ABSTRACT

Tuberculosis (TB) and the human immunodeficiency virus (HIV) are, individually, two of the world's greatest ongoing public health threats. In combination, the two diseases can be even more devastating. Several aspects of human immunodeficiency virus (HIV) infection-related tuberculosis (TB) and its treatment differ from those of TB in HIV-uninfected persons. The human immunodeficiency virus (HIV) pandemic has amplified the global burden of tuberculosis (TB), particularly in sub-Saharan Africa, where 82% of the world’s TB/HIV coinfection exists. HIV infection significantly increases the risk of developing and dying from TB and was associated with 350,000 TB deaths in 2010. Antiretroviral therapy has a profound effect on lowering the risk of TB in HIV-infected persons, but it can also be associated with immune reconstitution inflammatory disease and unmasking of previously subclinical disease. The comanagement of HIV and TB is challenging due to drug-drug interactions, overlapping drug toxicities, concerns about adherence, and the immune reconstitution inflammatory syndrome. However, the initiation of antiretroviral therapy (ART) during the course of TB treatment is necessary to improve survival, and the appropriate timing of ART is dependent on the level of immune suppression. Therefore, the management of TB must be well coordinated with HIV resources, prepared to rapidly diagnose HIV, assess immune status, and correctly treat both infections. In addition a much stronger focus on prevention needs to include concerted action with regard to HIV/AIDS prevention and addressing social determinants of disease such as poverty, malnutrition and overcrowding.

KEYWORDS: HIV/AIDS, Tuberculosis, Epidemiology, Clinical manifestations, Diagnosis Mortality, Treatment.

TUBERCULOSIS

Tuberculosis (TB) infection occurs when a susceptible person inhales droplet nuclei containing Mycobacterium tuberculosis organisms. The immune response usually limits multiplication of tubercle bacilli within 2 to 12 weeks after infection. However, viable bacilli persist for years, a condition referred to as latent TB infection (LTBI). Individuals with LTBI are asymptomatic and are not infectious. TB disease (clinically active disease, often with positive cultures) can develop soon after exposure (primary disease) or after reactivation of latent infection. In individuals with LTBI, the risk of reactivation with TB disease increases very soon after HIV infection.\(^1\)

The estimated annual risk of reactivation with TB disease among those with untreated HIV infection and LTBI is 3% to 16% and approximates the lifetime risk for HIV-uninfected individuals with LTBI (~5%).\(^2\) TB disease can occur at any CD4 T lymphocyte (CD4 cell) count, although the risk increases with progressive immunodeficiency.\(^3\) Antiretroviral therapy (ART) results in a prompt and marked decrease in the incidence of TB disease, an effect that has been documented in settings with low\(^4\) and high case rates.\(^5\) Even with the beneficial effects of ART, HIV-infected patients remain at higher risk of TB disease than the general population.

Clinical manifestations of TB

Pulmonary disease

Although HIV-infected persons with TB may have the classic symptoms of TB (eg, productive cough, chest pain, shortness of breath, hemoptysis, fever, night sweats, and/or weight loss), many such patients have few symptoms or have symptoms that are even less specific than those mentioned. It has been noted recently that a small proportion of HIV infected patients with TB are minimally symptomatic or asymptomatic, particularly in developing countries with a high burden of both HIV infection and TB. In addition, many HIV-infected patients with TB—particularly patients with advanced HIV disease and low CD4+ T lymphocyte counts—have atypical chest radiograph findings. For example, HIV-infected patients with TB are less likely to have cavitary pulmonary disease than are HIV-uninfected patients with TB, and up to 22% of HIV-infected persons with pulmonary TB have normal chest radiograph findings.\(^6\)
Smear-negative pulmonary disease
Consistent with the lower prevalence of cavitary disease, HIV-infected patients with TB have acid-fast smear-negative disease more frequently than do HIV-uninfected persons. Because sputum smear is the principal means of detecting TB in much of the world, smear-negative patients often do not receive a diagnosis and are often not treated promptly, if at all. The mortality rate is higher among such patients than among HIV-infected patients with smear-positive TB (because of delays in TB diagnosis in the former) and higher than among HIV-uninfected persons with smear-negative disease (because of HIV infection).\(^7\)

Subclinical disease.
Because of the aforementioned findings, it should not be surprising that HIV-infected patients with TB may frequently have so-called “subclinical” TB. Such disease is not recognized as TB, resulting in delays in diagnosis and treatment. Often the manifestations of TB do not become apparent until the patient has initiated antiretroviral therapy (see “Effect of Highly Active Antiretroviral Therapy [HAART] on TB Risk and Clinical Manifestations”). The natural history of subclinical TB in HIV-infected persons is not well understood. Unlike individuals without HIV infection, in whom TB may be a chronic, low grade condition, persons with HIV infection almost always experience progression of TB disease, ultimately leading to death in the absence of effective treatment. Thus, subclinical TB may represent the early stages of the disease that will inevitably progress to overt illness.\(^7\)

Extrapulmonary disease
HIV-infected persons are also more likely than HIV-uninfected persons to have extrapulmonary TB, which may or may not occur with concomitant pulmonary disease. Forty percent to 80% of HIV-infected persons with TB have extrapulmonary disease, compared with 10%–20% of HIV-uninfected persons. The risk of extrapulmonary TB increases with lower CD4\(^+\) lymphocyte count. The most common forms of extrapulmonary disease are lymphatic and pleural, but almost any site can be involved, including the bone and/or joint (particularly the thoracic spine), soft tissue (e.g., psoas muscle, which may be associated with spinal disease), central nervous system, and pericardium.\(^7\)

Epidemiology
Tuberculosis in the WHO South-East Asia Region:
One-third of the world’s burden of tuberculosis (TB), or about 4.9 million prevalent cases, is found in the World Health Organization (WHO) South-East Asia Region. The disease, which is most common among people in their productive years,\(^8\) has a huge economic impact. For instance, in 2006, TB caused India to lose an estimated 23.7 billion United States dollars.\(^9\) In a region where one-fourth of the world’s poorest live,\(^10\) TB can lead to catastrophic out-of-pocket expenditure\(^4\) and cause patients to lose an average of 3 to 4 months’ wages due to illness-related absence from work.\(^11\)

TB associated with human immunodeficiency virus (HIV) infection is also an important concern. The age groups most affected by these diseases overlap, and over 50% of those dually affected die.\(^12\) Thus, interventions targeting these individuals must be urgently scaled up.\(^13\) Fortunately, multidrug-resistant TB (MDR-TB) still occurs in fewer than 3% of new cases and 18% of retreatment cases in the region.\(^14\) However, the high TB incidence makes even these low percentages translate into a large number of patients. Extensively drug-resistant TB has also been reported in Bangladesh, India, Indonesia, Myanmar and Thailand.\(^15\)

The region is rising to these enormous challenges. Thanks to the expansion of high-quality TB services, case detection in the region had exceeded 69% by 2008 while treatment success rates have consistently surpassed 85% since 2003. WHO’s Stop TB Strategy, adopted by all countries of the region in 2006, has broadened the scope of services. A comprehensive intervention package for patients with HIV-associated TB is now available to more than 600 million inhabitants. All national TB programmes are establishing MDR-TB case management services. These were first expanded nationwide in Nepal. Thousands of private providers, hundreds of medical schools, corporate institutions, health facilities in non-health sectors and prisons are collaborating with national TB programmes through public-private partnerships.\(^16\)

More than 2 million patients are diagnosed annually by national TB programmes in the region, which thereby contribute greatly to global case detection. India alone notifies nearly 25% of all cases in the world. According to WHO estimates, TB prevalence, incidence and mortality in the region have declined steadily since 1990. However, these efforts will not suffice to achieve the TB targets set under Millennium Development Goal, which are to halve TB prevalence and mortality and reverse TB incidence by 2015.\(^13\)

National TB programmes must focus on immediate challenges. It is estimated that at least one-third of TB patients go undetected or get treated outside national programmes, mostly with poor outcomes. These patients contribute to disease transmission and are at greater risk of developing drug resistance and dying from TB. It is to address these concerns, while recognizing that 60–70% of patients in the region use private health care,\(^16,17\) that national programmes are working with thousands of public and private health-care providers. This initiative needs to be scaled up to ensure that TB services throughout the region comply with international standards for TB care. Preventing further drug resistance also calls for measures to reduce the widespread availability of over-the-counter drugs of uncertain quality and the irrational prescription of anti-TB drugs.
At the same time, strategies to improve communication and social mobilization are needed to overcome the socioeconomic and cultural barriers, such as poverty, stigma, gender inequality and discrimination against migrants, that limit access to TB services despite good geographical access in most parts of the region.\textsuperscript{18,19} National TB programmes must also focus more on research to develop cost-effective interventions, replicate successful approaches and explore the use of newer modalities for diagnosis and treatment that are now becoming available.

Further challenges arise from health systems constraints caused by chronic staff shortages, inadequate laboratory facilities, and weak procurement, supply chains and surveillance systems. These challenges need to be effectively addressed. Doing so would help national TB programmes to depend less on the semi-vertical systems that they established to overcome these constraints, while expanding DOTS programmes, over a decade ago.\textsuperscript{19}

Since the Stop TB strategy was launched, the scope of TB control activities has expanded beyond the capacity of national TB programmes to ensure quality services. Capacity needs to be urgently enhanced to support the rapid expansion of services for patients with MDR-TB and HIV-associated TB. Financial support from the Global Fund to Fight AIDS, Tuberculosis and Malaria and assistance through bilateral donors have served to strengthen capacity within both national programmes and health systems. However, a more sustainable solution calls for prioritizing ways to resolve the health systems constraints faced by all major health programmes through a stronger commitment to using domestic and external funding more effectively to improve health infrastructure, procurement, logistics, and information systems and to increase human resources for health. Weaknesses in oversight and financial management systems that undermine the effectiveness of external aid must be resolved under the stewardship of national governments. WHO, other technical partners and development agencies must support these efforts in the true spirit of the Paris Declaration on Aid Effectiveness.\textsuperscript{20}

IN U.S.
Rates of TB in the United States are declining, with 3.6 new cases per 100,000 population reported in 2010.\textsuperscript{21} (a total of 11,182 cases). The prevalence of LTBI in the general population of the United States is 4%.\textsuperscript{22} The incidence of HIV-related TB has declined more rapidly than the rate of active TB in the general population,\textsuperscript{23} which is probably related to the widespread use of ART. In recent years there have been fewer than 1000 new cases of HIV/TH co-infection identified per year in the United States.\textsuperscript{24,25} As with TB in the general U.S. population, HIV-related TB disease is increasingly seen in people born outside of the United States. Notably, TB disease has not decreased significantly in recent years among foreign-born persons with HIV disease in the United States.\textsuperscript{26} Despite these favorable epidemiological trends, TB remains an important opportunistic illness in the United States. In the era of potent ART, TB disease remained the second most common initial opportunistic illness in New York City.\textsuperscript{27} Unlike most opportunistic infections (OIs), TB is transmissible, particularly to others who are HIV-infected. Therefore, clinicians caring for patients with HIV must remain vigilant in efforts to prevent TB, knowledgeable about the clinical presentation of HIV-related TB, and cognizant of the complexities of cotreatment of HIV and TB.

HIV and tuberculosis in Africa
HIV and epidemiology of tuberculosis in Africa Burden of HIV/AIDS and tuberculosis Figure 23 summarises the disproportionate burden of HIV and tuberculosis infection and disease in Africa at the start of the new millennium. In 2003, an estimated 8-8 million new cases of tuberculosis resulted in 1-7 million deaths. 27% of these cases and 31% of these deaths arose in Africa, home to only 11% of the world’s population. HIV prevalence in tuberculosis patients is less than 1% in the Western Pacific region but 38% in Africa. In countries with the highest HIV prevalence, more than 75% of cases of tuberculosis are HIV-associated.

In Africa, tuberculosis is often the first manifestation of HIV infection, and it is the leading cause of death among HIV-infected patients. In hospital-based series, 40–65% of HIV-infected African patients with respiratory disease had tuberculosis. In primary health and chest clinic settings, tuberculosis was confirmed in 43–70% of adults with cough for 3 weeks or longer (chronic cough) in Zimbabwe, Kenya, and Malawi. Patients with tuberculosis now commonly present with atypical symptoms: M tuberculosis was isolated from 9% of adults with acute pneumonia in Kenya, 35% of people with cough for less than 3 weeks in Malawi, 23% of febrile HIV-infected inpatients in Tanzania, and 13% of HIV-infected patients with chronic diarrhea in Kenya. In Cote d’Ivoire, the Democratic Republic of Congo, and Kenya, 38–47% of autopsies in HIV-positive adults indicated tuberculosis as the cause of death, although tuberculosis had been diagnosed during life in only about half of those with autopsyproven disease. Increased risk for tuberculosis from HIV infection in Africa Comparison of HIV prevalence in general populations and tuberculosis patients shows that tuberculosis incidence was 8-3 times higher in HIV-positive than HIV-negative African people in 2003. In 2000, similar methods led to an estimated relative rate of 5-9, whereas estimates from individual cohort studies range from less than 5 to more than 20.3 Tuberculosis incidence increases with worsening immunosuppression, so that relative rates rise during the course of an HIV epidemic.

Tuberculosis incidence in African countries with high HIV prevalence Reported tuberculosis case rates rose by 6-4% per year in the WHO African region in the late 1990s,4 but with up to five-fold increases since 1990 in
some countries. Incidence might have peaked in some countries 18 but at very high rates. The high case rate in Africa contributed to a global rise in tuberculosis incidence of 1% in 2003, despite stable or declining rates in the rest of the world. Southern Africa has the highest prevalence of HIV infection and had the highest incidence of tuberculosis before the HIV/AIDS era. In the six southern African countries with adult HIV prevalence of more than 20%, tuberculosis case-notification rates are 461–719 per 100,000 per year; by comparison, the notification rate in the USA was 5 per 100,000 per year. True yearly rates in Africa are likely to be even higher because of under-diagnosis and under-reporting.\(^{18}\)

**TB Reactivation by HIV**

It is generally thought that one-third of the world's population is latently infected with *M. tuberculosis*.\(^{29}\) although the data supporting this notion may be questioned. Also, the rate of progression from infection to disease varies greatly. Approximately 10% of *M. tuberculosis*-infected individuals are thought to develop overt clinical disease and about half of them develop disease more than two years after infection; these cases are commonly named “reactivation” or post-primary TB.\(^{30}\) Thus, the lifetime risk of developing active TB in immunocompetent adults is estimated to be 5%–10% during their lifetime, but in HIV-positive individuals this risk is increased to 5%–15% annually.\(^{31}\)

The depletion of CD4\(^+\) T cells, which is a main feature of AIDS, is certainly an important contributor to the increased risk of reactivation of latent TB and susceptibility to new *M. tuberculosis* infection. There is also some evidence that CD8\(^+\) T cells play a role in the control of latent TB.\(^{32,33,34,35}\) Other mechanisms reported to facilitate *M. tuberculosis* infection and disease in individuals with HIV are up-regulation of *M. tuberculosis* entry receptors on macrophages,\(^{36}\) HIV manipulation of macrophage bacidal pathways,\(^{37}\) deregulated chemotaxis,\(^{38}\) and a tipped Th1/Th2 balance.\(^{39,40}\) It has also been shown that HIV impairs tumor necrosis factor (TNF)-mediated macrophage apoptotic response to *M. tuberculosis* and thus facilitates bacterial survival.\(^{41}\)

In the latent phase of TB, the bacteria are not completely eradicated despite a seemingly robust Th1 immune response. A failure or an alteration of the quality or levels of the protective adaptive immune responses or of the cross-talk with innate immune responses leads to reactivation of infection. Several immune mechanisms, such as increased levels of FoxP3* Treg cells,\(^{42}\) increased production of IL-27,\(^{43}\) TGF-β,\(^{44} PGE-2,\(^{45}\) SOCS1, or the decoy receptor D6,\(^{46}\) or diminished levels of IFN-γ, TNF, and polyfunctional specific T cells, are believed to play a role in such reactivation. Many of these factors, such as SOCS1 or IL-27, down-regulate the IFN-γ/IL-12 axis, thereby impairing bacterial control, while others, such as the D6 decoy receptor, are mainly anti-inflammatory, but may indirectly inhibit efficient bacterial clearance. Some of these mechanisms may also underlie HIV-infected patients' increased susceptibility to active TB.

Granulomas are organized cellular structures that constitute TB's pathologic hallmark. Mycobacteria are contained within the granuloma, which, by localizing infection and thus potentially preventing spread of the disease between hosts, probably contributes to protection. CD4\(^+\) T cells and TNF are important in maintaining granuloma organization. Granuloma formation may fail in individuals with a compromised immune system, and there are several hypotheses about how HIV exacerbates TB pathology through the manipulation of granulomas.\(^{46}\) Specifically, TB patients with AIDS present a dominant granulocytic infiltrate and necrosis without the typical caseous necrosis seen in non-HIV-infected TB granulomas. This has been associated with the killing of CD4\(^+\) cells in the granuloma, probably resulting in a direct disruption of granuloma structure and abolition of the containment of infection. Cavitary lesions are seldom encountered in patients with a CD4 T-lymphocyte count <200/mm.\(^{47}\)

As a result, while in the majority of adult patients TB is confined preferentially to the lungs, in HIV-infected patients TB can be a systemic disease involving multiple organs that lack well-defined granulomas and instead develop more diffuse lesions.\(^{48}\) All forms of extrapulmonary TB have been described in patients with HIV.

In macaques, SIV induces distortions in pro-inflammatory and anti-inflammatory T cell responses within the granuloma that may have significant effects on reactivation of latent TB. Reduction of T cell numbers also occurred within lung granulomas of monkeys co-infected with SIV compared with monkeys exclusively infected with TB.\(^{49}\) It is important to note that besides the known increased risk of disseminated disease in adults with HIV, there is a growing recognition from prevalence surveys of subclinically active TB infection in co-infected individuals.\(^{50}\)

**HIV associated TB and Mortality**

Patients with HIV-TB have high mortality risk and TB is a leading cause of death in HIV-infected patients in TB endemic countries, including those with free access to ART such as in Brazil. TB is also associated with an increased risk of AIDS-related deaths in men and women living in the United States. WHO estimates that there were a total of 456,000 HIV-TB deaths in 2007. This numbers equates to 33% of the number of incident HIV-TB cases that year. Moreover, this represents 23% of the estimated 2 million deaths from HIV/AIDS in 2007. Such deaths are routinely classified as ‘HIV deaths’ rather than ‘TB deaths’ in the International Statistical Classification of Diseases (ICD-10).\(^{51}\)
Deaths from HIV-TB have exacted a huge toll on the worst-affected communities in sub-Saharan Africa. In a rural South African community with high HIV prevalence, there has been an increasing trend in TB mortality since 1994 in HIV-infected but not HIV-uninfected TB patients, especially in young adults. In recent years the excess HIV-TB mortality has been 1.6-fold greater in women compared to men. Observed regional differences in death rates in Ugandan and Malawian patients with HIV-TB are likely due to differences in patient age and stage of HIV epidemic.\[54\]

Consistent with previous randomized clinical trials, cotrimoxazole prophylaxis significantly reduced mortality risk in HIV-infected pulmonary TB patients in Zambia. Together with post-mortem data from South Africa, these data highlight bacterial sepsis as a likely frequent cause of death in these patients.\[55\]

**Diagnosis of Tuberculosis Infection**

Initial diagnostic testing is directed at the anatomic site of symptoms or signs, such as the lungs, lymph nodes, and cerebrospinal fluid (CSF). Even in the absence of pulmonary symptoms or signs, the initial evaluation of a patient suspected of having HIV-related TB should always include a chest radiograph; pulmonary involvement is common whatever the CD4 cell count.\[32\]

However, chest radiography is an imperfect screen for sputum culture-positive TB, particularly in patients with advanced immunodeficiency. Therefore, sputum smear and culture should be considered in symptomatic patients with normal chest radiographs who are being evaluated for possible TB disease. Sputum smear-negative TB is common in HIV-infected patients, particularly those with advanced immunodeficiency and noncavitary disease.\[53\]

However, the yield of sputum mycobacterial culture is not affected by HIV or the degree of immunodeficiency. If a sensitive broth culture technique is used, the sensitivity of sputum culture is quite high. Smear and culture of three sputum specimens is recommended, in that there was a 10% incremental yield for broth culture between the second and third specimens in a recent large study of patients with HIV.\[56\]

Nodal involvement is common in HIV-related TB, and the combined yield of histopathology, smear, and culture from needle aspirates of enlarged lymph nodes is quite high.\[33\] Pleural fluid, pericardial fluid, ascites, and CSF should be sampled if there is clinical evidence of involvement. The yield of mycobacterial urine and blood cultures depends upon the clinical setting; in patients with advanced immunodeficiency, the yield of culture from these two readily available body fluids can be relatively high and may allow definitive diagnosis and a source for an isolate for drug-susceptibility testing. Nucleic-acid amplification (NAA) tests provide rapid diagnosis of TB, in contrast to the prolonged time needed for detection of mycobacterial growth, and can be considered for patients with advanced immunodeficiency who are at risk of rapid clinical progression of TB.\[57\]

**Treatment**

Treatment of suspected TB in HIV-infected individuals is the same as for those who are HIV uninfected and should include an initial four-drug combination of isoniazid, rifampin, pyrazinamide and ethambutol. An expanded initial regimen including at least moxifloxacin or levofloxacin and an aminoglycoside or capreomycin should be used if there is a significant concern about resistance to rifampin, with or without resistance to other drugs. A TB expert should be consulted if drug resistance is suspected.\[31\]

DOT is recommended for all patients with suspected HIV-related TB. The likelihood of treatment success is further enhanced with comprehensive case management, assistance with housing and other social support, and assistance in establishing or re-engaging with HIV care, if needed (i.e., enhanced DOT). Drug-susceptible TB is treated with a 2-month intensive phase of the 4 drugs previously listed. Ethambutol can be discontinued when susceptibility to isoniazid and rifampin has been confirmed. Pyrazinamide may be discontinued after 2 months. Thereafter, isoniazid and a rifamycin are used in the continuation phase of therapy. Intermittent dosing (administration less often than daily) of anti-TB treatment facilitates DOT. However, regimens that included twice- or thrice-weekly dosing during the intensive phase have been associated with an increased risk of treatment failure or relapse with acquired drug resistance to the rifamycin class. Therefore, daily therapy (5–7 days per week) given as DOT is recommended during the intensive phase. Daily (5–7 days per week) or thrice-weekly dosing is recommended during the continuation phase of therapy. Regimens that included once- or twice-weekly dosing during the continuation phase of therapy were associated with increased risk of treatment failure or relapse with acquired rifamycin resistance. Whether there is a difference between daily and thrice-weekly dosing during the continuation phase of therapy has not been adequately studied in randomized trials; in observational studies and a meta-analysis, thrice-weekly therapy during the continuation phase was not associated with an increased risk of adverse TB outcomes (i.e., treatment failure, recurrence, or acquired drug resistance).\[51\]

The optimal duration of TB treatment for patients with HIV infection and drug-susceptible TB disease is unknown. In general, the outcomes have been good with 6-month regimens (2 months of isoniazid, rifampin, pyrazinamide, and ethambutol, followed by 4 months of isoniazid and rifampin) given as DOT to patients with HIV co-infection. A randomized trial in the United States showed excellent and comparable outcomes of TB therapy among patients assigned to 6 months or 9 months of therapy, but the trial was underpowered. Two trials in high-burden settings showed higher risks of recurrent TB among patients treated with 6 months of therapy compared with those assigned to 9-76 or 12-month regimens. However, the applicability of these two trials...
is uncertain in low-burden settings in which ART is used, such as the United States. Pending the outcome of further studies, 6 months of therapy for most patients with HIV-related, drug-susceptible TB disease is recommended. Extension of therapy to 9 months is recommended for those with a positive 2-month sputum culture. Extension of therapy to 9 to 12 months is also recommended for patients with CNS involvement. Treatment for 6 to 9 months is recommended for patients with bone and joint TB.\[51\]

The duration of therapy should be based on number of doses received, not on calendar time because there may be substantial differences between dose number and calendar time if doses were missed due to poor adherence or for management of problems with tolerability or toxicity. Adjunctive corticosteroid therapy increases survival for patients with HIV-related TB involving the CNS\[84\] and pericardium. No trials to date have compared different doses and treatment durations of adjunctive corticosteroids. Dexamethasone was used in trials of adjunctive corticosteroids for CNS disease (0.3–0.4 mg/kg/day for 2–4 weeks, then taper 0.1 mg/kg per week until dose of 0.1 mg/kg, then 4 mg per day and taper by 1 mg/week; total duration of 12 weeks); prednisone or prednisolone was used in trials of pericardial disease (60 g/day and taper 10 mg per week; total duration of 6 weeks).\[51\]

### Treatment for TB in HIV positive patients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily</th>
<th>3x/week</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isoniazid</strong></td>
<td>5 mg/kg (usual dose 300 mg)</td>
<td>15 mg/kg (usual dose 900 mg)</td>
</tr>
<tr>
<td><strong>Rifampin</strong></td>
<td>10 mg/kg (usual dose 600 mg)</td>
<td>10 mg/kg (usual dose 600 mg)</td>
</tr>
<tr>
<td><strong>Rifabutin</strong></td>
<td>5 mg/kg (usual dose 300 mg)</td>
<td>5 mg/kg (usual dose 300 mg)</td>
</tr>
<tr>
<td>without HIV PI's, Efavirin (EFV), or RPV</td>
<td>150 mg(^a)</td>
<td>300 mg(^b)</td>
</tr>
<tr>
<td>with EVG/COBI/TDF/FTC</td>
<td>450-600mg</td>
<td>450-600mg</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>1000 mg (18.2–25.0 mg/kg)</td>
<td>1500 mg (27.3–37.5 mg/kg)</td>
</tr>
<tr>
<td>(weight-based dosing)</td>
<td>1500mg (20.0–26.8 mg/kg)</td>
<td>2500 mg (33.3–44.6 mg/kg)</td>
</tr>
<tr>
<td>56–75 kg</td>
<td>2000 mg (22.2–26.3 mg/kg)</td>
<td>3000 mg (33.3–39.5 mg/kg)</td>
</tr>
<tr>
<td>76-90 kg</td>
<td>2000mg(^c)</td>
<td>3000 mg(^c)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>800 mg (14.5–20.0 mg/kg)</td>
<td>1200 mg (21.8–30.0 mg/kg)</td>
</tr>
<tr>
<td>(weight-based dosing)</td>
<td>1200 mg (16.0–21.4 mg/kg)</td>
<td>2000 mg (26.7–35.7 mg/kg)</td>
</tr>
<tr>
<td>56–75 kg</td>
<td>1600 mg (17.8–21.1 mg/kg)</td>
<td>2400 mg (26.7–31.6 mg/kg)</td>
</tr>
<tr>
<td>76-90 kg</td>
<td>1600 mg(^c)</td>
<td>2400 mg(^c)</td>
</tr>
</tbody>
</table>

---

**Notes:**

- Acquired rifamycin resistance has been reported in patients with inadequate rifabutin levels while on 150 mg twice weekly dosing together with ritonavir-boosted PIs. May consider therapeutic drug monitoring when rifabutin is used with a ritonavir-boosted PI and adjust dose accordingly.

- Avoid co-administration of EVG/COBI/TDF/FTC with rifabutin, if possible. If used together, consider therapeutic drug monitoring and adjust dose accordingly.

- Monitor for therapeutic response and consider therapeutic drug monitoring to assure dosage adequacy in patients who weigh >90 kg.

### Drug-drug interactions in the treatment of HIV-related tuberculosis

The rifamycin class of antibiotics is the key to effective, short-course TB treatment. However, the rifamycins currently available (rifampin, rifabutin, and rifapentine) have clinically significant interactions with a number of ARV drugs. These drug-drug interactions are complex,
but most result from the potent induction by the rifamycins of genes involved in the metabolism and transport of ARV agents. The preferred cotreatment regimen for HIV-related TB disease is rifampin-based TB therapy with an ARV regimen of efavirenz plus two nucleoside(tide) analogues. Efavirenz-based ART is associated with excellent TB and HIV treatment outcomes and has low rates of serious toxicity.57

Rifampin has a more significant effect on the concentration of nevirapine, but clinical outcomes have been reasonably good among patients on a co-treatment regimen of rifampin-based TB treatment with an ARV regimen of nevirapine plus two nucleoside analogues.58 However, a recent randomized controlled trial showed that a once daily nevirapine regimen used with didanosine and lamivudine was inferior to a once daily efavirenz regimen used with the same NRTIs in HIV-associated TB treated with a rifampin regimen. For patients absolutely unable to take efavirenz due to intolerance or early pregnancy, nevirapine-based ART can be used, but the lead-in dose of nevirapine should be omitted for patients who are established on rifampin for at least 2 weeks and plasma HIV RNA levels should be monitored closely.58

For patients who have HIV strains resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs) or are unable to tolerate efavirenz and nevirapine, the preferred co-treatment regimen is rifabutin-based TB therapy with an ARV regimen that includes a ritonavir-boosted protease inhibitor (PI). The dramatic effects of rifampin on serum concentrations of lopinavir can be overcome by high-dose ritonavir59, but high rates of hepatotoxicity have been reported when adjusted ritonavir-boosted PIs were given with rifampin to healthy volunteers. Rifabutin has little effect on ritonavir-boosted lopinavir or atazanavir, and its co-administration results in moderate increases in darunavir and fosamprenavir concentrations.60

However, all PIs markedly increase serum concentrations of rifabutin (and one of its principal metabolites, desacetyl-rifabutin). Therefore, the dose of rifabutin must be decreased to avoid dose-related toxicity, such as uveitis.59

Special Considerations with Regard to Starting ART
Optimal management of HIV-related TB requires that both infections be addressed; sequential treatment of TB followed by HIV treatment is not recommended. Co-treatment of HIV and TB is complex because of the adherence demands of multidrug therapy for two infections, drug-drug interactions between the rifamycins and many ARV drugs, overlapping side effect profiles of antituberculosis and ARV drugs, and the frequency of immune reconstitution inflammatory syndrome (IRIS). Despite these substantial clinical challenges, co-treatment of HIV-related TB improves survival, particularly in patients with CD4 counts <50 cells/mm3; decreases the risk of additional opportunistic illnesses including TB; can achieve high rates of viral suppression; and may improve TB treatment outcomes.

Starting ART early in the course of TB treatment can complicate clinical management because of increased pill burden, drug toxicities, drug interactions, and IRIS events. However, recently completed randomized clinical trials demonstrate that ART can be safely given during TB treatment without jeopardizing HIV treatment responses and that ART reduces mortality and HIV-related illnesses.

CONCLUSION
HIV-TB accounts for a huge burden of morbidity and mortality, which, in light of revised WHO estimates in 2009, has previously been underestimated. The African continent bears the brunt of the vast majority of this disease burden and associated mortality. However, rates are also increasing in some middle- and high-income countries.

There should monitor the patient regarding compliance with ATT medication. Improving medication adherence and preventing exposures can reduce the prevalence of Tuberculosis among the people living with HIV/AIDS. There should be early detection of HIV associated Tuberculosis and patient follow-up to avoid drug resistance.

Monitoring of drug-drug interactions can reduce the pill burdening and mortality associated with adverse drug reactions.

In addition a much stronger focus on prevention needs to include concerted action with regard to HIV/AIDS prevention and addressing social determinants of disease such as poverty, malnutrition and overcrowding. To accelerate progress towards epidemiological impact targets, HIV-TB must move up the global public health agenda with increased resource allocation and concerted international action.

REFERENCES


56. Shriner KA, Mathisen GE, Goetz MB. Comparison of mycobacterial lymphadenitis among persons


