

Diagnosis and Management of HIV-related Tuberculosis

More than 11 million adults living with HIV/AIDS are also infected with tuberculosis. In some sub-Saharan countries, one-third of patients with tuberculosis have HIV. In others, TB affects more than half of those infected with HIV. The overlapping tuberculosis and HIV epidemics have had a devastating impact on TB morbidity, mortality, and control, and tuberculosis has become the leading killer of HIV-positive people.

As these numbers illustrate, expert management of tuberculosis is a critical component of the care and treatment of HIV/AIDS. ICAP strongly supports the use of tuberculin skin testing and treatment of latent TB infection (see Chapter 5.2). This chapter will focus on special issues in the diagnosis and management of HIV-TB.

Diagnosis of HIV-TB:

The same immunodeficiency that makes HIV-infected individuals vulnerable to tuberculosis can lead to diagnostic challenges and to delays in identifying TB in co-infected patients. Although patients with early HIV tend to have the “classic” clinical and radiographic manifestations of TB seen in HIV-negative populations, tuberculosis in patients with advanced AIDS may present quite differently.

A delay in the diagnosis of TB in patients with HIV can have a profound impact on outcome. One illustrative study in South Africa showed that patients with HIV who were found to have active TB disease on routine screening did much better than those who sought care for TB-associated symptoms; the second group was nearly six times more likely to die during TB treatment. By decreasing transmission and improving contact tracing, early diagnosis and treatment of TB benefits the community as well as the individual.

Given the challenges of identifying TB in HIV-infected populations, and the urgency of making a prompt and accurate diagnosis, clinicians caring for patients with HIV are urged to maintain a high index of suspicion of TB, to be familiar with the presentation of TB in immunocompromised patients, and to evaluate suspected cases quickly and systematically.

The majority of clinicians at HIV treatment sites are intimately familiar with tuberculosis, skilled in its diagnosis, and knowledgeable about local protocols and resources. To complement this expertise, we emphasize the following points about the diagnosis of HIV-TB:

- **Extrapulmonary TB is more common in patients with HIV-TB:**

With progressive immunodeficiency, extrapulmonary manifestations of TB become increasingly common. Patients with HIV-TB have more symptoms and signs of systemic infection – higher rates of fever, sweats, hepatosplenomegaly, and diarrhea, for example – suggesting that HIV-related immunosuppression prevents containment of TB to a single organ system. The majority of TB-infected patients with CD4 cell counts under 100 cells/mm³ have extrapulmonary TB; most have coexisting pulmonary TB.

Common sites of extrapulmonary TB in patients with HIV include peripheral lymph nodes (cervical > axillary > inguinal) and central lymph nodes (mediastinal > hilar > intra-abdominal). Disseminated disease may include serosal TB (pleural, pericardial, peritoneal), central nervous system manifestations such as meningitis and tuberculoma, soft tissue abscesses, and bone disease.

Of note, TB is the most common cause of adenopathy in HIV-infected patients in sub-Saharan Africa, and fine-needle aspiration (FNA) is an excellent test in this setting. FNA is a rapid and sensitive test for TB adenitis; adverse events are rare and results are often available the same day.

- **Smear-negative pulmonary TB is more common in patients with HIV-TB:**

People with HIV are much more likely than HIV-negative patients to have smear-negative pulmonary tuberculosis. In one study, 43 percent of HIV-infected patients had smear-negative TB compared with 24 percent of HIV-negative patients. The prevalence of smear-negative TB will be a diagnostic challenge for programs that are dependent on the results of sputum smears, and familiarity with the clinical and radiographic appearance of HIV-TB will be critically important at such sites.

- **Radiographic patterns are different in patients with HIV-TB:**

The degree of immunodeficiency in patients with HIV also affects the chest x-ray manifestations of TB (Table 1). “Typical” chest x-ray findings – upper lobe predominance, fibronodular infiltrates, and cavitory lesions – are often seen in HIV-infected patients with relatively high CD4 counts. In contrast, patients with advanced disease are much less likely to have “typical” findings and are more likely to have involvement of the lower and middle lung zones, intrathoracic adenopathy, miliary and/or reticulonodular patterns, and pleural or pericardial involvement. In other words, the chest x-ray of a TB patient with advanced AIDS may look nothing like classic TB. It is critically important for providers to understand this relationship, so that patients with HIV-TB can be recognized and treated.

Table 1: Chest x-ray findings in HIV-TB

Early HIV disease	Advanced HIV disease
<ul style="list-style-type: none"> • Upper lobe predominance • Cavities • Pleural disease 	<ul style="list-style-type: none"> • Lack of cavitation • Intrathoracic adenopathy • Lower + middle lobe infiltrates • Miliary and reticulonodular infiltrates • Pleural + pericardial involvement

- **The diagnosis of TB in HIV-infected children is particularly challenging**

While the diagnosis of pediatric tuberculosis is particularly difficult, it can be even more challenging to diagnose active TB disease in HIV-infected infants and children. Symptoms are often nonspecific, sputum samples are difficult to obtain, smear-negative pulmonary TB is not uncommon, and radiologic manifestations are protean. Exposure to an individual with active TB disease is often an important clue in the evaluation of a sick child or one who is failing to thrive, and evaluation of all close contacts and household members should be a routine step in the treatment of adults with TB. Programs should follow local/national guidelines for the diagnosis of pediatric TB disease, i.e. use of tuberculin skin testing in conjunction with signs and symptoms. It should be noted that TST can be nonreactive in children with HIV/TB so the diagnosis is often made based upon clinical signs and symptoms. As in adults, FNA can be a useful diagnostic tool.

- **TB is often a household illness**

Whether the 'index case' is an adult or a child, there are may be additional individuals in the household with latent TB infection and/or active TB disease. As always, careful evaluation of all close contacts and household members should be a routine step – keeping in mind that other family members may also be HIV-infected.

Management of HIV-TB:

TB treatment is defined by national TB programmes, and ICAP strongly supports coordination of care with TB clinics. The gravity of HIV/TB, however, requires that clinicians at both HIV and TB treatment sites develop expertise in the treatment of co-infected patients.

HIV-associated tuberculosis is more lethal than the TB seen in HIV-negative individuals. In one representative study, 14 percent of patients with HIV-TB died within 6 months of TB diagnosis, in contrast to 0.5 percent of patients with TB alone. In order to ensure the best outcomes for co-infected patients, clinicians should prioritize the appropriate treatment of tuberculosis, the highest level of adherence with TB therapy (ideally via DOTS), and the use of antiretroviral treatment (ART) in eligible patients.


- **Timing of TB treatment and ART initiation**

In adults, pulmonary tuberculosis defines WHO stage 3 disease and extrapulmonary tuberculosis defines WHO stage 4 disease (see Chapter 5.1). International guidelines recommend antiretroviral treatment for adult stage 3 patients who have symptoms referable to HIV/AIDS and CD4 counts of 350 or less; ART is strongly recommended for all adult stage 4 patients irrespective of CD4 count. Treatment of these patients with ART is uncontroversial. A separate question is *when* to commence ART in patients with tuberculosis – during TB treatment, or after TB treatment is completed?

For adult patients with advanced HIV disease, the use of highly active ART appears to markedly reduce the risk of death during and shortly after TB therapy. Conversely, patients with higher CD4 counts have a relatively low risk of death from TB, and have less to gain from concurrent ART. The present consensus is that adult HIV-infected patients with extrapulmonary disease, and/or CD4 counts of 200 or less will benefit the most from ART during TB treatment. Definitive data on the best time to start ARV in patients with TB are not currently available.

Thus, for adult patients with HIV-associated TB who are not already receiving ART, the decision regarding timing of initiation of anti-TB and anti-HIV medications is guided by HIV disease stage (see Figure 1). Individuals with greater than 200 CD4 cells and without evidence of extrapulmonary disease may be treated for TB first; once the intensive (rifampin-containing) phase of TB treatment is complete, antiretroviral treatment should then be initiated. In contrast, when a patient has 200 or fewer CD4 cells and/or extrapulmonary TB, ART should not be deferred. As a rule, the best approach for these patients is to start TB treatment, monitoring carefully for adverse events. If anti-TB medications are tolerated without difficulty, an appropriate ART regimen should be initiated 4 to 8 weeks later. As below, substantial interactions between rifampin and several antiretroviral agents necessitate the use of specific ARVs when rifampin-containing anti-TB regimens are used (Figure 2).

Figure 1:

HIV-infected patient, not on ART, newly diagnosed with TB	
 HIV stage determines the timing of ART initiation:	
Not eligible for ART (see Chapter 5.3)	Treat TB, monitor HIV as per routine
Eligible for ART but > 200 CD4, no extrapulmonary TB	Treat TB first – defer initiation of ART until rifampin-containing regimen complete
Eligible for ART and ≤ 200 CD4 and/or extrapulmonary TB	Treat TB and HIV <ul style="list-style-type: none"> • In general, TB rx is initiated 4-8 weeks prior to ART initiation • Rifampin-compatible ART regimen required

A similar approach should be taken for children with HIV/TB. Those with advanced disease (WHO III/CDC C) or severe immune suppression (CD4% <15%) generally warrant immediate treatment of both infections. For children with less severe

manifestations of HIV infection, ART initiation can be delayed. ARV treatment can be initiated 4-8 weeks after TB therapy is begun, or deferred until TB treatment is complete if the child is clinically and immunologically stable. Consultation with an expert in the care of HIV-infected children with tuberculosis, if available, may be beneficial.

- **Drug-drug interactions**

Antiretroviral agents have multiple interactions with other medications, and should never be prescribed without a careful review of each patient's regimen, including herbal and traditional medicines. This issue is of particular concern in patients with tuberculosis because of the serious interactions between ARVs and rifampin, a cornerstone of TB treatment. Inexpert use of either ARVs or TB medications in HIV-infected patients can lead to failure of and resistance to either or both class of drug, with grave implications for both individual patients and their communities. This does not mean that rifampin should be avoided, as non-rifampin-containing TB regimens are less successful. Similarly, it does not mean that patients on TB medications should not receive ART, just that the intervention should be reserved for those who will benefit the most and delivered by clinicians with expertise in co-treatment.


Details of the interactions between ARVs and anti-TB medications can be found in Appendix B. Briefly, rifampin moderately lowers blood levels of the non-nucleoside reverse transcriptase inhibitors efavirenz and nevirapine. Rifampin also markedly reduces blood levels of most protease inhibitors, which, as a rule, should not be used with rifampin.

International guidelines recommend a first-line regimen of two nucleoside analogs (lamivudine + stavudine or zidovudine) and efavirenz for patients being treated for HIV-associated TB. Thus, the following recommendations can be made for adult patients who are not pregnant or likely to become pregnant:

- Patients already taking ART at the time of TB diagnosis:
 - 3TC + ZDV (D4T) + EFV: no change required
 - 3TC + ZDV (D4T) + NVP: change to 3TC + ZDV (D4T) + EFV
 - 3TC + ZDV (D4T) + ABC: no change required
 - Second-line or protease-inhibitor-containing regimens: expert consultation recommended
- Patients initiating ART during TB treatment
 - 3TC + ZDV (D4T) + EFV

Expert consultation is required for patients intolerant of these regimens, for pregnant patients, and for young children (see Figure 2).

Figure 2:

HIV-infected patient, on ART, newly diagnosed with TB	
 Adjustments in ART regimen may be required to avoid drug-drug interactions:	
Current regimen:	Change to:
3TC + ZDV(D4T) + NVP	1. Nonpregnant adults: 3TC + ZDV(D4T) + EFV 2. Pregnant (or likely to become pregnant): expert consultation 3. Children \geq 3 years: 3TC + ZDV(D4T) + EFV 4. Infants and children < 3 years: 3TC + ZDV(D4T) + ritonavir
3TC + ZDV(D4T) + EFV	No change required
3TC + ZDV(D4T) + ABC	No change required
2 nd -line regimen	Expert consultation recommended

During pregnancy, concerns about the use of efavirenz – contraindicated in the first trimester due to its association with birth defects – must be balanced by the need for a potent and tolerable rifampin-compatible regimen. When both ART and anti-TB medications are indicated during the first trimester, a reasonable option is the use of two nucleoside analogs and abacavir. When treating women in the later stages of pregnancy, many experts will recommend two nucleoside analogues and efavirenz. As noted, consultation regarding the treatment of pregnant patients with HIV-associated TB is strongly advised. For co-infected children younger than three years, in whom efavirenz should not be used, current guidelines recommend the use of two nucleoside analogs and ritonavir. Abacavir may also be an option, particularly if ritonavir is not well tolerated.

- **Overlapping toxicities of HIV and TB medication:**

In addition to the drug-drug interactions above, which guide ART selection, overlapping toxicity profiles also complicate the simultaneous treatment of HIV and TB. As the patients being treated for HIV-TB have advanced immunodeficiency and all are taking multiple medications, it is not surprising that adverse drug events are common among this population. In one cohort study, 34 percent of patients stopped HIV or TB therapy at least temporarily. Far fewer – one percent – needed to discontinue therapy permanently.

It is important for both providers and patients to be vigilant about identifying medication toxicity, and careful, frequent clinical monitoring is essential. Patients should be familiar with important symptoms – nausea, vomiting, abdominal pain, jaundice (yellow eyes, darkened skin), darkened urine – and should know to seek help promptly if these occur. Patients with pre-existing liver disease, pregnant woman, and heavy alcohol drinkers require particular care. Baseline liver function tests should be performed on all patients treated with ART and TB medications, and repeated in individuals in whom symptoms suggestive of hepatotoxicity occur.

Starting many drugs at the same time – at least seven medications, in the case of HIV-TB – presents a diagnostic challenge if adverse events do occur. Several of the drugs cause rash, nausea, hepatitis or neuropathy; these may also be caused by other medicines prescribed to patients with HIV-TB, such as co-trimoxazole. Other symptoms, particularly fever, can be caused by immune reconstitution, as above. When confronted with such symptoms, it is difficult to guess which drug is the offending agent.

Given these complexities, providers should have a systematic approach to managing adverse drug events:

- ✓ A careful inventory of medications should be taken – is the patient taking all the medications prescribed? Is s/he taking any additional medications, herbal or traditional agents? When, precisely, were the medications initiated?
 - ✓ Next, an assessment of severity should be made. Is nausea mild, or does it interfere with nutrition? Is the rash disseminated or associated with systemic symptoms? (Tables 3 and 4 in Chapter 5.3 define severe / grade 3 clinical and laboratory toxicities).
 - ✓ Mild adverse effects can be managed symptomatically. If patients have severe toxicity, however, medications may need to be stopped. Depending on the clinical situation, providers may decide to stop all ARVs, all TB medications, or all drugs. It should go without saying that stopping *some* ARVs or *some* TB medications is unwise and risks the development of drug resistance.
 - ✓ If medications are stopped and symptoms resolve, expert consultation may be required prior to re-initiating therapy.
 - ✓ Very few events result in the *permanent* discontinuation of medications, and first-line TB drugs (particularly INH and rifampin) should not be permanently discontinued unless there is evidence that they caused a significant side effect.
 - ✓ As always, doing one thing at a time will make it easier to identify the cause of an event!
- **Immune reconstitution events:**

With vigorous immune reconstitution due to ART, some HIV-infected patients develop TB-related complications in the first few months after initiation of ARVs. This transient paradoxical worsening of TB symptoms can include an increase in manifestations of TB at prior sites and/or new manifestations of disease. Such “immune reconstitution events” (IRE) are common – occurring in 10 to 36 percent of patients in clinical trials – and it is important for both patient and provider to be aware that they may occur.

Immune reconstitution events are typically closely associated with starting ART, occurring days to weeks after ART initiation. The reactions are difficult to differentiate from those that might be associated with TB symptoms or TB treatment failure, and it is prudent to consider both possibilities. IREs often last days to months, and symptoms often wax and wane. Table 2 lists typical symptoms and signs of immune reconstitution events.

Risk factors for immune reconstitution events include lower CD4 count and a shorter time between initiation of TB treatment and initiation of ART. All patients being treated for TB and HIV should be informed of the possible side effects, but patients in this high-risk category should be particularly aware of what symptoms to look for (“you may feel like the TB is coming back”) and what to do if symptoms occur.

Table 2: Symptoms and Signs of Immune Reconstitution Events

- **Hectic fever**
- **New or worsening lymphadenitis** - peripheral or central nodes
- **New or worsening pulmonary infiltrates**
- **New or worsening pleuritis, pericarditis, or ascites**
- Intracranial tuberculomas, worsening meningitis
- Disseminated skin lesions
- Epididymitis, hepatosplenomegaly, soft tissue abscesses

When evaluating patients with possible IREs, providers should systematically exclude TB treatment failure via clinical reassessment and repeat sputum studies. Other HIV-related complications, such as another opportunistic infection or a malignancy, should also be excluded. Once these protocols have been followed, and IRE is the leading diagnosis, management is dictated by clinical severity. Although there are many uncertainties about the optimal management of this syndrome, it is clear that patients with relatively mild events require only reassurance and close clinical follow-up. Fevers and pain often respond to nonsteroidal anti-inflammatory agents. Severe manifestations – enlarging lymph nodes that compromise ability to move the neck, swallow, or breathe, an enlarging tuberculoma in the central nervous system, worsening meningitis or respiratory failure – should be treated with corticosteroids. In this setting, it may also be necessary to stop antiretroviral treatment for a time. The optimal duration of steroid therapy has not been studied, but many experts would attempt to taper the steroids after several weeks if there has been a good response.

Treatment adherence

The importance of adherence assessment and support is discussed at length in Section 2. Treatment of HIV-TB introduces some special challenges, including the number of medications, the potential adverse events noted above, and the fact that HIV and TB are often treated by different clinicians at different locations. It is critically important to establish a close relationship with the local TB treatment program. If care is provided at different sites, caution, communication, and collaboration are vital. Where possible, TB treatment should be delivered via directly observed therapy, the current standard of care. DOT visits should be used to reinforce adherence with both TB and HIV medications and medication pickup should be coordinated where possible.

As always, care should be taken to ensure that the patient is ready for antiretroviral therapy. Patients should understand that ART is potentially life-saving, but that it is more complicated than once-daily TB treatment and will require multiple new medications. Intensive patient education and support is appropriate.

Coordination of HIV and TB treatment

All HIV/AIDS treatment programs should establish formal linkages to TB treatment programs. The World Health Organization strongly recommends joint TB/HIV strategic planning at every level, from policy and planning to clinical care and community mobilization. WHO similarly urges that all patients with tuberculosis be offered testing for HIV and all patients with HIV be routinely screened for active TB disease and for latent TB infection. Collaboration between local HIV/AIDS and TB programs, therefore, should be routine.

Each ICAP site will need to work with the local TB program to optimize reporting of TB cases and contact tracing within families. Access to TB medications via DOT should be ensured. Coordination of care will be dependent on timely communication regarding management decisions and the results of diagnostic tests. Involving staff from the TB program in training activities is often quite helpful.

Appendix A: Principles of HIV-TB Management

- Identification and treatment of latent TB infection
 - ✓ see Chapter 5.2
- Early identification of active TB disease
 - ✓ high index of suspicion for TB
 - ✓ familiarity with presentation of TB in immunocompromised hosts
 - ✓ routine screening via symptom checklist
 - ✓ rapid and systematic evaluation of suspected cases
- Prompt treatment of patients with TB disease
 - ✓ Collaboration/communication with local TB program
 - ✓ Patient education and adherence support
 - ✓ Initiate TB medications via DOT where possible
 - ✓ Manage side effects as needed
- Use of ART for appropriate patients
 - ✓ Assess stage of HIV disease, current CD4 count
 - ✓ Assess patient readiness for ART
 - ✓ Inform TB program of decision and plans
 - ✓ Discuss side effects and possibility of immune reconstitution events with patient and TB program
 - ✓ Provide patient education and adherence support
 - ✓ Initiate ART for appropriate patients (usually 4-8 weeks after starting TB therapy)
- Close and consistent follow up
 - ✓ Weekly visits after ART initiation as per ICAP guidelines
 - ✓ Careful monitoring for side effects/ immune reconstitution events
 - ✓ Ongoing adherence support
 - ✓ Coordination of HIV and TB services (medication pick-up, patient education, DOT) where possible
 - ✓ Ongoing communication with TB program

**Appendix B:
Recommendations for Co-Administering Selected ARVs with Rifampin**

Antiretroviral agent	ARV dose change	Rifampin dose change	Comments
Nevirapine	Rifampin and nevirapine should not be used together		Nevirapine concentration decreased. Very limited data regarding co-administration.
Efavirenz	None	None	Efavirenz concentration (AUC) decreases by 22%, no change in rifampin concentration. Some experts recommend increasing dose of efavirenz, although data to support this approach are limited.
Ritonavir	None	None	Ritonavir concentration (AUC) decreases by 35%, no change in rifampin concentration
Indinavir	Rifampin and indinavir should not be used together		Indinavir concentration (AUC) decreases by 89%.
Nelfinavir	Rifampin and nelfinavir should not be used together		Nelfinavir concentration (AUC) decreases by 89%.
Lopinavir/ ritonavir (Kaletra™)	Rifampin and lopinavir/ritonavir (Kaletra™) should not be used together.		Lopinavir concentration (AUC) decreases by 75%; trough levels decrease by 99%.