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# **Guidelines for the Clinical Management of TB and HIV Co-infection in Ghana**



**August 2007**

# GUIDELINES FOR THE CLINICAL MANAGEMENT OF TB AND HIV CO-INFECTION IN GHANA

August 2007



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**World Health Organization**

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## Foreward

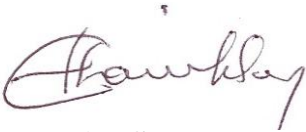
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There is a complex relationship between human immunodeficiency virus (HIV) and tuberculosis (TB), which fuels both epidemics in a synergistic way, resulting in a worsening of the morbidity and mortality attributable to each infection. TB is the most important opportunistic infection in HIV and the leading cause of mortality and morbidity among people living with HIV (PLWHIV) across sub-Saharan Africa, including Ghana. Meanwhile, HIV is fanning the TB epidemic in Ghana.

This situation is of great concern and has prompted a coordinated national response to reduce and control these infections. A significant part of this response is the close collaboration between the National HIV/AIDS Control Programme (NACP) and the National Tuberculosis Control Programme (NTP). The NACP and NTP worked together closely to develop this manual, in collaboration with their partners SHARP, QHP and WHO. This manual, Guidelines for the Clinical Management of TB and HIV Co-infection, is a quick reference tool to be used by all care providers in clinical settings to manage patients appropriately and to help fight the dual TB and HIV epidemics in Ghana.

While the provision of highly active antiretroviral therapy (HAART) now covers all regional hospitals and is scaling up into all district hospitals, the provision of directly observed therapy short course (DOTS) for TB treatment covers almost all districts in Ghana. Thus it is expected that this manual will be one of the tools health workers will benefit from by forging closer collaboration between the two programmes' increasing efficiency and in eliminating overlaps to reduce costs.

This manual is a pocket guide and a simple reference tool available to all care providers at all levels of health care provision for easy management of PLWHIV and TB patients reporting to the facility for care. It provides simple steps and algorithms for the health worker to provide standardized care, and to ensure that proper and adequate care is provided to the patient suffering either condition.



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## Acronyms and Abbreviations

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ABC	Abacavir
AFB	Acid fast bacillus
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral therapy/treatment
ARV	Antiretroviral
CAT	Computerized axial tomography (CT Scan)
CD4	Subgroup of T-lymphocytes carrying CD4 antigens
CMV	Cytomegalovirus
CNS	Central nervous system
CT	Counselling and testing
CTX	Co-trimoxazole
CXR	Chest x-ray
DNA	Deoxyribonucleic acid
DOT	Directly observed therapy/treatment
DOTS	Directly observed therapy short course
DT	Diagnostic testing for HIV
EFV	Efavirenz
EPTB	Extrapulmonary tuberculosis
FDC	Fixed dose combination
H	Isoniazid
HAART	Highly active antiretroviral therapy/treatment
HE	Isoniazid - ethambutol combination tablet
HIV	Human immunodeficiency virus
HR	Isoniazid - rifampicin combination tablet
HRE	Isoniazid - rifampicin - ethambutol combination tablet
HRZE	Isoniazid - rifampicin - pyrazinamide - ethambutol combination tablet
HT	Isoniazid - thiacetazone combination tablet
IM	Intramuscular
IMCI	Integrated management of childhood illnesses
IRS	Immune reconstitution syndrome

IV	Intravenous
LIP	Lymphocytic interstitial pneumonitis
LPV/RTV	Ritonavir boosted lopinavir – Lopinavir/r
NACP	National AIDS and STI Control Programme
NNRTIs	Non-nucleotide reverse transcriptase inhibitors
NRTIs	Nucleotide/nucleoside reverse transcriptase inhibitors
NSAID	Non-steroidal anti-inflammatory drug
NTP	National Tuberculosis Control Programme
OI	Opportunistic infection
PCP	Pneumocystis carinii pneumonia
PCR	Polymerase chain reaction
PIs	Protease inhibitors
PLWHIV	People living with HIV
PTB	Pulmonary tuberculosis
QHP	Quality Health Partners
R	Rifampicin
RCT	Routine offer of HIV counselling and testing
S	Streptomycin
SCC	Short-course chemotherapy for TB treatment
SHARP	Strengthening HIV/AIDS Response Partnerships
SHE	Streptomycin - isoniazid - ethambutol combination tablet
SHT	Streptomycin - isoniazid – thiacetazone combination tablet
SMX	Sulfamethoxazole
SSM	Sputum smear microscopy
TB	Tuberculosis
TBM	TB meningitis
TMP	Trimethoprim
TMP-SMX	Trimethoprim - sulfamethaxole (co-trimoxazole)
TST	Tuberculin skin test
WHO	World Health Organization

# 1. Introduction

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## 1.1 Interaction between HIV and TB and the Implications

There is a complex relationship between infection with human immunodeficiency virus (HIV) and tuberculosis (TB) infection that results in a synergistic increase in their prevalence, morbidity and mortality. The occurrence of both infections is a great public health problem looming as a potential pandemic, in Ghana, as is in other African countries. This should be of great concern and spur immediate action to reduce and control these infections. The interaction between HIV and TB is summarized in the following:

### **In HIV:**

- TB is a most important opportunistic disease;
- TB is infectious not only to HIV-infected persons but also to non-infected persons;
- TB causes severe illness and increases progression to AIDS; and
- TB kills – it is the number one killer in HIV.

### **In TB:**

- HIV is the main risk factor for progression from latent TB infection to active disease;
- HIV increases TB incidence;
- HIV leads to hot spots of TB transmission;
- HIV increases morbidity in TB patients because of HIV-related diseases;
- HIV increases adverse drug reactions to TB treatment;
- HIV increases TB case fatality rates; and
- HIV increases risk of recurrent TB.

## **1.2 The Situation in Ghana**

No systematic, nationwide study has been conducted on the prevalence of HIV and TB co-infection in Ghana. However, it is estimated that the influence of HIV on TB has been increasing such that in 1989 while about 14% of TB cases could be attributed to AIDS, by the year 2009 about 59% of the projected TB cases will be attributed to the HIV/AIDS epidemic. Hospital studies have shown that the prevalence of HIV in TB patients is approximately 25-30% and that as many as 50% of patients with chronic cough could be HIV positive. Autopsies done in Accra found that the proportion of TB deaths increased from 3.2% in 1987-88 at the beginning of the HIV epidemic to 5.1% in 1997-98. At the Korle-Bu Teaching Hospital, 30% of people living with HIV (PLWHIV) present with TB and TB accounts for 40-50% of HIV deaths, while HIV is an important cause of medical deaths.

## **1.3 Purpose**

In view of the rapidly changing face of the HIV epidemic and the emergence of an epidemic of TB/HIV co-infection, it is necessary to have an easy-to-use reference manual tailored to Ghanaian health care providers' needs, to assist them in managing cases presenting to their clinics with the co-infection. This manual is thus meant to be a quick reference guide to clinicians and care providers in the HIV/ART, TB and the general clinics to help manage patients reporting with either disease. Medical specialists, medical officers, clinical residents, medical students nurses and pharmacists will find this manual useful, specifically in the area of TB and HIV co-infection.

This document is not a comprehensive reference manual but rather one that attempts to comprise all the salient issues regarding the management of dually infected individuals. It

should be used in conjunction with the National TB Training Manual and its workbook, the National ART Treatment Guidelines and other TB/HIV reference materials.

## 2. Diagnosis of Pulmonary TB In HIV Co-infected Adults

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The diagnosis of TB in patients infected with HIV presents certain difficulties depending on the degree of immunosuppression at the time of diagnosis. TB can occur at any point in the course of progression of HIV. As the immunity declines in HIV, the clinical presentation of TB also changes because the body is not able to prevent the growth and spread of *Mycobacterium tuberculosis*. Therefore, disseminated and/or extrapulmonary TB occurs more commonly, although pulmonary tuberculosis (PTB) is still the most common form of TB disease in PLWHIV.

### 2.1 Diagnostic Approach

The approach to diagnosing PTB in HIV-infected adults is the same as that for PTB in HIV-negative persons. This consists of clinical screening by assessment of symptoms and signs, followed with sputum smear microscopy. The cornerstone of diagnosis of PTB in PLWHIV remains sputum smear microscopy. See the NTP Training Manual for details.

For adults known or suspected of HIV infection, follow the diagnostic algorithm in Figure 1 on page 10. However, the steps should be expedited. All PLWHIV should have a chest x-ray (CXR) done in addition to sputum microscopy in the first instance. Where available, a CD4 count is helpful in interpreting the evidence. If the CD4 cell count is high (>250), then expect the typical presentation and CXR changes; however, if not, then expect atypical presentations and x-ray changes.

## 2.2 Clinical Features

PLWHIV with relatively good CD4 cell counts (>250) have TB similar to HIV-negative persons while those with lower CD4 cell counts have atypical presentation. This latter makes it difficult to diagnose PLWHIV co-infected with TB.

In the immunosuppressed AIDS patient, the clinical features of TB tend to be non-specific, with a predominance of systemic symptoms (night fever and night sweats, weight loss, decreased energy, generalized lymph node swellings) and a higher incidence of extrapulmonary TB. Other atypical presentation of TB, such as diarrhoea, enlarged liver and spleen, are also seen more frequently in late stages of HIV infection. See Table 1.

**Table 1** Impact of HIV Infection on TB Presentation

<b>Symptom/Sign</b>	<b>HIV + (%)</b>	<b>HIV – (%)</b>
Dyspnoea	97	81
Fever	79	62
Sweats	83	64
Weight loss	89	83
Diarrhoea	23	4
Hepatomegaly	41	21
Splenomegaly	40	15
Lymphadenopathy	35	13



## **2.3 Sputum Smear Microscopy**

Sputum smear microscopy (SSM) is still the cornerstone of PTB diagnosis in PLWHIV. The use of SSM is detailed in the NTP Training Manual. The proportion of SSM positivity in TB/HIV patients depends on the degree of immunosuppression. SSM in early HIV infection, when immunosuppression is minimal and the CD4 count is relatively good, is more often positive (80%) as in HIV-negative patients. SSM is more often negative in late HIV infection. This makes it difficult to diagnose PTB in PLWHIV, especially in advanced stages.

## **2.4 CXR**

All PLWHIV should have a CXR as part of the initial work-up of the respiratory system. This is because many diseases affect this system and it is difficult to differentiate them on clinical grounds alone. The first screening for PTB is still SSM and no patient should be diagnosed as PTB without a SSM being done. Thus, if a patient is a TB suspect and the HIV status is not known, a CXR is not done on the first visit; rather SSM and HIV counselling and testing (CT) are done first. If the sputum is acid fast bacillus (AFB) positive (at least two SSM are positive) then a CXR is not needed to diagnose PTB. If however, the SSM is not positive (at least two sputum specimens are negative) then a CXR is necessary to help in diagnosing PTB. The other indications for CXR are:

- Suspected complication(s) of PTB e.g., pleural effusion, pneumothorax, pericardial effusion; and
- Severe or ongoing haemoptysis (coughing up blood).

## **2.5 Role of Sputum Culture for AFB in PLWHIV**

As discussed above, it is more difficult to diagnose PTB in PLWHIV because of the non-specific nature of the symptoms

and SSM is often negative, particularly in advanced HIV infection. Since TB is an important opportunistic infection (OI) and a major cause of death in PLWHIV, it is important that every effort is made to diagnose TB in HIV. TB culture is therefore being established in all regional hospitals to enable early diagnosis of TB in sputum smear negative cases in which TB is suspected.

If an initial SSM is negative in a person with HIV infection, a CXR should be examined, SSM repeated, and sputum sent for bacterial culture and AFB culture. Results for sputum culture for AFB would be available in four to six weeks or earlier, therefore clinical judgement is made in the interim as to whether the patient has TB and managed as appropriate. The teaching hospitals would be equipped to perform quicker TB cultures to shorten the time for making TB diagnosis, especially in drug resistant TB. The culture results confirm or refute the clinical diagnosis.

## 2.6 Summary of the Impact of HIV on PTB Presentation and Diagnosis

Table 2 summarizes the effect of HIV and its severity on the presentation and features of PTB.

**Table 2** Summary of the Impact of the Stage of HIV Infection on PTB Presentation

Features of PTB	Stage of HIV Infection	
	Early	Late
Clinical Picture	Often resembles post primary PTB	Often resembles primary PTB
Sputum Smear	Often positive	Often negative
CXR	Upper lobe infiltrations Cavities (often) Bilateral infiltrates Pulmonary fibrosis and shrinkage	Often middle-lower lobe interstitial infiltrates No cavities Intra-thoracic lymph nodes Pleural and pericardial involvement

## 2.7 Differential Diagnosis of PTB in HIV

There are many other diseases in HIV-positive persons that present in a similar way to that of PTB. It is often difficult to tell them apart as they may have the same symptoms, signs and CXR findings. Three other common pulmonary diseases are:

### 1. Acute bacteria pneumonia

This is quite common in HIV-positive patients. It usually has an acute onset with a shorter history of days (three to five days). The most common cause is *Streptococcus pneumoniae*, which is

sensitive to the penicillins (amoxicillin) and co-trimoxazole. It is important to note that acute bacteria pneumonia can occur superimposed on PTB, especially in the severely immunosuppressed.

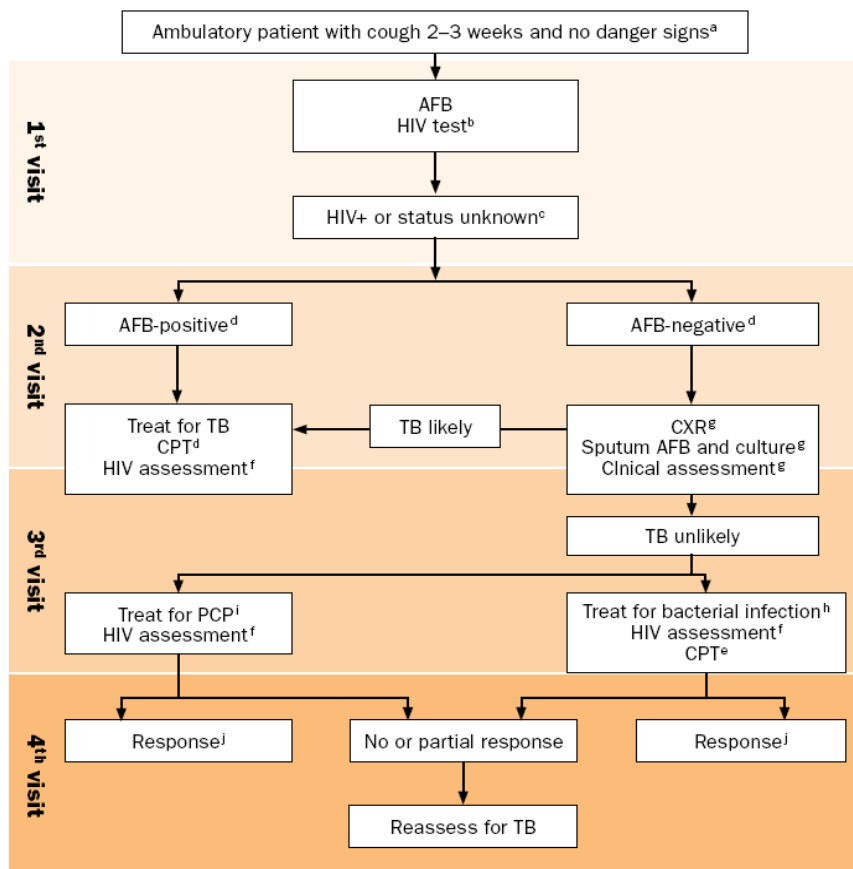
## **2. Kaposi sarcoma**

This is easily recognized when it presents with dark nodules on the skin and mucous membranes. It presents in the lungs as cough, fever, haemoptysis and shortness of breath, which are difficult to differentiate from PTB. The CXR may show a nodular or diffused infiltrate spreading out from the hilum of the lungs.

## **3. Pneumocystis jirovecii pneumonia (PCP)**

This is said to be rare in Africa but it may be more common than currently thought. The patient usually presents with a dry cough, severe dyspnoea and a high respiratory rate. The CXR may be normal despite the severe presentation of difficulty in breathing. The CXR may also show a bilateral diffuse interstitial shadowing. Any localizing features on CXR such as lobar consolidation or abscess indicate other diagnosis and not PCP.

**Figure 1** Algorithm for the Diagnosis of TB in Ambulatory HIV-positive Patients



Source: Improving the Diagnosis and Treatment of Smear-negative Pulmonary and Extrapulmonary Tuberculosis Among Adults and Adolescents.

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

<sup>b</sup> For countries with adult HIV prevalence rate  $\geq 1\%$  or prevalence rate of HIV among tuberculosis patients  $\geq 5\%$ .

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

<sup>d</sup> AFB-positive is defined as at least one positive and AFB-negative as two or more negative smears.

<sup>e</sup> CPT= Co-trimoxazole preventive therapy.

<sup>f</sup> HIV assessment includes HIV clinical staging, determination of CD<sub>4</sub> count if available and referral for HIV care.

<sup>g</sup> 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.

<sup>h</sup> Antibiotics (except fluoroquinolones) to cover both typical and atypical bacteria should be considered.

<sup>i</sup> PCP: *Pneumocystis carinii* pneumonia, also known as *Pneumocystis jirovecii* pneumonia.

<sup>j</sup> Advise to return for reassessment if symptoms recur.

### 3. Diagnosis of Pulmonary TB in HIV Co-infected Children

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It is difficult to diagnose PTB in children and even more so in HIV-infected ones because:

- several HIV-related diseases including TB present in the same way;
- weight loss is a common problem in HIV-positive children; and
- interpretation of the tuberculin skin test (TST) is even more unreliable than usual. An immunocompromised child may have a negative TST despite having TB.

#### 3.1 Clinical Features

The clinical features used to suspect PTB in children are not so useful. (See Table 3.)

**Table 3** Impact of HIV Infection on the Usefulness of Features Used to Diagnose PTB in Children

<b>Diagnostic feature</b>	<b>Impact of HIV</b>
Chronic symptoms	Less specific
Smear positive contact (if parent)	Less specific
Malnutrition or failure to thrive	Less specific
Positive tuberculin skin test	Less sensitive
Characteristic CXR abnormalities	Less specific
Satisfactory response to TB treatment	Less sensitive

#### 3.2 CXR

The CXR features are non-specific.

### 3.3 Differential Diagnosis of PTB in HIV-infected Children

The differential diagnosis of PTB in HIV-infected pneumonia are:

- Bacterial pneumonia;
- Lymphocytic interstitial pneumonitis (LIP);
- *Pneumocystis jirovecii* pneumonia (PCP);
- Viral pneumonia;
- Pulmonary lymphoma; and
- Fungal lung disease.

LIP is the most common HIV-related lung disease in children and can be confused with PTB or miliary TB. A child with LIP may also have:

- generalized, enlarged lymph nodes, which are painless and mobile;
- bilateral, non-tender parotid gland enlargement; and
- finger clubbing.

CXR findings include bilateral hilar lymph node enlargement and bilateral diffuse reticulonodular infiltration. Diagnosis can only be confirmed by lung biopsy.

If you are unsure of the diagnosis, treat the child with antibiotics for five to seven days and repeat the CXR after two weeks.



## 4. Diagnosis of Extrapulmonary TB in HIV Co-infected Adults and Children

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Extrapulmonary TB (EPTB) can occur at any age and is more common in HIV-infected adults and children. Table 4 below shows the distribution of TB by sites among both HIV-positive and negative patients. The most common sites of EPTB are shown in Table 5.

**Table 4** Distribution of TB and HIV Status

Site	HIV + (%)	HIV – (%)
Pulmonary	40	72
Extrapulmonary	34	16
Pulmonary + Extrapulmonary	26	12
Pleural	31	19
Pericardial	15	3
Lymph node	19	3

Many patients, particularly those HIV positive with EPTB, have PTB in addition.

**Table 5** Most Common Sites of EPTB in the HIV Infected

• Serosal effusions: pleural, pericardial > ascites;
• Lymphadenopathy – Peripheral nodes: cervical > axillary > inguinal; and central nodes: mediastinal > hilar, abdominal;
• Miliary TB;
• CNS: TB meningitis, tuberculoma;
• Disseminated TB (with mycobacteraemia); and
• Soft tissue abscesses.

**PRACTICAL POINT**

If a patient has features of extrapulmonary TB, look for pulmonary TB as well by sending sputum for smear microscopy for AFB.

#### **4.1 Diagnostic Approach**

The diagnosis of EPTB in the HIV positive is often very difficult and follows that in HIV negative as described in the NTP Training Manual. The diagnosis of EPTB is only made by the medical officer.

## 5. Diagnosis of HIV Infection in Adults with TB

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TB is a common OI in HIV and for many patients the first presentation of HIV may be that of TB.

### 5.1 Clinical Features

As discussed previously, the presentation of TB and HIV are similar and therefore difficult to differentiate. However, some clinical features are more common in HIV positive than negative patients and these are shown in Table 6.

**Table 6** The Clinical Clues of HIV Infection in TB Patients

Past history	<ul style="list-style-type: none"><li>• Sexually transmitted infection or partner with HIV</li><li>• Herpes zoster (shingles)</li><li>• Severe and/or recurrent bacteria infection (sinusitis, pyomyositis)</li><li>• Recent treated TB (relapse/recurrent TB)</li></ul>
Symptoms	<ul style="list-style-type: none"><li>• Weight loss (&gt;10 kg or &gt;20% of original weight)</li><li>• Diarrhoea (&gt;1 month)</li><li>• Retrosternal pain on swallowing</li><li>• Burning feeling in feet</li></ul>
Signs	<ul style="list-style-type: none"><li>• Scar of herpes zoster</li><li>• Pruritic (itchy) papular skin rash</li><li>• Kaposi sarcoma</li><li>• Generalized lymphadenopathy</li><li>• Oral candidiasis</li><li>• Angular cheilitis (sore at corner of lips)</li><li>• Oral hairy leukoplakia</li><li>• Severe infection of the gums (necrotizing gingivitis)</li></ul>

	<ul style="list-style-type: none"> <li>• Severe mouth ulcers</li> <li>• Persistent painful genital ulceration</li> </ul>
Blood count	<ul style="list-style-type: none"> <li>• Unexplained anaemia</li> <li>• Low white cell count (particularly low total lymphocyte count)</li> <li>• Low platelet count</li> </ul>

**PRACTICAL POINT**

Always look into the mouth of any TB patient and look for the many features that are highly suggestive of HIV infection.

## 5.2 HIV Counselling and Testing in Adult TB Patients

Practically, the clinical diagnosis of HIV infection is the HIV antibody test in persons older than two years. For those younger, particularly those less than 18 months, the definitive diagnosis is through the detection of the virus using the p24 antigen, PCR or viral culture. These latter tests are also used for diagnosis of HIV during the window period (before three to eight weeks of infection when antibody levels are not detectable). Because of the overlapping incidence of HIV and TB infection, the similar presentations and the synergistic effect of each disease on the other in the one patient, it is national policy that all TB patients should be routinely offered CT for HIV according to national guidelines at all health facilities. The benefits of HIV CT in TB patients are:

- patients may want the chance to know their status;
- better diagnosis and management of other HIV-related illnesses;
- avoidance of drugs, such as thiacetazone, with a high risk of side effects in HIV positives;

- change in behaviour leading to decreased HIV transmission;
- use of co-trimoxazole and other OI preventive measures to reduce morbidity and mortality from OIs;
- education of patients and relatives on HIV prevention
- improvement in medical care; and
- early entrance of HIV-positive patients into the continuum of prevention, care and support of HIV positive.

The offering of CT at health facilities initiated by the health personnel is called **routine offer of counselling and testing (RCT) with patient opt out**. Each patient has the right to refuse testing (patient opt out) and his/her refusal should not prejudice or affect the health care of that patient. However, every patient must be counselled before the test (pre-test counselling) so that his/her choice is informed. For good medical care, a clinician needs to know the HIV status of every patient. Therefore, if the patient does not want to know his/her status, respect this, but do seek his/her permission to do the test for your knowledge so as to provide the best medical care appropriate for the patient's condition. This method of HIV testing of the patient is called **diagnostic HIV testing (DT)**. A patient who has diagnostic HIV testing may later change his/her mind and be told his/her status after post-test counselling. All tested patients should have post-test counselling during which the results are discussed. The policy is to use two rapid HIV tests, which use different methodologies to detect the antibodies. See the National Guidelines for CT.

## 6. Diagnosis of HIV Infection in Children with TB

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HIV infection in children may show in many ways. The clinical signs are often non-specific and the diagnosis of HIV in young children is often very difficult.

### 6.1 Clinical Clues to HIV Infection in Children

Table 7 shows some clinical features which should make you suspect HIV infection in children with TB.

**Table 7** Clinical Signs Suggestive of HIV Infection in Children

<ul style="list-style-type: none"><li>• Weight loss or failure to thrive in a breastfed infant before six months of age</li><li>• Recurrent bacterial infections</li><li>• Prolonged fever (&gt;1 month)</li><li>• Oropharyngeal candidiasis</li><li>• Persistent cough</li><li>• Bilateral parotid gland enlargement</li><li>• Generalized rash</li><li>• Chronic diarrhoea</li><li>• Recurrent abscesses</li></ul>	<ul style="list-style-type: none"><li>• Extensive fungal skin infection</li><li>• Generalized lymph node enlargement</li><li>• Recurrent common infections, e.g., upper respiratory tract infections</li><li>• Enlarged spleen</li><li>• Enlarged liver</li><li>• Persistent severe anaemia</li><li>• Recurrent herpes simplex</li><li>• Kaposi sarcoma</li><li>• Acquired rectovaginal fistula</li><li>• Delay in development</li></ul>
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Although many of these features are strongly suggestive of HIV, confirmation is necessary by HIV testing.

## 6.2 HIV Testing in Children with TB

The diagnosis of HIV in children with TB is the same as that for children without TB. This is detailed elsewhere<sup>1</sup> and is summarized as follows:

A child is HIV infected if the following criteria are met:

1. The child is less than 18 months who is HIV positive<sup>2</sup>; or
  - is born to an HIV positive mother with positive viral culture or HIV DNA PCR; or
  - meets the clinical criteria for AIDS diagnosis based on the WHO staging system (see Guidelines for Antiretroviral Therapy in Ghana); and/or
  - has an absolute lymphocyte count of less than  $2500 \times 10^6$  cells/mm<sup>3</sup> or CD4 percentage less than 20%.
2. A child is 18 months or more with positive HIV antibody detection; or
  - meets any criteria outlined in (1) above.

Clinically, in children under 18 months old, the diagnosis of HIV infection is based mainly on clinical features in the baby and a positive HIV test in the mother. Circulating antibodies from the mother may still be present in the baby less than 18 months and hence the HIV test on the baby's blood is not reliable.

Pre- and post-test counselling of parents (preferably both together but at least the mother) should be done in children suspected of TB disease.

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<sup>1</sup> Guidelines for Antiretroviral Therapy in Ghana, GHS/MOH, 2005.

<sup>2</sup> A child less than 18 months who tests positive should be retested after 18 months. A child who tests negative after 18 months is a sero-reverter and therefore is not infected.

## **7. Standardized TB Case Definitions and Treatment Categories, and Staging for HIV**

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### **7.1 Standardized TB Case Definitions and Treatment Categories**

The TB case definitions and treatment categories for HIV-infected patients diagnosed with TB are the same as those for HIV-uninfected patients. The site of the disease in the body defines the type of tuberculosis. Eighty percent of tuberculosis occurs in the lung tissue and is called pulmonary TB (PTB) and the other 20% can occur anywhere in the body e.g., in the lymph nodes, intestines, bone and meninges. This is known as extrapulmonary TB (EPTB).

There are two types of PTB:

- 1. Sputum smear-positive pulmonary tuberculosis (Sm+ PTB).**

This is a patient with sputum in which mycobacterium have been found on microscopy.

- 2. Sputum smear-negative pulmonary tuberculosis (Sm-PTB).**

This is a patient with sputum smears negative for mycobacterium on microscopy, but x-ray evidence consistent with active tuberculosis, which does not clear with ordinary antibiotics. In some cases even though sputum smears are all negative for mycobacterium on microscopy, the culture is positive for mycobacterium tuberculosis.

#### **Extrapulmonary Tuberculosis (EPTB)**

This is TB occurring anywhere other than the actual lung tissue. It includes TB inside the chest but outside the lung tissue. This means that TB of the lymph nodes of the chest and TB of the



pleura are classified as EPTB. Examples of EPTB include pleural, glandular, intestinal, miliary, meningeal, bone, urogenital, skin and eye tuberculosis.

EPTB is relatively more common in HIV-positive patients than in HIV-negative patients. Diagnosis of EPTB is difficult and an experienced medical officer must confirm this as the correct diagnosis. EPTB is not infectious but many patients with EPTB may also have pulmonary TB. If so, they will be infectious.

**Always check the sputum of a patient with EPTB for tubercle bacilli!**

All TB patients have been categorized into three major groups for easy treatment. This categorization and their corresponding treatment regimen are detailed in Table 8 below.

**Table 8** Recommended Treatment Regimens for Each Treatment Category<sup>3</sup>

Patient Category	Definition	Initial Phase <sup>4</sup> Treatment	Continuation Phase Treatment
		Daily (28 doses/month)	Daily (28 doses/month)
<b>I</b>	<b>All New Cases</b> - New smear-positive PTB - New smear negative PTB - Concomitant HIV disease - EPTB	<b>2 (HRZE)<sup>5</sup></b> = 56 doses of HRZE	<b>4 (HR)</b> = 112 doses of HR
<b>II</b>	<b>Previously treated sputum smear-positive PTB</b> - Relapse - Treatment after interruption - Treatment failure.	<b>2 S(HRZE)</b> + <b>1 (HRZE)</b> = 84 doses of HRZE +56 doses of S	<b>5 (HRE)</b> =140 doses of HRE
<b>III<sup>6</sup></b>	<b>Children under 12 years</b>	<b>2 (HRZ)</b> = 56 doses of HRZ	<b>4 (HR)</b> = 112 doses of HR

## 7.2 Clinical Staging of HIV Infection

HIV-infected patients who are diagnosed with active TB are in WHO clinical stage 3 (if PTB) or stage 4 (if EPTB). Below are further details of WHO clinical staging.

<sup>3</sup> NTP Training Manual, Chapter 6, Prescribing Correct Treatment Regimens.

<sup>4</sup> Direct observation of treatment intake is required, and always in regimens including rifampicin.

<sup>5</sup> Streptomycin may be used instead of ethambutol. In meningitis, ethambutol should be replaced by streptomycin.

<sup>6</sup> In children with meningitis, add streptomycin in the initial phase.

# **WHO Clinical Staging of HIV/AIDS for Adults and Adolescents with Confirmed HIV Infection**

## **Primary HIV Infection**

Asymptomatic

Acute retroviral syndrome

## **Clinical stage 1**

- Asymptomatic
- Persistent generalized lymphadenopathy.

## **Clinical stage 2**

- Moderate unexplained weight loss (less than 10% of presumed or measured body weight)
- Recurrent respiratory tract infections (sinusitis, tonsillitis, bronchitis, otitis media, pharyngitis)
- Herpes zoster
- Angular cheilitis
- Recurrent oral ulceration
- Papular pruritic eruptions
- Seborrhoeic dermatitis
- Fungal nail infections.

## **Clinical stage 3**

- Unexplained<sup>7</sup> severe weight loss (more than 10% of presumed or measured body weight)
- Unexplained chronic diarrhoea for longer than one month
- Unexplained persistent fever (intermittent or constant for longer than one month)
- Persistent oral candida

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<sup>7</sup> Unexplained refers to where the condition is not explained by other disease conditions.

- Oral hairy leukoplakia
- Pulmonary tuberculosis
- Severe presumed bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia, excluding pneumonia)
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
- Unexplained anaemia ( $<8$  g/dl ), neutropenia ( $<500/\text{mm}^3$ ) and or chronic thrombocytopenia ( $<50\ 000/\text{mm}^3$ ).

#### **Clinical stage 4**

- HIV wasting syndrome
- Pneumocystis pneumonia
- Recurrent severe presumed 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 candida of trachea, bronchi or lungs)
- Extrapulmonary TB
- Kaposi 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, penicilliosis)

- Recurrent septicaemia (including non-typhoidal salmonella)
- Lymphoma (cerebral or B cell non-Hodgkin)
- Invasive cervical carcinoma
- Atypical disseminated leishmaniasis.

## **WHO Clinical Staging of HIV/AIDS for Infants and Children with Confirmed HIV Infection**

### **Primary HIV Infection**

Asymptomatic (intra-, peri-, or post-partum)

Acute retroviral syndrome.

### **Clinical Stage 1**

- Asymptomatic
- Persistent generalized lymphadenopathy.

### **Clinical Stage 2**

- Unexplained persistent hepatosplenomegaly
- Papular pruritic eruptions
- Extensive wart virus infection
- Extensive molluscum contagiosum
- Recurrent oral ulcerations
- Unexplained persistent parotid enlargement
- Lineal gingival erythema
- Herpes zoster
- Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis)
- Fungal nail infections.

### **Clinical Stage 3**

- Moderate unexplained malnutrition not adequately responding to standard therapy
- Unexplained persistent diarrhoea (14 days or more)
- Unexplained persistent fever (above 37.5 intermittent or constant, for longer than one month)
- Persistent oral candida (after first six to eight weeks of life)
- Oral hairy leukoplakia
- Acute necrotizing ulcerative gingivitis/periodontitis
- Lymph node TB
- Pulmonary TB
- Severe recurrent presumed bacterial pneumonia
- Symptomatic lymphoid interstitial pneumonitis
- Chronic HIV-associated lung disease including bronchiectasis
- Unexplained anaemia ( $<8\text{g/dl}$ ), neutropenia ( $<500/\text{mm}^3$ ) or chronic thrombocytopenia ( $<50\,000/\text{mm}^3$ )
- HIV-associated cardiomyopathy or HIV-associated nephropathy.

### **Clinical Stage 4**

- Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy
- Pneumocystis pneumonia
- Recurrent severe presumed bacterial infections (e.g., empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)
- Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration or visceral at any site)
- Extrapulmonary TB
- Kaposi sarcoma

- Oesophageal candidiasis (or candida of trachea, bronchi or lungs)
- Central nervous system toxoplasmosis (after one month of life)
- HIV encephalopathy
- Cytomegalovirus infection retinitis or CMV infection affecting another organ, with onset at age over one month
- Extrapulmonary cryptococcosis including meningitis
- Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis, penicilliosis)
- Chronic cryptosporidiosis
- Chronic isosporiasis
- Disseminated non-tuberculous mycobacteria infection
- Acquired-HIV associated rectal fistula
- HIV-associated tumours including cerebral or B cell non-Hodgkin lymphoma
- Progressive multifocal leukoencephalopathy.

## **8. Management of HIV-infected Patients with Active TB**

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The management of two diseases (HIV and TB) in a co-infected patient presents issues that need to be addressed. These issues, related to the treatment of TB in TB/HIV patients and the treatment of HIV in TB patients, are:

- response to TB treatment in patients with HIV;
- case fatality during TB treatment in patients with HIV;
- drug-drug interactions;
- immune reconstitution syndrome;
- overlapping ARV and TB drug side effects;
- adherence with multi-drug therapy for two infections; and
- coordinating care between TB and HIV care providers.

### **8.1 Response of HIV-positive TB Patients to Anti-TB Treatment**

Patients who complete short-course chemotherapy (SCC) show the same clinical, radiographic and microbiologic response whether they are HIV-positive or HIV-negative. However, on average, weight gain is less and the recurrence rate may be higher in HIV-positive than in HIV-negative patients. In view of the latter, give prolonged treatment (greater than two to three months) to poor responders and severe TB such as TB meningitis (TBM), TB of bone and pericardium.

When TB recurs after previous cure, there are two possibilities:

- a) true relapse (reactivation of persisters not killed by anti-TB drugs);
- b) re-infection (due to re-exposure to another source of infection).



TB recurrence in HIV-positive patients is treated using the same drug regimen (Category II) as for HIV-negative patients (see Table 8 and NTP Training Manual).

## 8.2 Case-fatality

HIV-positive TB patients have a much higher case-fatality during and after anti-TB treatment compared with HIV-negative patients. In sub-Saharan Africa, up to 30% of HIV-positive smear-positive TB patients die before the end of treatment.<sup>8</sup> Early deaths (less than 30 days of TB treatment) are often due to TB while later deaths are related to complications of HIV.

The prognosis is worse in HIV-positive smear-negative TB patients than smear-positive TB ones. The more severe the HIV infection (as indicated by the CD4 count) and/or the TB disease (as indicated by the pattern of TB disease or organ(s) affected), the worse the case fatality:

- Severity of HIV – below CD4 350, the lower the CD4 count the higher the case fatality
- Severity of TB – case fatality is PTB<EPTB<PTB+EPTB (disseminated TB).

Case-fatality is lower in TB/HIV patients treated with SCC than with the old, standard regimen (2SHT or SHE/10HT or HE). This is partly because SCC is a more effective anti-TB treatment. Also, the rifampicin in SCC has broad-spectrum antimicrobial activity and would reduce deaths due to HIV-related bacterial infections during SCC.

Self-administered treatment was associated with a higher mortality among HIV-positive TB patients compared with directly observed treatment (DOT).

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<sup>8</sup> Harries AD, Hargreaves NJ, Chimzizi R, Salaniponi FM. Highly active antiretroviral therapy and tuberculosis control in Africa: synergies and potential.

The case fatality in TB/HIV patients on TB treatment is four to ten times reduced by treatment with ARVs at the same time. ART also reduces the incidence of OIs, the recurrence of TB and the incidence of TB.

### **8.3 Drug-drug Interactions in Co-treatment of TB and HIV**

Treatment of both TB disease and HIV at the same time is complicated by drug-drug interactions between rifampicin and the antiretroviral drug groups: non-nucleoside reverse transcriptase (NNRTIs) and protease inhibitors and (PIs). Rifampicin stimulates the activity of the cytochrome P450 liver enzyme system, which metabolizes the PIs and NNRTIs. This can lead to decreased blood levels of PIs and NNRTIs. PIs and NNRTIs can also enhance or inhibit this same enzyme system, and lead to altered blood levels of rifampicin. These potential drug-drug interactions may result in ineffectiveness of ARV drugs, ineffective treatment of TB or an increased risk of drug toxicity.

Fortunately, the drug-drug interaction between rifampicin and efavirenz is minimal, particularly in Africans (rifampicin reduces the blood levels of efavirenz by about 15-25%). For patients who are 60 kg or less there is no need to adjust the dose of efavirenz. For those who are more than 60 kg, the dose of efavirenz is increased from 600 to 800 mg to compensate for any potential decrease in blood levels. Note that efavirenz use is limited to men and women outside of child-bearing age unless adequate contraception is ensured.

## 8.4 Immune Reconstitution Syndrome (IRS)

Occasionally, patients with HIV-related TB may experience a temporary exacerbation of symptoms, signs and/or radiographic manifestations of TB after beginning anti-HIV treatment. This paradoxical reaction in HIV-infected patients with TB is thought to be a result of immune reconstitution. This occurs as a result of the reactivation of the dormant immune system after the commencement of HAART especially within the first six weeks of treatment when TB is disseminated and CD4 cell counts are low. However immune reconstitution may occasionally occur after six weeks to a year.

Symptoms and signs may include high fever, lymphadenopathy, expanding central nervous system lesions and worsening of CXR findings. A thorough evaluation is necessary to exclude other causes, particularly TB treatment failure, development of other OIs or drug fever, before diagnosing a paradoxical reaction.

For the management of IRS:

- Inform patients about the possibility of an event after starting ARV;
- No need to stop or change TB or ARV treatment;
- Symptomatic treatment with non-steroidal anti-inflammatory drug (NSAID);
- Add steroids for severe symptoms to suppress the enhanced immune response for a short period of time; and
- Give “short and sharp” treatment of hydrocortisone or prednisolone 1 mg/kg body weight once a day for 14-21 days.

## 8.5 Overlapping ARV and TB Drug Side Effects

Anti-TB and ARV drugs have similar side effect profiles. For example, isoniazid can cause peripheral neuropathy and so do the nucleoside reverse transcriptase inhibitors (NRTIs): didanosine, zalcitabine and stavudine. When given together there is a potential of added toxicity. Skin rashes may occur during treatment with the anti-TB drugs, pyrazinamide, isoniazid and rifampicin and also with the ARVs nevirapine, abacavir and efavirenz. These overlapping side effects also make it difficult to differentiate the causative drug when they occur during treatment of TB and HIV concurrently.

### Managing adverse events during treatment of HIV-TB

- Do one thing at a time – make it easier to decide the cause of an event.
- Stop all medications for severe adverse events.
- Use sequential re-challenge to decide the cause of an event.
  - Restart with the drug that is least likely to have caused the adverse event at the lowest dose (usually a third of the normal dose).
  - Review the patient daily to see if the adverse event has occurred. If not then increase the dose daily until full dose is achieved.
  - Add the next drug least likely to have caused the adverse event and increase the dose in the absence of recurrence of the adverse event.
  - Repeat these steps until the drug producing the adverse event is found.
  - Generally restart with the anti-TB drugs first.
- Don't switch from the first-line TB drugs (especially H and R) without evidence of an association with a significant side effect. (See NTP Training Manual for more details.)

- Remember immune reconstitution events as a possible cause of adverse events during treatment.

## **8.6 Adherence with Multi-drug Therapy for Two Infections**

Treatment of both HIV and TB involves the use of multiple drugs in many tablets. In the past a patient may take as many as 12 anti-TB drugs and if ARVS are added the total may be as many as 18 tablets depending on the regimen. In addition, patients usually are on nutritional supplements, and OI prophylactic drugs. These put a high strain on patients' drug adherence, which is complicated by considerations of timing of drug ingestion and relation to meals. To offset these, both anti-TB and ARVs are now being made in fixed-dose combinations (FDCs) to reduce the number of tablets taken a day. See the NTP Training Manual and ART Treatment Guidelines for the FDCs used in Ghana. It is important that TB/HIV co-infected patients are given the necessary support and encouragement to adhere to treatment. Obviously, unless absolutely necessary, adherence considerations would indicate that as much as possible the two drug treatments should be staggered; the TB treatment is given first. See section 8.8 below for detailed discussion.

## **8.7 Coordinating Care between TB and HIV Care Providers**

The management of the patient co-infected with TB and HIV should be patient-centred recognizing that there are “two diseases, one patient and one health care system”. As much as possible, care of TB and HIV patients should be seamlessly integrated to ensure this. If, however, there are separate TB and HIV care programmes at a facility, close collaboration with well-established referral and close linkage systems should be in place to ensure the best care of TB/HIV co-infected patients.

See the Technical and Policy Guidelines for TB/HIV Collaboration in Ghana.

## **8.8 Treating TB and HIV in TB/HIV Co-infected Patients**

The issues of treating both TB and HIV discussed above form the basis of treatment of the two diseases. Practically, the considerations are:

- which disease to treat first;
- the drug regimens; and
- the timing of concurrent drug treatment.

### **Which Treatment First?**

In patients with HIV-related TB, the priority is to treat TB, especially smear-positive TB (to stop continued TB transmission). This is in line with the principle of treating all OIs before starting ART. Please see the Guidelines for Antiretroviral Therapy in Ghana.

### **Which Drug Regimen?**

The drug regimens used to treat TB in an HIV-infected patient are the same as those for the HIV-negative patient. In the new NTP policy, thiacetazone should not be used for the treatment of TB in Ghana. Where its use is still being phased out, it should be noted that this drug is contraindicated in HIV-infected patients due to the risk of severe toxicity. Streptomycin is also no longer included in the treatment of new TB patients because of the risk of exposure to HIV from needle-stick injury. The NTP routinely use anti-TB drugs in FDC tablets. Please refer to the NTP Training Manual for information on modes of action of anti-TB drugs and recommended TB treatment regimens for new and retreatment cases.

### **PRACTICAL POINT**

Anti-TB drug treatment is the same for HIV-positive and HIV-negative TB patients, with one exception: do not give thiacetazone to HIV-positive TB patients (increased risk of severe and sometimes fatal skin reactions).

The preferred drug regimen for ART consists of efavirenz plus zidovudine and lamivudine. See ART Treatment Guidelines for details.

### **Timing of Concurrent Drug Treatment**

The timing of the addition of ART to anti-TB treatment is determined by the severity of the HIV disease (indicated by the clinical staging and CD4 cell count) and the likelihood of HIV disease progressing to death. Careful evaluation is necessary in judging when to start ART. Table 9 shows the different scenarios of the timing and regimens of concurrent treatment. Similarly, if the patient is already on ART, adjustments to the regimen must be made as described below.

#### ***Patient not on ART***

If a patient is diagnosed with smear-positive TB as the first manifestation of HIV infection, and does not appear to be at high risk of dying with a CD4 count greater than 350, withhold ART until after TB treatment. If however, the CD4 is between 250 and 350, it may be safer to defer ART until the initial phase (two months) of TB treatment has been completed.

In some situations, it will be necessary to start TB treatment and ART at the same time. For example, if a patient has a high risk of death during the period of TB treatment (i.e., disseminated TB and/or CD4 count  $<250/\text{mm}^3$ ), it may be necessary to start ART concomitantly with TB treatment.

**Table 9** Recommended Timing and Regimens for Co-treatment of HIV-related TB

<i>CD4 Cell Count</i>	<i>ART Regimen</i>	<i>TB Regimen</i>	<i>Comments</i>
CD4<50 mm <sup>3</sup>	<ul style="list-style-type: none"> <li>Start immediately.</li> </ul> <p><b>Options:</b> Zidovudine+ Lamivudine+ Efavirenz*</p> <p><i>Or</i></p> <p>Stavudine + Lamivudine+ Efavirenz*</p>	<ul style="list-style-type: none"> <li>Start immediately.</li> </ul> <p>Regimens as per NTP guidelines based on TB diagnostic category.</p>	<p>Start both therapies in cases of severe forms of TB irrespective of CD4 count (e.g., TB meningitis) based on clinician's judgment.</p> <p>Efavirenz is contraindicated in: - Pregnancy** - CNS presentations.</p> <p>Do not use efavirenz in women of childbearing age unless effective contraception is assured.</p>



<p>CD4 &lt;250mm<sup>3</sup></p>	<ul style="list-style-type: none"> <li>• Start as soon as TB therapy tolerated (after two to four weeks)</li> </ul> <p><b>Options:</b> Zidovudine+ Lamivudine+ Efavirenz (EFV)*</p> <p><i>Or</i></p> <p>Stavudine + Lamivudine+ Efavirenz*</p> <p>Second line: Alternatives to the efavirenz portion of the regimen include: LPV/RTV<sup>∞</sup> (400/100 mg bid) and ABC<sup>Δ</sup>.</p>	<ul style="list-style-type: none"> <li>• Start immediately.</li> </ul> <p>Regimens as per NTP guidelines based on TB diagnostic category.</p>	<p>Efavirenz is contraindicated in:</p> <ul style="list-style-type: none"> <li>- Pregnancy**</li> <li>- CNS presentations.</li> </ul> <p>Do not use efavirenz in women of childbearing age unless effective contraception is assured.</p>
<p>CD4 250 - 350mm<sup>3</sup></p>	<ul style="list-style-type: none"> <li>• Start after the initial phase of TB treatment completed.</li> </ul> <p><b>Options:</b> Zidovudine+ Lamivudine+ Efavirenz*</p> <p><i>Or</i></p> <p>Stavudine + Lamivudine+ Efavirenz*</p> <p>Second line: Alternatives to the EFV portion of the regimen include: LPV/RTV<sup>∞</sup> (400/100 mg bid) and ABC<sup>Δ</sup>.</p>	<ul style="list-style-type: none"> <li>• Start immediately.</li> </ul> <p>Regimens as per NTP guidelines based on TB diagnostic category.</p>	<p>Efavirenz is contraindicated in:</p> <ul style="list-style-type: none"> <li>- Pregnancy**</li> <li>- CNS presentations.</li> </ul> <p>Do not use efavirenz in women of childbearing age unless effective contraception is assured.</p>

CD4>350 mm <sup>3</sup>	<ul style="list-style-type: none"> <li>• Re-evaluate with repeat CD4 count after TB treatment.</li> </ul>	<ul style="list-style-type: none"> <li>• Start immediately.</li> </ul>	
CD4 not available	<ul style="list-style-type: none"> <li>• If patient has pulmonary TB (i.e. HIV Stage III), start after the initial phase of TB treatment is completed.</li> <li>• If patient has extrapulmonary TB (i.e. HIV Stage IV), start as soon as TB therapy tolerated (after two to four weeks).</li> </ul>	<ul style="list-style-type: none"> <li>• Start immediately.</li> </ul>	Timing of ART initiation should be based on clinical judgement in relation to signs of immuno-deficiency and clinical staging.

\* The usual dose of efavirenz should be increased from 600 mg to 800 mg in those who weigh more than 60 kg to correct for the potential decrease in blood levels of efavirenz in the presence of rifampicin.

\*\* In the case of an HIV-infected pregnant woman diagnosed with TB in whom ART is indicated, a regimen containing efavirenz may be initiated **after** the first trimester. Efavirenz can be continued after delivery if effective contraception can be assured.

△ABC = Abacavir. The combination ABC+ lamivudine+ zidovudine is NOT RECOMMENDED due to known virologic failure. However, for the duration of TB treatment (six months) this regimen may be used in pregnant women and children under three years. The regimen is then changed back to standard first-line treatment after completion of the TB treatment.

∞ LPV/RTV is a ritonavir-boosted lopinavir which requires secure cold chain. It can however be stored at a maximum temperature of 35°C for one month. Therefore patients who do not have refrigeration should not be given more than one month's supply.

### ***Patient already on ART***

With the restoration of the immune system from ART, HIV-infected patients are less likely to develop TB while on ART. When TB occurs in patients already on ART, it may signal treatment failure of the ART regimen and/or drug resistance or, potentially, a missed TB diagnosis on initial screening.

1. If TB is diagnosed within six months of initiation of ART, it should not be taken as ART treatment failure. The ART regimen should be adjusted for simultaneous administration with the rifampicin anti-TB treatment as indicated in Table 10.
  
2. If TB is diagnosed more than six months after initiation of ART then the following evaluation should be performed to exclude ART failure:
  - CD4 cell count;
  - Assess ART adherence
    - If adherence is found to be adequate, send specimen for viral load and/or HIV resistance testing;
  - Assess patient for clinical and other immunological evidence of disease progression (see Guidelines for Antiretroviral Treatment); and
  - In the absence of CD4 count if the TB is:
    - pulmonary, then it is not ART failure
    - EPTB, then it is ART failure.

Refer the patient to a TB/HIV specialist for management on an individual basis.

**Table 10** ART Recommendations for Patients Diagnosed with TB within Six Months of Initiating ART and Being Treated with Short-course Anti-TB Chemotherapy Containing Rifampicin in Ghana

	<b>ART Regimen at time of TB diagnosis</b>	<b>Treatment Options</b>
First-line ART	Zidovudine+ Lamivudine+ Efavirenz  <i>Or</i> Stavudine+ Lamivudine+ Efavirenz	<ul style="list-style-type: none"> <li>• No change in regimen</li> </ul>
	Zidovudine+ Lamivudine+ Nevirapine  <i>Or</i> Stavudine+ Lamivudine+ Nevirapine	<ul style="list-style-type: none"> <li>• Substitute nevirapine with efavirenz or</li> <li>• Continue with nevirapine<sup>Δ</sup></li> </ul>
Second-line ART*	Didanosine + Abacavir + Lopinavir/r	<ul style="list-style-type: none"> <li>• No change in regimen but adjust dose of ritonavir<sup>Δ∞</sup></li> </ul>
	Didanosine + Abacavir + Nelfinavir	<ul style="list-style-type: none"> <li>• Substitute LPV/RTV for nelfinavir and adjust dose of ritonavir<sup>Δ∞</sup></li> </ul>

<sup>Δ</sup> Carefully monitor clinical and laboratory features for hepatotoxicity (high ALT) when nevirapine or PI is given with rifampicin.

\* Substitutions involving second-line drugs should be done by an HIV/TB specialist.

<sup>∞</sup> The dose of ritonavir is increased to 400 mg.

## **8.9 Monitoring of HIV-infected TB Patients with Sputum Smear-positive TB**

The monitoring protocols for HIV-infected patients receiving TB treatment are the same as for HIV-uninfected patients. Please see the NTP Training Manual for further details on monitoring response to TB treatment.

## **8.10 The Role of Adjuvant Steroid Treatment in TB/HIV Patients**

Although steroids may further depress the immunity and increase the risk of OIs in HIV-positive patients, on balance TB/HIV patients are still likely to benefit from the use of steroids for the same indications as applied to HIV-uninfected TB patients. These include:

- TB meningitis (decreased consciousness, neurological defects, or spinal block);
- TB pericarditis (with effusion or constriction);
- TB pleural effusion (when large with severe symptoms);
- Hypoadrenalism (TB of adrenal glands);
- TB laryngitis (with life-threatening airway obstruction);
- Severe hypersensitivity reactions to anti-TB drugs;
- Renal tract TB (to prevent ureteric scarring); and
- Massive lymph node enlargement with pressure effects.

Dosages of adjuvant steroids are the same as those recommended for HIV-uninfected adults and paediatric TB patients. Please see the NTP Training Manual for details.

## **9. Side Effects of Anti-TB Drugs In HIV-positive TB Patients**

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Adverse drug reactions are more common in HIV-positive than in HIV-negative TB patients. Risk of drug reaction increases with increased immunosuppression. Most reactions occur in the first two months of treatment.

### **9.1 Rash**

This is the most common reaction. Fever often precedes and accompanies the rash. Mucous membrane involvement is common. The usual drug responsible is thiacetazone, although streptomycin and rifampicin are sometimes to blame. Severe skin reactions, which may be fatal, include exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis. For this reason, thiacetazone is no longer used in the new treatment regimen in Ghana.

### **9.2 Other Reactions**

The most common reactions necessitating change in treatment include gastrointestinal disturbance and hepatitis. There may be an increased risk of rifampicin-associated anaphylactic shock and thrombocytopenia. For a symptom-based approach to management of drug side-effects, see the NTP Training Manual.

## 10. Treatment and Prevention of Other HIV-related Diseases in TB/HIV Patients

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In general, OIs in HIV-infected patients with TB are managed as in HIV-infected patients without TB. Please see the National Guidelines on Management of Opportunistic Infections for details. Below are a few special circumstances related to TB/HIV patients.

### 10.1 Respiratory Problems in Adults

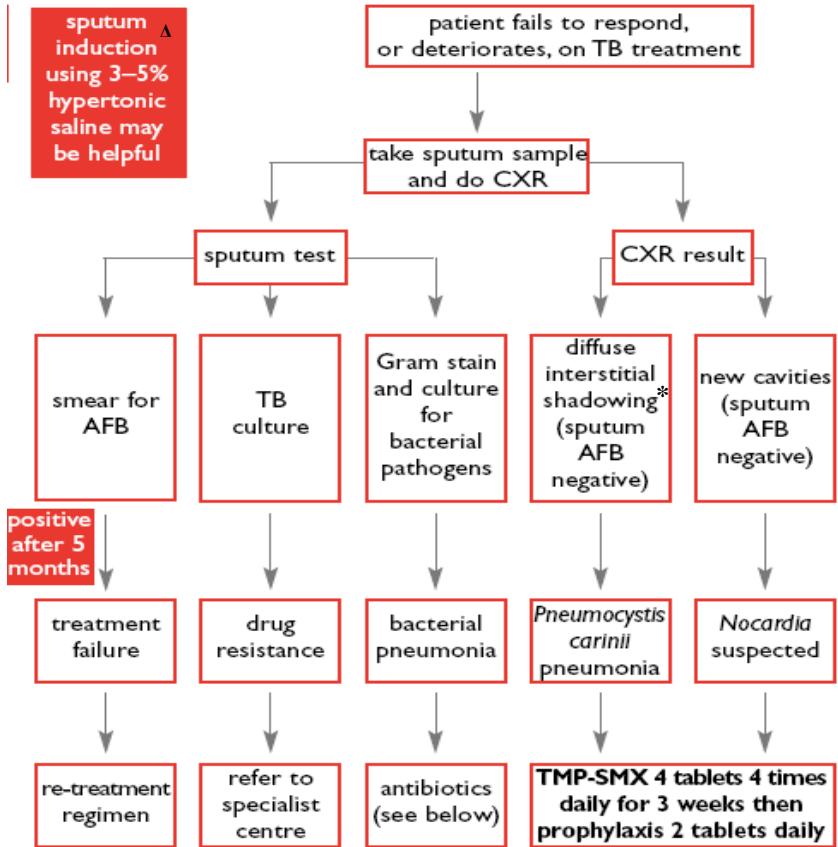
Some TB/HIV patients fail to improve, or may even deteriorate, during anti-TB treatment. They continue to have or develop new respiratory problems, e.g., cough, breathlessness, chest pain. First, adherence to their TB therapy should be assessed. If adherence appears adequate, consider the following possibilities.

**Table 11** Diagnoses and Other Possibilities

<b>Original Diagnosis</b>	<b>Possibilities</b>
Sputum smear-negative TB	Incorrect diagnosis e.g., other pathogens, heart failure, chronic obstructive airways disease
Sputum smear-positive TB	Patient not adherent to anti-TB treatment; drug-resistant TB; superimposed infection with other pathogens

The flow chart below shows the management approach in HIV-positive TB patients who fail to respond or deteriorate while on anti-TB treatment.

**Figure 2** The Management Approach in HIV-positive TB Patients Who Fail to Respond or Deteriorate While on Anti-TB Treatment



Source: TB/HIV: A Clinical Manual, 2<sup>nd</sup> edition.

\* Diffuse interstitial shadowing could be kaposi sarcoma or fungal pneumonia e.g. Cryptococcus.

<sup>Δ</sup> Sputum induction must be done in a place away from other patients.



The table below shows the main bacterial pathogens responsible for superimposed pneumonia in smear-positive TB patients and their treatment.

**Table 12** Pathogens and Treatments

<b>Pathogen</b>	<b>Treatment</b>
<i>Streptococcus pneumoniae</i>	penicillin or TMP-SMX
<i>Haemophilus influenzae</i>	amoxycillin or TMP-SMX
<i>Staphylococcus aureus</i>	flucloxacillin or chloramphenicol
Gram-negative bacilli	chloramphenicol (and gentamicin if necessary)

## 10.2 Respiratory Problems in Children

HIV-infected children with TB are also more susceptible to other respiratory diseases and more likely to die despite TB treatment. An important reason for a poor response to TB treatment is that the child does not have PTB. The difficulties in diagnosing PTB in children mean that it may be confused with other causes of HIV-related lung disease. Most children who receive treatment for PTB are smear-negative cases. If they do not improve on TB treatment, consider other diagnoses, e.g., LIP or cardiac disease. In all cases, consider poor treatment adherence as a cause of poor treatment response. Mixed respiratory infections are a particular feature of HIV-infected children. It is common for children with TB to develop bacterial pneumonia as a complication. The main bacterial pathogens are those listed above. Treatment should follow Ghana's Integrated Management of Childhood Illnesses (IMCI) guidelines.

If the child has severe pneumonia, admit to hospital and give crystalline penicillin and chloramphenicol 25 mg/kg each intramuscularly or intravenously four times a day (and oxygen if necessary). If the child does not improve within 48 hours, switch to gentamicin 5 mg/kg IM once a day and cloxacillin 50 mg/kg IM or IV every six hours. Cephalosporins may be used if available. HIV-infected children with presumed TB may have LIP either as an alternative diagnosis or occasionally as a mixed infection. LIP is also often complicated by acute bacterial pneumonia. Clinical features that suggest LIP are:

- generalized symmetrical lymphadenopathy;
- non-tender parotid enlargement; and
- finger clubbing.

Typical CXR features are a bilateral reticulonodular interstitial pattern and adenopathy. If the child with LIP has persistent respiratory distress, give prednisolone 1–2 mg/kg daily for two to four weeks and then reduce gradually over two weeks.

## 11. Co-Trimoxazole Prophylaxis for TB/HIV Patients

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### 11.1 Primary Chemoprophylaxis in Children

Co-trimoxazole (CTX) should be offered to all HIV-exposed infants from six weeks of age, using the following criteria:

- Any child born to an HIV-infected woman irrespective of whether the woman received ART in pregnancy;
- Any child who is identified as HIV-infected within the first year of life by PCR (polymerase chain reaction), HIV serology or by a clinical diagnosis of HIV infection (according to National Guidelines on Management of Opportunistic Infections); and
- Children older than 15 months who have had a pneumocystis carinii event, have symptomatic HIV infection, an AIDS-defining illness or a CD4+ lymphocyte percentage less than 15%.

The dose should be 150 mg TMP and 750 mg SMX per m<sup>2</sup> body surface area, three times per week. If co-trimoxazole syrup is not available, for an infant of six weeks, give half a co-trimoxazole tablet (TMP 80 mg/SMX 400 mg) daily on Monday, Wednesday and Friday.

## 11.2 Secondary Chemoprophylaxis in Adults

Several severe or life-threatening OIs in HIV-positive patients have high recurrence rates after initial successful treatment. Life-long secondary prophylaxis is generally recommended for all PLWHIV. When put on HAART the CD4 cell count of PLWHIV tends to increase until it reaches normal levels. It is thus recommended that for patients on HAART, secondary prophylaxis with co-trimoxazole (TMP-SMX) should be continued till their CD4 cell count is greater than 500 cells/uL and sustained for six months. Co-trimoxazole prophylaxis can be stopped after that period. Table 13 below shows recommended drug regimens for secondary chemoprophylaxis in adults.

**Table 13** Pathogens and Drug Regimens

<b>Pathogen</b>	<b>Drug Regimen (first choice)</b>
<i>Pneumocystis carinii</i>	trimethoprim 80 mg/sulfamethoxazole 400 mg (TMP-SMX) 2 tablets daily
<i>Toxoplasma gondii</i>	sulfadiazine 500 mg 4 times daily + pyrimethamine 25 mg daily  <i>Or</i>  trimethoprim 80 mg/sulfamethoxazole 400 mg (TMP-SMX) 2 tablets daily
<i>Mycobacterium avium complex</i>	clarithromycin 500 mg twice daily + ethambutol 15mg/kg once daily  <i>Or</i>  azithromycin 500 mg once daily + ethambutol 15 mg/kg once daily
<i>Cryptococcus neoformans</i>	fluconazole 200 mg once daily

<i>Histoplasma capsulatum</i>	itraconazole 200 mg twice daily
Cytomegalovirus	Ganciclovir
Salmonella species (not <i>S. typhi</i> ) bacteraemia	ciprofloxacin 500 mg twice daily for 6–8 months

## 12. References

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