compare costs. Similarly, in many countries, there are rapid advances occurring in HIV care and treatment, which could impact the frequency with which TB is diagnosed, the types of TB diagnosed, and the outcomes of patients treated for TB. Conducting this study prospectively will help control for these factors.
- (2) **Observational:** The study will involve no experimental diagnostic test 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 likely occur in a phased manner. The observational study design, therefore, allows for both implementation of guidelines and a quasi-experimental assessment of impact. For reasons described above, a randomized clinical trial design is not ethically appropriate. Involving multiple centres will allow for comparison of the impact on programs and will be useful.

5.2 Study description

A setting refers to 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 TB cases and if they are implementing either the existing (2003) or the revised (2006) recommendations. The settings implementing the revised recommendations should also have to implement the revised recording and reporting formats according to national guidelines (The documents are available from the WHO website at www.who.int/tb). Ideally, allocation of setting will be done as a concealed, randomized process; but because this study is being conducted in a program context, other factors may need to be considered in selection of sites, including availability of personnel, infrastructure, and budget. For example the availability of necessary tests and services (e.g. HIV testing, Chest X ray, Culture etc.) would determine to select an intervention site.

How the non-intervention sites are chosen may also have to be non-random. There may be substantial variation in practice across and within settings that need to be considered for the selection. In those countries that already changed their national guidelines into the revised guidelines, those settings which have not implemented the revised guidelines for the duration of the evaluation can be selected as non-intervention sites. The ideal non-intervention site will have a standardized approach to TB diagnosis and such practice should be consistent with national guidelines and, if possible with the 2003 WHO guidelines.

Before data collection begins, both intervention sites and non-intervention 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 about the revised guidelines, basic diagnosis and management of TB 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 potentially associated with such trainings, non-intervention sites will undergo similar training focusing on the 2003 guidelines.

5.3. Suggested Studies

Within each setting (intervention and non-intervention), several evaluations will occur to measure input, process, output, outcome, and impact of the revised guidelines. These suggested studies can be conducted either as independent studies or part of a bigger study, depending on local context and the interest of the research groups. Table 1 below describes the types of studies and indicators they will measure.

5.3.1. 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 human resources development and infrastructure required to implement the revised guidelines. As much as possible, identical information will be obtained from the sites implementing the 2003 guidelines 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 for healthcare workers and trainers), transportation of persons and specimens, construction, equipment, supplies, reagents and consumables, standard diagnostic procedures (e.g., microscopy, radiography, culture, HIV testing), anti-TB therapy, antibiotics prescribed for bacterial infection.

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.

5.3.2 Study #2: Patient satisfaction survey

A survey will be performed on TB suspects to determine their satisfaction with the diagnostic process in facilities implementing the revised guidelines compared to those implementing the 2003 guideline.

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

Table 1. Study tools to be used during evaluation, populations to be studied, and indicators that will 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	TB suspects attending health facilities	Process	Satisfaction of patients with speed and quality of services, as measured through patient survey
3	Questionnaire	Healthcare providers working at health facilities	Process	Satisfaction of providers with clinical practice guidelines, as measured through provider survey
4	Case report form	TB suspects attending health facilities	Output	Proportion of pulmonary TB suspects with at least two sputum smears collected, with a chest radiograph performed, with a sputum culture performed
			Output	Proportion of pulmonary TB suspects that complete diagnostic evaluation
			Output	Proportion of pulmonary TB suspects that die before diagnostic evaluation completed, before beginning TB treatment, and two months after initial contact with health services for TB diagnosis
			Output	Proportion of pulmonary TB suspects with known HIV status
			Output	Proportion of pulmonary TB suspects given a non-TB diagnosis
5	Case report form	TB patients treated in health facilities	Outcome	Proportion of pulmonary TB cases diagnosed as smear-negative
			Outcome	Proportion of pulmonary TB cases with known HIV status
			Outcome	Days between onset of cough and treatment for TB and days between initial contact with health services for TB diagnosis and treatment of TB
			Impact	Proportion of pulmonary TB cases that die two months into treatment and six months into treatment (or at end of treatment), stratified by smear status
			Impact	Proportion of pulmonary TB cases that complete treatment, stratified by smear status

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

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

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

v. Enrollment procedure

- (1) Persons presenting to the healthcare facility will be identified as TB suspects using routine criteria for that facility and a register will be maintained of all TB suspects (see below)
- (2) Study staff will present TB 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 TB evaluation. Patient consent or refusal to participate in the survey will be recorded in the roster.
- (3) After two months, study staff will review the roster and, according to sampling criteria established, attempt to contact TB suspects that were evaluated during the first month of the study. Subsequent roster reviews will occur every month.
- (4) Study staff will attempt to contact patients to perform the survey. The survey may be administered over the phone or in person, depending on the logistics at each site. If a patient cannot be contacted, patients will continue to be selected from the roster of TB suspects that consented 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.

vi. Consent: Patients will be asked for consent to participate in this survey. Consent will be verbal and brief, because no sensitive healthcare information is being collected and such surveys are part of routine healthcare practice in many settings. Contact information for TB suspects, such as address or telephone, may already be collected routinely for financial, administrative, or public health reasons. In that situation, then individual sites will make a determination of whether it is ethically appropriate to use that information for selecting TB suspects for the satisfaction survey.

vii. Study instruments: A study instrument will be developed based on site-specific needs. Minimum data elements to include are patient ratings of: speed of service, comprehensiveness of service; affordability of service; perception of attention to individual needs; overall satisfaction with service.

5.3.3. Study #3: Healthcare provider survey

A survey will be performed on healthcare providers to determine their satisfaction with the clinical practice guidelines.

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

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

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

iv. Enrollment procedure

- (1) A supervisor at the healthcare facility will prepare a roster of all healthcare providers meeting the inclusion criteria.
- (2) At the beginning of the study period, all healthcare providers will be provided with the questionnaire.
- (3) At the end of the study period, (at the end of six month) an identical questionnaire will be administered.

v. Consent: healthcare providers will be asked for consent to participate in this survey. Consent will be written. It will be brief, because no sensitive information is being collected.

vi. Study instruments: A study instrument will be developed. Minimum data elements will include: basic questions about TB 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 diagnostic process: availability, speed, quality; individual perception about current guidelines in the clinic for smear-negative TB diagnosis: feasibility, speed, quality, overall satisfaction and open-ended questions about satisfaction with process for diagnosis of TB in HIV-infected patients

5.3.4. Study #4: TB suspect outcome review

Case report forms will be completed for all TB suspects to measure program 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 used routinely will be needed for this component of the study.

i. Case definition: The definition of a TB suspect is found in the section under “Patient satisfaction survey” above.

ii. Inclusion criteria: All persons meeting the case definition who seek healthcare at a participating facility during the enrollment period.

iii. Exclusion Criteria: None.

iv. 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 (or existing practice) and 2006 guidelines will be calculated based on the epidemiologic situation and baseline program performance in participating sites.

v. Enrollment procedure:

- (1) Persons presenting to the healthcare facility will be identified as TB suspects using routine criteria for that facility and a register will be maintained of all TB suspects.
- (2) Patients will be informed broadly 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 TB suspects, using a separate study form or a modification of existing clinical records (see below).
- (4) For patients that do not complete the diagnostic evaluation, healthcare facilities will use existing contact information (e.g., telephone, address, treatment supporters) to contact patients two months after their initial contact with health services for TB diagnosis to determine if they are still alive or not and, if they died, when death occurred.

vi. Consent: TB programs routinely collect and review medical records of TB suspects to assess program performance, such as 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 program performance. Although the number of data components being reviewed is likely greater than what is routinely done, the process and intent is similar.

vii. Study instruments: Healthcare facilities routinely collect standard data about patients. The extent of such routine data collection varies depending on facility and provider practice. For this evaluation, healthcare 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 TB suspect identifying number, age, sex, district, date when first presented to clinic, cough, date when cough began, other symptoms, HIV diagnosis (status: positive / negative / unknown and date of HIV diagnosis), sputum smear (dates, results), sputum culture (date, result) chest radiograph (date, findings), antibiotics taken before visit and after initial visit (prescribed /self-procured/name and dosage), date of TB diagnosis, final diagnosis (if not diagnosed with TB) and date of last evaluation in clinic.

5.3.5. Study #5: TB patient outcome review

Case report forms will be completed for all TB patients to measure program outcome and impact 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 used routinely will be needed for this component of the study.

i. Case definition: A TB patient will be defined as any person diagnosed with TB and advised to begin on anti-TB medications. The definitions of smear-positive vs. smear-negative TB will be

according to the guidelines being implemented at the study site (e.g., 2003 / existing practice or 2006 guidelines).

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

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

iv. 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 (or existing practice) and 2006 guidelines will be calculated based on the epidemiologic situation and baseline program performance in participating sites.

v. Enrollment procedure

- (1) Patients will be registered and begun on TB treatment as is routine practice in the healthcare facility.
- (2) Patients will be informed broadly 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 TB register and patient records will be abstracted during the course of the study. No specific procedures will be used for enrollment or withdrawal from the study, since patients will be treated according to routine practice.

vi. Consent: see above section 4.34.

vii. Study instruments: Healthcare facilities routinely collect standard data about patients. The extent of such routine data collection varies depending on facility and provider practice. If necessary, healthcare 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 TB suspect identifying number, TB patient registration identifying number, TB registration date, HIV clinical stage, CD4 count, dates and dosage of co-trimoxazole prescribed, dates, dosage and

regimen of anti-retroviral therapy, TB treatment regimen, presence or absence of adverse events during TB treatment, sputum conversion result (if smear-positive at the beginning of treatment), treatment outcome and date of treatment outcome.

5.4. Study time line

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 desired.

5.5 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 that attend follow-up visits, if such incentives are part of routine care.

5.6. Data handling and analysis

Statistical methodology, data collection, planned tables and figures may vary depending on investigators conducting the evaluation. Public health programs related to TB and HIV are changing rapidly throughout the world. The study is designed as an observational study to evaluate the impact of implementing the revised recommendations, but other changes may occur in the health system at the same time, e.g. wider availability of ART, active case finding for HIV or TB that identifies patients at an earlier stage of either disease. Such events will need to be considered when interpreting findings from the studies.

5.7. Identifying, managing and reporting adverse events

Adverse events are common during treatment of HIV-associated TB, including drug reactions, hospitalization, and death. As part of routine public health practice, TB control programs 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, by definition of being registered for TB treatment, have access. Otherwise, patients will not be exposed to any physical or psychological risks beyond those normally encountered during routine clinical care.