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HIV-Associated Tuberculosis: Update on Prevention and Treatment

Kerry L Dierberg, MD, MPH[1] and **Richard E Chaisson, MD**[1,2]

[1]Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

[2]Center for Tuberculosis Research, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

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Introduction

Tuberculosis continues to be one of the leading causes of death from infectious disease worldwide, and it is the leading opportunistic infection and cause of mortality among people with human immunodeficiency virus (HIV) infection.[1,2] People with HIV infection are at increased risk for reactivation of latent TB infection and acquisition of new TB infection when compared to HIV-uninfected persons, and they are less likely to present with classic clinical or radiographic findings of TB.[3–7] Additionally, treatment of HIV-related TB is complicated by overlapping drug toxicities and drug-drug interactions between antiretroviral therapy and anti-TB therapy, as well as the risk for development of immune reconstitution inflammatory disease.

Screening for symptoms of TB in all people with HIV infection, use of isoniazid preventative therapy for those with latent TB infection, earlier diagnosis and treatment of active TB disease, and early initiation of antiretroviral therapy are essential for controlling the spread of TB. This review will provide an overview and updates on the prevention and treatment of TB in HIV-infected persons.

Epidemiology

Based on World Health Organization (WHO) reports, there were 8.7 million new cases of TB and 1.4 million deaths from TB worldwide in 2011. The largest burden of TB was in Asia and Africa, which accounted for 59% and 26% of all cases, respectively. Among the 22 highburden countries, 26% of all incident cases were in India and 12% were in China, followed by South Africa (6%) and Pakistan (5%). Approximately 3.7% of all new TB cases and 20% of previously treated cases have multidrug-resistant TB (MDR TB, characterized by resistance to isoniazid and rifampin), with over 60% of these cases in India, China and

Correspondence to: Richard E. Chaisson, MD, 1550 Orleans St., 1M.08, Baltimore, MD 21287, rchaiss@jhmi.edu.

Russia. It is estimated that 9% of the MDR TB cases are extensively drug-resistant TB (XDR TB, MDR TB with additional resistance to fluoroquinolones and injectable agents).[2]

It is estimated that 1.1 million (13%) of all TB cases are co-infected with HIV, and approximately 80% of these cases are in Africa. Of the 1.4 million deaths globally from TB in 2011, approximately 400,000 were HIV-associated TB deaths. HIV testing for all TB patients is recommended; however, this remains a significant challenge for many TB programs. In 2011, it is estimated that approximately 40% of all notified TB cases had HIV testing, which is a substantial increase from 3.1% in 2004, but this remains insufficient given the growing burden of TB-HIV co-infection.[2]

TB and HIV continue to be leading causes of morbidity and mortality for women and children.[1,2,8] In 2011, an estimated 2.9 million and 500,000 cases of the 8.7 million incident cases occurred in women and children, respectively. There were an estimated 500,000 million deaths among women attributable to TB in 2011, and approximately 40% of these also had HIV infection, making TB a greater killer of women than complications of childbirth.[2]

In the United States, the rates of TB have continued to decline, with a total of 10,521 new cases (incidence 3.4 per 100,000) reported to the U.S. Centers for Disease Control (CDC) in 2011. However, foreign-born persons and racial/ethnic minorities continue to be affected disproportionately, with rates 12 times greater than in U.S.-born persons. The highest incidence of TB was reported in persons from Mexico (21.3%), Philippines (11.5%), Vietnam (8.2%), India (7.6%) and China (5.6%). Of the 81% of TB cases with a documented HIV test, 7.9% tested HIV positive.[9]

HIV infection continues to be the most important biological risk factor for developing tuberculosis. Other classic risk factors for developing TB include poverty, overcrowding and malnutrition. However, it is also known that smoking doubles a person's risk for developing TB infection. Alcohol consumption, diabetes, and immunosuppressive therapy with steroids, tumor necrosis factor (TNF) antagonists or other immune-modulating medications also increase risk for TB.[1]

Prevention

Screening for TB

HIV-infected persons are at increased risk for developing TB disease both from recent infection and from reactivation of latent infection. The risk of reactivation of latent TB is approximately 5–10% per year for HIV-infected persons, compared to a 10% lifetime risk for HIV-uninfected persons.[4] In countries with generalized HIV epidemics, TB is a common presenting sign of HIV infection, and in areas with low rates of HIV infection the prevalence of HIV is substantially higher than in the general population. Based on these risks, the WHO recommends integrated TB and HIV services. Specifically, all people with active TB disease should be tested for HIV. If they are HIV-infected, they should receive trimethoprim-sulfamethoxazole prophylaxis and be assessed for the need for antiretroviral therapy.[4,10,11]

All HIV-infected patients should be screened for symptoms of TB (intensified case finding) and then evaluated with specific diagnostic studies if symptoms are present. In highburden settings, patients without active TB should receive isoniazid preventative therapy (IPT), as well as antiretroviral therapy to reduce TB risk. In low-burden settings such as the US, IPT or other preventive regimens should be targeted at those with latent TB infection as documented by a positive tuberculin skin test or positive interferon-gamma release assay. Screening should be performed at the time of HIV diagnosis and regularly thereafter,

especially in settings where TB burden is high.[1,12] The CDC also recommends that all HIV-infected persons in the US be screened for active and latent TB at the time of diagnosis of HIV, and then yearly based on risk of TB exposure.[4]

Standardized TB screening for all HIV-infected patients provides the opportunity to diagnose and treat active disease earlier and to identify patients who are eligible for IPT. HIV-infected persons may present with classic symptoms of TB, including cough, fever, night sweats and weight loss; however, many will have minimal symptoms, making the diagnosis of active TB difficult. In addition, because extrapulmonary TB is extremely common in HIV-infected individuals, clinical presentations may vary greatly. This continues to be a significant obstacle to screening HIV patients for TB and for uptake of IPT.

Despite recommendations that all HIV-infected patients be screened for TB, the best symptom screening criteria remains unclear. In 2011, Getahun et al published the results of a meta-analysis aimed at developing a standardized TB symptom-screening rule for HIV-infected persons. Based on the results of this study, the best screening rule was the presence of any one of the following symptoms: current cough (any duration), fever, night sweats, or weight loss. The overall sensitivity and specificity of this rule was 78.9% and 49.6%, respectively, with a high negative predictive value (90–97%), suggesting that the absence of these four symptoms is effective for excluding active TB and identifying people eligible for IPT.[8,12,13] These screening criteria have also been shown to be effective for HIV-infected pregnant women.[14]

However, as suggested by the sensitivity of just under 80%, the use of WHO-recommended symptom screening will still miss approximately 20% of TB cases among HIV patients.[5]

Diagnostic testing for TB is challenging, particularly in resource-limited areas, and sputum acid-fast smears have extremely low sensitivity in the setting of HIV infection. Culture using liquid media such as the Mycobacterial Growth Indicator Tube (MGIT, BD, Franklin Lakes, NJ) increases sensitivity to >95% but culture is expensive, time-consuming and requires BSL3 laboratory facilities. Recently, rapid molecular diagnostic assays have been introduced which can detect *Mycobacterium tuberculosis* in sputum and other specimens in as little as 90 minutes, and which can also detect gene mutations associated with drug resistance. The Xpert MTB/RIF (Cepheid, Sunnyvale, CA) is a cartridge-based system that has high sensitivity (70–90%) for *M. tuberculosis* and detects rifampin resistance with >95% accuracy.[15,16] Several line probe nucleic acid amplification assays also detect *M. tuberculosis* and several forms of drug resistance, including MDR and XDR, in as little as two hours. Details of these diagnostic methods are beyond the scope of this paper and the reader is referred to a recent review of this topic.

A tuberculin skin test (TST) or interferon-γ release assays (IGRAs) can by helpful in diagnosing latent TB infection, but neither is 100% sensitive or specific and HIV-infected patients may have false-negative results.[4] The *QuantiFERON-TB Gold In-tube* (QGIT) and the T-SPOT.*TB* IGRAs have been approved by the US Food and Drug Administration (FDA) and the WHO for diagnosis of latent TB infection; however, the WHO does not recommend use of these tests is low- and middle-income countries.[17] Studies have not demonstrated increased accuracy of the IGRAs for diagnosis of latent TB and discordance in test results between IGRAs and TST have been demonstrated. However, IGRAs are less likely to be false positive in persons who previously received BCG vaccination.[18,19]

Treatment of Latent TB Infection

Several studies have demonstrated the benefit of isoniazid preventive therapy for latent TB infection, with 44–58% reduction in the risk of TB.[12,20,21] A Cochrane systematic review

published in 2010 of 12 trials demonstrated that IPT reduced the risk of active TB by 64% in HIV-infected participants with a positive TST but only by 14% in TST negative individuals.[20]

Several recent studies have focused on the optimal regimen and treatment duration for latent TB in HIV-infected persons. Prior studies have demonstrated a 32–64% reduction in TB risk with 6–9 months of isoniazid or isoniazid plus rifampin for 3 months.[20,21]

A randomized, controlled trial conducted in South Africa demonstrated no significant differences in rates of TB or death in HIV-infected adults treated for latent TB infection with rifapentine (900 mg) plus isoniazid (900 mg) once weekly for 3 months, rifampin 600 mg plus isoniazid 900 mg twice weekly for 3 months, or isoniazid (300 mg/day) continuously for up to 6 years compared to a control regimen of isoniazid daily for 6 months. A large study in mostly HIV-seronegative individuals also found that once weekly rifiapentine and isoniazid for 12 weeks was non-inferior to 9 months of daily isoniazid for treating latent TB infection, and this regimen has been endorsed by the CDC.[21]

The use of continuous IPT is an appealing option for high-burden settings, as it theoretically should also protect patients from disease due to reinfection. In the study by Martinson and colleagues, the as-treated analysis found that the risk of TB and death was significantly reduced while participants took isoniazid, but this benefit was lost if treatment was discontinued.[21] In a randomized, double-blind trial comparing 6 months vs. 36 months of isoniazid in patients with HIV conducted in Botswana, a significantly lower risk of TB was seen with 36 months of isoniazid, though this benefit was found only in those who were TST positive. The lack of benefit for TST negative patients is puzzling, as prevention of disease due to new infections should accrue to all patients in this high burden setting; however, it is possible that TST positive individuals are at higher risk of reinfection than TST negatives, and therefore continuous isoniazid therapy is protective for this population particularly.[24]

IPT has been shown to be safe and effective in reducing the risk of TB in HIV-infected mothers. TB during pregnancy and the postpartum period is associated with increased maternal mortality, TB in the infant, and vertical transmission of HIV, so screening for latent TB and use of IPT is essential as a part of maternal health care.[8,25]

The CDC currently recommends the following treatment regimens for latent TB in HIV-infected individuals:[4,9,22]

- Isoniazid daily for 9 months (recommendation strength: AII),
- Isoniazid daily for 6 months (recommendation strength: CI),
- Rifampin daily for 4 months (recommendation strength: BIII), or Rifapentine plus isoniazid once weekly for 3 months (recommendation strength: BI) in antiretroviral therapy-naive patients only.[23]

Antiretroviral therapy

Studies have shown that antiretroviral therapy reduces risk of developing TB and death in HIV-infected persons; however, the risk continues to remain higher than in HIV-uninfected persons. A recent meta-analysis found that antiretroviral therapy was associated with reductions in rates of TB ranging from 57 to 84%, depending on the CD4 cell count at which treatment began. The HIV Prevention Trials Network (HPTN) 052 trial of early initiation of antiretroviral therapy to prevent HIV transmission in discordant couples also demonstrated that individuals randomized to early antiretroviral therapy had a 50% reduction in the risk of TB, emphasizing the benefits of earlier treatment of HIV infection.[26] Protection against TB is further optimized when IPT is combined with antiretroviral therapy; synergistic protection

was found in one study of South African patients who received both IPT and antiretrovirals when compared to the protection afforded by either treatment alone.[8,27,28] A recently completed trial of patients with advanced HIV infection who were receiving antiretroviral therapy showed a >50% reduction in rates of TB for patients randomized to receive isoniazid versus those randomized to placebo.[29]

Clinical Manifestations of HIV-associated TB

Tuberculosis continues to be the leading opportunistic infection and cause of mortality among people with HIV infection and is often the presenting condition for patients with undiagnosed HIV.[1,2,11] People with HIV infection who acquire new TB infections have a greatly increased likelihood of progression to active disease, and mortality rates due to TB are higher in HIV-infected persons than in HIV-uninfected individuals.[11]

Pulmonary TB

Pulmonary TB is the most common form of TB in both HIV-infected and HIV-uninfected individuals. HIV-infected persons may present with classic symptoms of pulmonary TB, including cough, hemoptysis, fever, weight loss and night sweats; however, HIV-infected persons frequently present with minimal or atypical symptoms, making the diagnosis of TB more difficult for clinicians. Patients with a CD4 cell count > 350 cells/mm^3 are more likely to have a similar presentation to HIV-uninfected individuals than patients with advanced immunosuppression.[3–5,7]

Several studies have also demonstrated that HIV-infected persons are more likely to have “non-classical” or atypical findings on chest radiograph when compared to HIV-uninfected persons, including non-cavitary infiltrates, miliary disease, pleural effusions or normal chest radiographs.[6,7,35] Patients with HIV-associated TB are more likely to have smearnegative disease, likely due in part to the lack of cavitary lung disease.[7,11,36]

The combination of atypical or minimal symptoms and radiologic findings and increased likelihood of having a negative sputum AFB smear often results in a delay in diagnosis of HIV-associated TB and delay in initiation of treatment. Most HIV patients with subclinical TB will eventually develop symptoms of their disease; however, often when the disease is much more advanced. HIV-infected patients with subclinical TB who are started on antiretroviral therapy are also likely to present with symptoms of TB as their immune system recovers, which is referred to as “unmasking” immune reconstitution inflammatory syndrome (IRIS).[37–39] Screening of patients beginning antiretroviral therapy for active TB using culture, Xpert MTB/RIF or other sensitive diagnostic modalities can identify those with subclinical disease, allowing for earlier initiation of anti-TB therapy and preventing IRIS.

Drug-resistant TB

Multidrug-resistant TB (MDR TB) is TB that is resistant to isoniazid and rifampicin, and extensively drug-resistant TB (XDR TB) is MDR TB that is also resistant to a fluoroquinolone and at least one injectable agent (capreomycin, kanamycin, amikacin). Mortality rates are high for HIV-infected patients who develop drug-resistant TB, with rates up to 90% for those infected with XDR TB. Based on WHO guidelines, all HIV-infected patients diagnosed with TB should have drug susceptibility testing (DST) at the start of TB therapy. Clinicians should have a high index of suspicion for drug-resistant TB if the patient remains sputum smear negative or is clinically failing first line anti-TB treatment.

Extrapulmonary TB

Patients with HIV are more likely to develop extrapulmonary disease and disseminated TB disease than HIV-uninfected individuals, especially at lower CD4 counts.[11,40] More than half of all patients with HIV-related TB who undergo a thorough workup have extrapulmonary disease, most of whom also have pulmonary TB. In patients with prominent pulmonary symptoms and signs, extrapulmonary manifestations of TB may be overlooked.

The most common forms of extrapulmonary disease in patients with HIV infection are TB lymphadenitis, pleural TB, TB meningitis and disseminated TB with bacteremia. Other sites of disease in HIV-associated TB include the abdomen (peritoneum, gastrointestinal tract, liver, kidneys), bone and joint, pericardium, genitourinary system, and soft tissues.[11]

Treatment of HIV-associated TB

The WHO, the US Public Health Service and the Department of Health and Human Services all recommend that all HIV-infected individuals diagnosed with TB should receive anti-TB treatment and antiretroviral therapy; in resource limited settings, the WHO also recommends that all patients receive trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis, while US and European guidelines restrict this recommendation to patients with CD4 cell counts <200 cells/mm^3.[11] Details on use of antiretroviral therapy are provided below.

Pulmonary TB

Based on current guidelines, the treatment of HIV-associated pulmonary TB is the same as treatment in HIV-uninfected individuals. Patients with pulmonary TB should receive 2 months of intensive therapy with a standard 4-drug regimen (isoniazid, rifampin, pyrazinamide and ethambutol), followed by 4 months of continuation therapy with a 2-drug regimen (isoniazid and rifampin). All patients should receive pyridoxine (vitamin B6) 50 mg daily to prevent peripheral neuropathy associated with isoniazid.[3,11]

Several studies have demonstrated lower recurrence rates in HIV-infected patients with TB when treated for a longer duration. A study conducted in the former Zaire that compared 6 months vs. 12 months of rifampicin-based therapy demonstrated lower recurrence rates in those treated for 12 months, though longer therapy did not improve survival.[41] A randomized control trial evaluating standard 6-month therapy compared to 6 months of therapy, followed by isoniazid preventive therapy, showed a significant impact of secondary isoniazid therapy on risk of TB recurrence.[42] It is unclear whether the reduced recurrence rates in these studies was due to decreased relapse or reinfection, but it is likely that prolonged isoniazid controls disease due to reinfection in high-burden settings, as rates of recurrence in patients treated in the US do not appear to be elevated.[43] These findings suggest that longer duration of therapy, or standard 6-month therapy followed by isoniazid preventative therapy, may be indicated in high-TB burden settings where the risk of reinfection is high, and the WHO recommends use of IPT in patients with HIV previously treated for TB.[44] Risk of recurrence is also decreased by treatment with antiretroviral therapy. A study in Brazil found that use of antiretroviral therapy reduced recurrent TB by 50%.[45]

Extrapulmonary TB

As with pulmonary TB, current guidelines recommend using the same treatment regimens and duration for HIV-associated extrapulmonary TB as for extrapulmonary TB in HIV-uninfected individuals.[3,11] Patients with TB meningitis or pericardial TB should also receive corticosteroid therapy. Specific treatment guidelines are based on the site of disease and are summarized in Table 1.

Drug-resistant TB

All patients with HIV-related TB should have DST performed at the time of TB diagnosis, if possible.[3] For patients diagnosed with TB who do not have baseline DST, susceptibility testing should be performed at the time of clinical failure or relapse, given high mortality rates from MDR and XDR TB in HIV-infected patients.[11] Choice of an MDR or XDR TB regimen should be guided by DST results whenever possible. For patients diagnosed with Xpert MTB/RIF who are found to have resistance to rifampin, additional susceptibility testing for both first-line and second-line drugs must be performed.

Directly observed therapy (DOT) is recommended for all patients receiving treatment of HIV-associated TB. If possible, patients should receive daily treatment under DOT, as studies have demonstrated decreased relapse rates in patients receiving daily therapy vs. intermittent therapy.[11,46] The WHO now recommends daily treatment under DOT for all patients with HIV-associated TB.[11]

Per WHO recommendations, trimethoprim-sulfamethoxazole (TMP-SMX) is currently recommended for all HIV-infected individuals at the time of TB diagnosis and throughout the duration of TB treatment. Studies have demonstrated decreased mortality in HIV-infected TB patients. TMP-SMX is known to prevent *Pneumocystis jirovecii* pneumonia and may reduce risk for bacterial infections, such as gastrointestinal tract disease, and malaria.[11,47]

TB in Pregnancy

TB in women poses special challenges but is critically important, as transmission of HIV and TB to the fetus and poor obstetric and perinatal outcomes are common when TB is not recognized and properly treated.[3,8,11,25] The WHO currently recommends treatment with standard regimens as listed in Table 1, including use of pyrazinamide. However, pyrazinamide is not recommended in the United States due to limited safety data in pregnancy, though its use is warranted when clinicians determine that the benefits outweigh the risks.[3] Streptomycin should be avoided in pregnant women because of known risk of ototoxicity in the fetus.[11,48] All infants born to mothers with TB should receive IPT once active TB is ruled-out.[11] Both the WHO and CDC recommend breastfeeding if the mother is on first-line anti-TB therapy.[3,11,25]

Role of Antiretroviral Therapy in Treatment of HIV-associated TB

Because TB is a clinical manifestation of immunodeficiency and independently increases the risk of HIV progression and death, highly active antiretroviral therapy (ART) is recommended for all HIV-infected individuals diagnosed with TB, regardless of CD4 cell count.[11,49–56] Several recent studies have helped provide guidance on the best timing for initiation of ART after TB treatment is started. The SaPIT trial in South Africa demonstrated significantly lower mortality for patients who received integrated TB and HIV therapy compared to delaying ART until TB therapy was completed. The CAMELIA study showed that Cambodian patients with advanced HIV infection (median CD4 count 25 cells/mm^3) had a 34% lower risk of dying if ART was initiated within 2 weeks of starting TB therapy compared with beginning antiretroviral therapy at 8 weeks. The STRIDE and SaPIT studies both found that immediate initiation of ART (2 weeks) substantially lowered the risk of death or developing a new AIDS diagnosis for patients with CD4 counts <50 cells/mm^3 compared to later initiation (8 weeks), but no benefit for patients with higher CD4 counts. Based on the results of these trials, the US Department of Health and Human Services (DHHS) recommends initiating ART based on the following guidelines:[57]

- If CD4 cell count is < 50 cells/mm3, initiate ART within 2 weeks of starting TB therapy.
- If CD4 cell count is ≥ 50 cells/mm3 and patients have clinical disease of major severity (including low Karnofsky score, low body mass index, low hemoglobin, low albumin, organ system dysfunction, or extent of disease), initiate ART within 2–4 weeks.
- If CD4 cell count is ≥ 50 cells/mm3 but without severe clinical disease, initiation of ART can be delayed but should be started within 8–12 weeks of starting TB therapy.

For patients with TB meningitis, ART should not be started within 2 weeks of initiating TB treatment, regardless of CD4 cell count, due to increased risk for central nervous system immune reconstitution inflammatory syndrome (IRIS) and associated poor outcomes, including death. For these patients, ART should be delayed for up to 8 weeks.[58]

While the early initiation of ART in patients with HIV-associated TB has been shown to significantly reduce mortality and progression of HIV disease, it has also been associated with IRIS. TB IRIS is most common in the first 3 months after initiation of ART and in patients with a CD4 cell count <100 cells/mm^3 at the time that ART is initiated.[4,11,37,38,54,56]

IRIS often presents with fever, new or worsening pulmonary infiltrates, new or worsening serositis, enlarged lymph nodes or apparent worsening of disease at another site. IRIS is a diagnosis of exclusion, and other causes of these symptoms, such as another opportunistic infection, malignancy or TB treatment failure, should be ruled-out prior to making this diagnosis. Diagnostic criteria for IRIS developed by an international working group of experts have been published and are shown in Table 2.[39]

Up to one third of all patients receiving combined therapy for TB and HIV will develop IRIS, though most patients have only mild to moderate symptoms and the condition is rarely fatal.[59] Management of IRIS depends on clinical symptomatology and is directed at reducing inflammation and drainage of abscesses or fluid collections. Some patients can be managed with nonsteroidal anti-inflammatory agents, but many patients will require corticosteroid treatment for improvement in symptoms. A randomized placebo-controlled trial conducted in South Africa demonstrated that treatment with prednisone 1.5 mg/kg/day for 2 weeks followed by 0.75 mg/kg/day for 2 weeks significantly improved symptoms and reduced the need for invasive procedures or hospitalization.[60] While most patients can be managed with corticosteroids alone, the exception is patients with TB meningitis. These patients have increased risk of central nervous system IRIS and severe adverse events and death associated with early initiation of ART.[58] Treatment in this situation may require increased dosage of corticosteroids, intracranial pressure management with frequent lumbar punctures, and neurosurgical intervention.

Drug-drug Interactions

Treatment of HIV-related TB is complicated by overlapping drug toxicities and by drug-drug interactions between antiretroviral therapy and anti-TB therapy. The most important drug interactions to consider occur between rifamycins and antiretroviral medications, including nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors. Drug-drug interactions also occur with use of integrase inhibitors and with CCR5 receptor antagonists.[61–64]

The rifamycins (rifampin, rifabutin, and rifapentine) are CYP450 enzyme inducers, which can increase the metabolism of drugs cleared by this pathway. Co-treatment of TB and HIV requires close attention to selection and dosing of rifamycins and antiretrovirals (Table 3).[61] Rifampin has been shown to increase the clearance of NNRTIs, including efavirenz and nevirapine.[4,61–63] Rifampin decreases exposure to nevirapine by approximately 50% and results in higher rates of virologic failure than when the drug is used without rifampin. Exposure to efavirenz is reduced by 20–25% by co-administration of rifampin, but virologic outcomes are not affected. Some authorities recommend increasing efavirenz dosage from 600 to 800 mg daily when co-administered with rifampin, but clinical and virologic data do not support this advice, and patients treated with standard dosages of efavirenz while taking rifampin-based TB therapy do not have compromised outcomes.

Conversely, rifampin co-administration with protease inhibitors results in 80–98% reductions in exposure and compromise antiretroviral therapy. Therefore, rifabutin is the preferred rifamycin with protease inhibitor-based regimens as it is only a very weak inducer of CYP450 isoenzymes. Boosted protease inhibitor regimens using ritonavir increase serum concentrations of rifabutin and can lead to clinically important toxicity, including uveitis. Consequently, dosing of rifabutin during protease inhibitor-based ART needs to be adjusted; previous guidelines recommended a dosage of 150 mg every other day, but more recent data support use of a dosage of 150 mg daily or 300 mg every other day to ensure adequate exposure to the anti-tuberculosis effect of rifabutin and prevent the development of rifampin-resistant TB.[61]

Conclusion

Given the increased risk of TB disease and associated high mortality in patients with HIV infection, clinicians should have a high index of suspicion for TB in patients with HIV, even in patients with minimal or atypical symptoms. Aggressive diagnostic efforts using sensitive assays should be applied to HIV-infected individuals with signs or symptoms of TB. Treatment of latent TB infection, early initiation of antiretroviral therapy, and early treatment of active TB disease are essential to reduce the burden of HIV-associated TB, as well as to prevent further TB transmission.

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Key Points

- Tuberculosis (TB) is the leading cause of opportunistic infection and mortality among HIV-infected persons.
- All HIV-infected patients should be screened for TB and treated for latent TB infection (LTBI) if there is no evidence of active TB disease. In low-burden areas, preventive therapy should be targeted at those with documented latent TB infection.
- All patients with HIV-associated TB should receive standard anti-TB therapy and early initiation of antiretroviral therapy..
- Treatment of HIV-associated TB is often complicated by development of immune reconstitution inflammatory disease.
- Co-administration of TB treatment and antiretroviral therapy can be complicated by overlapping drug toxicities and drug-drug interactions.

Table 1

Management of HIV-associated TB[3,11]

Site of Disease	First-line anti-TB regimen[1]	Duration of treatment[2]	Use of steroids	Other Recommendations[3]
Pulmonary	Induction phase: HRZE	2 months	No	
	Continuation phase: HR	4 months	No	
Pleural	Induction phase: HRZE	2 months	No	Thoracentesis for symptomatic relief; surgical debridement for empyema
	Continuation phase: HR	4 months	No	
Lymphadenitis	Induction phase: HRZE	2 months	No	Excision of large or fluctuant lymph nodes may be required
	Continuation phase: HR	4 months	No	
Meningitis	Induction phase: HRZSm	2 months	Yes	Dexamethasone 12mg/kg × 3 weeks, followed by taper over 3–5 weeks; Poor CNS penetration of ethambutol, so replaced by Streptomycin; Fluoroquinolones (moxifloxacin or levofloxacin) can also be used. ART should be delayed due to increased risk of TB IRIS
	Continuation phase: HR	7–10 months	Yes	
Pericardium	Induction phase: HRZE	2 months	Yes	Prednisone (11 wks): 60mg/day × 4wks, 30mg/day × 4wks, 15mg/day × 2wks, then 5mg/day × 1wk Surgery may be required if constrictive pericarditis develops
	Continuation phase: HR	4 months	Yes	
Bone/Joint	Induction phase: HRZE	2 months	No	Surgical decompression of spinal disease in cases of cord compression or spinal instability
	Continuation phase: HR	7 months	No	
Abdominal (peritonitis enteritis)	Induction phase: HRZE	2 months	No	
	Continuation phase: HR	4 months	No	
Urogenital (renal, GU tract)	Induction phase: HRZE	2 months	No	Surgery may be indicated for obstructive uropathy
	Continuation phase: HR	4 months	No	
Disseminated	Induction phase: HRZE	2 months	No	
	Continuation phase: HR	4 months	No	

Note: H, Isoniazid; R, rifampin; Z, pyrazinamide; E, ethambutol; Sm, streptomycin; ART, highly active antiretroviral therapy.

[1] All patients with pulmonary and extrapulmonary TB should receive pyridoxine 50mg daily.

[2] Duration of therapy may be extended in cases of slow clinical response

[3] DOT recommended for treatment of all forms of TB. TMP-SMX recommended throughout course of TB treatment in all HIV-infected patients. Timing of ART initiation based on CD4 cell count and site of disease.

Table 2

Diagnostic Criteria for Immune Reconstitution Inflammatory Syndrome (adapted from Reference 36)

1) Active TB prior to initiation of ART, with initial response to TB treatment, or
2) Onset of TB-related IRIS symptoms within 3 months of ART initiation, re-initiation or regimen change in the setting of treatment failure (Unmasking IRIS).
Patients must meet at least 1 major criterion or 2 minor criteria:
Major criteria:
New or enlarging lymph nodes; cold abscesses or other local tissue involvement.
New or worsening radiological features of TB
New or worsening central nervous system (CNS) tuberculosis
New or worsening serositis
Minor criteria:
New or worsening constitutional symptoms
New or worsening respiratory symptoms
New or worsening abdominal pain with peritonitis, hepatomegaly, splenomegaly, or abdominal lymphadenopathy
3) Exclusion of alternative diagnoses.

Table 3

Management of Drug Interactions between HIV medications and Rifamycins used in TB treatment[61,64]

HIV medication	Rifampin vs Rifabutin*	Interaction	Recommendation
Protease Inhibitors (with ritonavir)			
Lopinavir, fosamprenavir, atazanavir, saquinavir, indinavir, darunavir, and tipranavir	Rifabutin	Modest decreases in PI exposure; ritonavir increases rifabutin exposure, potentially resulting in toxicity	Decrease rifabutin dose to 150 mg every other day; usual PI and ritonavir dose; Rifampin not recommended
NNRTIs			
Efavirenz (EFV)	Rifampin	Rifampin reduces efavirenz exposure by ~25%	No change in dosing; some recommend increasing EFV dose to 800 mg
	Rifabutin	Efavirenz increases rifabutin clearance by 30%–40%	Increase rifabutin dose to 450–600 mg daily (or 600 mg 3 times weekly)
Etravirine (ETV)	Rifabutin	Bidirectional interaction	Use rifabutin 300mg daily; Rifampin or rifapentine not recommended; if ETV given with ritonavir-boosted PI, then do not use rifabutin
Rilpivirine (RVP)	Rifabutin	Rifabutin decreases RVP AUC by 46%	Contraindicated; Rifapmin also contraindicated
Nevirapine (NVP)	Rifabutin	Rifampin reduces nevirapine AUC by 37%–58% and Cmin by 37%–68%	Coadminister at usual doses; Avoid rifampin due to increased virologic failure
Integrase Inhibitors			
Raltegravir (RAL)	Rifabutin	Rifabutin reduces RAL trough by 20%, but RAL AUC is not affected	Administer rifabutin 300 mg daily with RAL 400 mg twice daily; Rifampin not recommended, but if used give RAL 800mg twice daily and monitor virologic response closely
Coreceptor Inhibitor			
Maraviroc (MVC)	Rifabutin	Modest impact of rifabutin on	Administer MVC 300 mg
		MVC exposure likely	twice daily and rifabutin 300 mg daily; Rifampin not recommended but if used increase MVC to

Note: PI, protease inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitors; AUC, area under the curve; Cmax, maximum plasma concentration of drug; Cmin, minimum concentration of drug. Additional information is available at: http://www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/default.htm

*Rifapentine should not be used when co-administered with antiretroviral medications unless in the context of a clinical trial.