Perspective

Current Issues in the Diagnosis and Management of Tuberculosis and HIV Coinfection in the United States

Approximately 10% of new cases of tuberculosis (TB) in the United States occur in HIV-infected persons. HIV infection dramatically increases the risk of TB, and this increased risk is present throughout the course of HIV infection. TB and HIV coinfection complicates the course and treatment of both diseases. Isoniazid preventive therapy and antiretroviral therapy both substantially reduce the risk of developing active disease in persons with latent TB infection. Antiretroviral therapy should be given during treatment for active TB, as mortality was reduced by 56% with initiation of antiretroviral therapy before the completion of TB therapy. In addition, for patients with low CD4+ cell counts (<200/µL), starting antiretroviral therapy during the intensive phase of TB treatment reduced mortality by 34% compared with delaying antiretroviral therapy until 8 weeks after TB treatment initiation. This article summarizes a presentation by Anne F. Luetkemeyer, MD, at the International AIDS Society–USA continuing medical education program held in May 2010 in San Francisco.

In 2008, 1.37 million new cases of tuberculosis (TB) occurred in HIV-infected persons worldwide, with an estimated nearly half-million deaths due to TB in HIV-infected individuals (World Health Organization, 2009). Prevalence rates of TB in HIV infection are highest (≥50%) in areas of sub-Saharan Africa, and are substantial in many other locales worldwide (Figure 1). Globally, TB is one of the most frequent causes of mortality in HIV disease, accounting for an estimated one-third of AIDS-related deaths in some series. Extraordinarily high mortality rates are associated with multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB in HIV coinfection.

In the United States, an 11.4% decrease was reported in TB incidence in 2009 from 2008, although this figure may represent underreporting (Centers for Disease Control and Prevention, MMWR, 2010). Approximately 50% of new TB cases occurred in California, New York, Florida, and Texas. HIV coinfection is present in approximately 10% of new TB cases, and the rate of coinfection has plateaued over the past several years after gradually decreasing through the 1990s (Figure 2). One of the drivers of TB infection is reactivation disease in foreign-born individuals, which accounts for up to 77% of active infections (Cattamanchi et al, Int J Tuberc Lung Dis, 2006). Nationwide, 60% of TB cases occurred in foreign-born individuals, exceeding the TB rate in individuals born in the United States. Since 2003, the TB rate in US-born individuals has declined more rapidly than the rate in the foreign-born population (Figure 3). Effective diagnosis and treatment of latent TB infection (LTBI) in at-risk individuals is key for TB reduction in the United States. Ongoing challenges to implementation of current US guidelines for diagnosis and treatment of LTBI have limited effective LTBI therapy (Walter et al, Clin Infect Dis, 2008). These data suggest that TB in the United States is here to stay and will continue to be a concern for high-risk populations such as those infected with HIV.

Bidirectional Effects of Tuberculosis and HIV Coinfection

Coinfection with HIV may worsen the course and complicate the diagnosis and management of TB. The effects of HIV infection on TB include altered clinical presentation, such as increased paucibacillary and disseminated TB, which increases the challenge of making an accurate and timely diagnosis.

Throughout the course of HIV disease, there is an increased risk of acquisition of, reactivation of, and reinfection with TB, despite treatment with antiretroviral drugs (Havlir et al, JAMA, 2008). Overall, HIV-infected patients have an estimated 20- to 37-fold higher risk of acquiring TB than do HIV-uninfected persons, and this risk remains elevated throughout the course of HIV disease. There is an estimated 2-fold greater risk of TB acquisition at the time of HIV seroconversion and a continuous increase in risk during CD4+ cell count decline. Patients with CD4+ cell counts less than 100/µL have a nearly 10 times higher risk of acquiring TB than do patients with counts greater than 500/µL, despite effective antiretroviral therapy (Lawn, Myer et al, AIDS, 2009). TB risk increases during the months immediately following antiretroviral therapy initiation, likely as the result of unmasking of unrecognized subclinical disease. Thereafter, the risk of acquiring TB decreases during effective antiretroviral therapy but never returns to the level of risk in HIV-uninfected persons (Lawn, Myer et al, AIDS, 2009; Lawn et al, AIDS, 2006).

The effects of TB on HIV infection include an increase in HIV viral load (reported in some but not all studies), further suppression of CD4+ cell count, increased risk of opportunistic infections, and increased mortality. High early mortality in TB and HIV coinfection, particularly at low CD4+ cell counts, has been observed despite antiretroviral therapy in resource-limited settings (Lawn, Little, et al, AIDS, 2009). Further, overlapping toxicities of drugs used to treat TB and HIV infections complicate delivery of effective therapy.

Dr Luetkemeyer is assistant professor of medicine at the University of California San Francisco.
Preventive Therapy in Latent Tuberculosis Infection


Isoniazid preventive therapy (IPT) and antiretroviral therapy are effective in preventing active TB in patients with LTBI. For example, a retrospective study in an observational cohort in Brazil (total of >17,000 person-years) demonstrated that risk of TB in HIV-infected patients was reduced by 52% with antiretroviral therapy alone, 68% with IPT alone, and 80% with both (Golub et al, *AIDS*, 2007). In the Haitian CIPRA (Comprehensive International Program of Research on AIDS) HT001 trial, antiretroviral therapy initiation was associated with a 50% reduction in TB incidence (Severe et al, *N Engl J Med*, 2010). A systematic review reported a 32% risk reduction for TB with isoniazid in HIV coinfection (Akololo et al, *Cochrane Database Syst Rev*, 2010). Isoniazid has been associated with reduced mortality when added to antiretroviral therapy in some epidemiologic settings; data from a South African cohort showed a further 53% reduction in mortality when isoniazid was added to antiretroviral therapy compared with antiretroviral therapy alone (Innes, CROI, 2010). Also, IPT has not been convincingly associated with the emergence of isoniazid resistance (Balcells et al, *Emerg Infect Dis*, 2006). Isoniazid treatment is generally safe and well tolerated, although monitoring is recommended particularly for patients with hepatic dysfunction.

Diagnosis of Latent Tuberculosis Infection

Tuberculin skin testing with purified protein derivative (PPD), the historical standard for diagnosing LTBI, has many limitations. These include a dependence on the operator for correct administration and interpretation of the test, an association with false-positive results stemming from cross-reactivity with nontuberculous mycobacteria, and the requirement for a return patient visit within a specified time window for results to be read. In many US urban clinics, the return visit rate for TST interpretation may be as low as 35% (Chaisson et al, *J Acquir Immune Defic Syndr* Hum Retrovirol, 1996).

Interferon gamma (IFN-γ) release assays (IGRAs) are alternative tests for LTBI diagnosis. IGRAs measure levels of IFN-γ released after incubation with mycobacterial antigens that are more specific to *Mycobacterium tuberculosis* than those used in the TST. Two IGRAs are approved by the US Food and Drug Administration for commercial use in the United States; one assay measures free IFN-γ and the other, an enzyme-linked immunosorbent spot (ELISPOT)-based assay, measures IFN-γ-releasing cells. Unlike for the TST, IGRAs do not currently have different cutoff values based on TB risk categories, including HIV infection. Therefore, results are given simply as positive, negative, or indeterminate. Some false-positive results have been observed in *M kansasii*.
infection, as the RD1-encoded antigens used in IGRAAs are also found in M. kansasi. No cross-reactivity with bacille Calmette-Guérin has been observed. The estimated specificity of both types of commercial assay is 98% or greater in low-TB-prevalence settings, and the assays appear to perform at least as well as TSTs in this setting (Pai et al, J Biosci Bioeng, 2004; Chapman et al, AIDS, 2002; Pathan et al, J Immunol, 2001).

Clinicians need to recognize that an indeterminate result on an IGRA means that the result cannot be interpreted because of either an inability of the antigen to stimulate cells or an excessive background IFN-γ level. An indeterminate result does not suggest that the test is likely negative or positive. The test can be repeated, which may yield an interpretable result. However, if a second result is indeterminate, further IGRA testing is not advisable until there has been a change in the patient’s immune status (eg, after initiating antiretroviral therapy). A second indeterminate result should be followed with a TST or, if there is concern regarding active pulmonary TB, a chest x-ray. In patients with HIV infection, both types of IGRA are more likely to yield indeterminate results at lower CD4+ cell counts, with estimated frequencies of indeterminate results of 15% to 16.5% at counts less than 100/µL and 8% to 11% at counts of 100/µL to 200/µL (Hoffmann and Ravn, Eur Infect Dis, 2010). However, positive or negative results from IGRA testing in patients with lower CD4+ cell counts are considered reliable for use in clinical decision making.

**Active Tuberculosis Infection**

The clinical presentation of TB in HIV infection is affected by the degree of underlying immune suppression. At CD4+ cell counts greater than 350/µL, TB disease is most often limited to the lungs, histopathologic results are similar to those in HIV-seronegative patients (ie, granuloma with or without caseation), and extrapulmonary involvement, when present, usually is nodal or pleural (Burman and Jones, Semin Respir Infect, 2003). In advanced HIV infection, pulmonary involvement is still the most common TB presentation; however, extrapulmonary involvement is observed in approximately 70% of patients with CD4+ cell counts less than 100/µL, and up to 50% of those with CD4+ cell counts greater than 50/µL will have positive TB blood cultures. Histopathologic examination reveals poorly formed or absent granuloma. On radiography, classic findings such as cavities are less common with CD4+ cell counts less than 350/µL, and up to 21% of patients have a chest x-ray that appears normal despite sputum that is TB culture–positive (Chamie et al, Int J Tuberc Lung Dis, 2010; Burman and Jones, Semin Respir Infect, 2003).

With regard to testing, negative TST or IGRA results cannot rule out active TB. IGRA testing, for example, has a sensitivity for active disease that ranges from 80% to as low as 60% in some studies. Negative results from sputum smears also do not rule out TB, particularly in HIV infection; 50% to 62% of HIV-infected patients with positive results from pulmonary TB culture have negative acid-fast bacillus (AFB) smear results (Monkongdee et al, Am J Respir Crit Care Med, 2009; Getahun et al, Lancet, 2007). Although associated with a lower TB burden, untreated smear-negative pulmonary TB is a well-documented source of TB transmission (Tostmann et al, Clin Infect Dis, 2008; Hernández-Garduño et al, Thorax, 2004; Behr et al, Lancet, 1999). Even the gold standard of culture for TB can be imperfect; culture-negative clinical TB is a well-recognized entity. Thus, clinical suspicion for TB is essential in appropriately diagnosing and excluding TB in HIV infection.

Rapid TB diagnostic tests have been developed, including nucleic acid–based tests that can detect both TB and rifampin resistance with results available in less than 1 day; these will be extremely useful for HIV patients, in whom AFB smear is particularly

---

**Figure 2.** Estimated percent of HIV coinfection in persons reported with tuberculosis in the United States, 1993-2008. Adapted from Centers for Disease Control and Prevention, 2009.

**Figure 3.** Number and rate of tuberculosis (TB) cases in US-born and foreign-born persons in the United States from the National TB Surveillance System. Data from 2009 are provisional. Adapted from Centers for Disease Control and Prevention, MMWR, 2010.
Issues in the Treatment of Tuberculosis and HIV Coinfection

Recommendations for treatment of drug-susceptible TB in HIV-infected patients are essentially the same as for HIV-uninfected patients, with a standard 6-month rifamycin-based regimen that is extended to 9 months in cases of delayed clinical or microbiologic response (as indicated by positive culture or continued symptoms at 2 months). Patients with CD4+ cell counts less than 200/µL should receive daily therapy (Burman, Clin Chest Med, 2005).

Recent data have helped clarify the optimal timing for initiating antiretroviral therapy in patients being treated for TB. The SAPIT (Starting Antiretroviral Therapy at Three Points in Tuberculosis Therapy) trial in South Africa demonstrated that antiretroviral therapy should not be deferred until TB treatment is completed. Virologic response was not compromised and mortality was reduced by 56% when antiretroviral therapy was initiated before completion of TB therapy (Abdool Karim et al, N Engl J Med, 2010). The mortality benefit was observed for patients with CD4+ cell counts less than 200/µL as well as for patients with counts greater than 200/µL, although few deaths occurred in the latter group.

The recently reported CAMELIA (Cambodian Early Versus Late Introduction of Antiretrovirals) study found—in AFB-smear-positive, HIV-infected patients with CD4+ cell counts less than 200/µL—a mortality benefit in starting antiretroviral therapy 2 weeks after TB treatment initiation versus waiting 8 weeks to start. The CAMELIA study population had very low CD4+ cell counts, with a median of 25/µL, and the majority of subjects had counts less than 50/µL (Blanc et al, IAC, 2010). As expected, earlier initiation of antiretroviral therapy was associated with more than twice the rate of TB immune reconstitution syndrome (IRIS; incidence per 100 person-months, 4.05 vs 1.44; P < .001). Given these data, initiation of antiretroviral therapy shortly after the start of TB treatment appears safe and efficacious and may decrease mortality, particularly in those with advanced HIV disease, despite the association with an increased risk of IRIS. Ongoing trials such as ACTG (AIDS Clinical Trials Group) 5221 and the immediate– versus early–antiretroviral therapy initiation groups of SAPIT may help further clarify optimal timing for antiretroviral therapy initiation (eg, whether concomitantly with TB therapy or after the intensive phase of 4-drug TB therapy has been completed) for patients with less severely depressed CD4+ cell counts.

Rifamycins (eg, rifampin, rifabutin) are key to effective TB therapy, but use of these drugs is complicated by HIV coinfection. HIV-infected patients may be more prone to the emergence of rifamycin resistance than HIV-seronegative persons, particularly if dosing is inadequate or intermittent (Swaminathan et al, Clin Infect Dis, 2010). In addition, rifamycins have important drug interactions with many antiretroviral drugs. For example, in terms of interactions with nonnucleoside analogue reverse transcriptase inhibitors (NNRTIs), rifampin reduces the area under the concentration-time curve (AUC) to 78% of normal for efavirenz and 69% of normal for nevirapine. Efavirenz may be preferable for use with rifampin because of the somewhat greater effect of rifampin on nevirapine drug levels and concern over subtherapeutic exposure to nevirapine in patients already receiving rifampin.

In a South African study, efavirenz-based antiretroviral therapy (at standard 600-mg dosing) for non–TB-infected patients was associated with virologic outcomes that were similar to those observed for rifampin-treated TB patients, whereas nevirapine treatment was associated with inferior virologic suppression when coadministered with rifampin (Boull et al, JAMA, 2008). Although some investigators recommend an increase of efavirenz to 800 mg when coadministered with rifampin, several studies have demonstrated that the 600-mg dosage allows for adequate levels of efavirenz in the majority of patients and provides HIV virologic suppression equivalent to that in non–TB-infected patients. Rifabutin is an alternative to rifampin but must be administered at higher doses, which may lead to increased adverse effects.

If NNRTIs cannot be used (eg, because of drug resistance, pregnancy, or HIV-2 infection), protease inhibitors (PIs) are an option. Rifampin, however, dramatically reduces PI AUC and trough concentrations. Attempts to overcome this effect by increasing ritonavir or other PI dosage have resulted in considerable toxicity including hepatitis. Thus, use of rifampin with PIs is not currently recommended if other options are available.

In contrast, rifabutin results in modest increases in AUC and trough values (10% to 20%) of the PIs. Thus, the current recommendation for patients receiving ritonavir-boosted PIs is to reduce the rifabutin dose from 300 mg daily to 150 mg 3 times per week, keeping in mind that this dose of rifabutin is inadequate if PI therapy is discontinued. However, accumulating reports describe well-documented, acquired rifamycin resistance when rifabutin has been administered at 150 mg every other day in conjunction with ritonavir-boosted PIs (Boulanger et al, Clin Infect Dis, 2009; Jenny-Avital and Joseph, Clin Infect Dis, 2009). Thus, higher doses of rifabutin may be indicated for patients receiving ritonavir-boosted PIs. Many clinics are now using rifabutin 150 mg daily for such patients while the ideal rifabutin dosing for coadministration with PIs is reexamined.

Raltegravir may be an option for antiretroviral treatment during TB therapy. As rifampin reduces the AUC and trough values of raltegravir (Wenning et al, Antimicrob Agents Chemother, 2009), the current recommendation is to increase raltegravir dosage to 800 mg.
twice daily. It is unclear if this dose adjustment is clinically necessary, and studies evaluating drug–drug interactions between raltegravir and rifampin are currently under way. Regarding nucleoside analogue reverse transcriptase inhibitors (nRTIs), these drugs do not have substantial drug–drug interactions with rifamycins.

New drugs are in development that may eventually offer the option of shortening TB therapy and increasing its effectiveness. The investigative adenosine triphosphate synthetase inhibitor TMC-207 has shown a 2-month culture conversion rate for MDR-TB of 48% compared with 9% for optimized background therapy (Diacon et al, N Engl J Med, 2009), and a number of novel TB drugs are in development (including PA-824, OPC-67683, and SQ109).

**Immune Reconstitution Inflammatory Syndrome**

TB IRIS appears to comprise 2 distinct syndromes. Paradoxical IRIS, consists of a worsening of TB despite effective TB treatment and often is observed in the context of initiation of antiretroviral therapy. The other form is called unmasking IRIS, which consists of a new presentation of TB (or other opportunistic infection) after antiretroviral therapy initiation, often with an atypical or exaggerated presentation (Meintjes et al, Lancet Infect Dis, 2008). The risk of IRIS increases the lower the CD4+ cell count and the shorter the time between the initiation of TB therapy and the initiation of antiretroviral therapy (Lawn et al, AIDS, 2007).

As there is no definitive test for IRIS, it is crucial to ensure that the development of another opportunistic infection or the emergence of drug-resistant TB is not mistaken for the syndrome. IRIS is usually not life-threatening and in most cases can be treated symptomatically. However, IRIS occurring in central nervous system (CNS) or meningeal TB can be severe and in some cases lethal; initiation of antiretroviral therapy in CNS TB therefore merits a heightened level of caution and close monitoring for development of IRIS. Nonsteroidal antiinflammatory drugs are often used in mild to moderate TB IRIS, but efficacy has not been convincingly demonstrated. Prednisone may be indicated for severe IRIS (1 mg/kg for 4–6 weeks, although longer treatment may be required). A 4-week course of prednisone reduces hospitalization and the need for outpatient procedures in cases of TB IRIS but may increase the risk of additional infections (Meintjes et al, AIDS, 2010). Interruption of antiretroviral therapy should be avoided if at all possible. The potential for IRIS as a possible complication should be discussed with TB patients at the start of antiretroviral therapy, as IRIS is a frequent complication during treatment of mycobacterial infections.

Presented by Dr Luetkemeyer in May 2010. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Luetkemeyer in November 2010.

**Financial Disclosure:** Dr Luetkemeyer has received research grants from Gilead Sciences, Inc, Bristol-Myers Squibb, Pfizer Inc, and Merck & Co, Inc.

**Suggested Reading**


Blanc FX, Sok T, Laureillard D, et al. Significant enhancement in survival with early (2 weeks) vs. late (8 weeks) initiation of highly active antiretroviral treatment (HAART) in severely immunosuppressed HIV-infected adults with newly diagnosed tuberculosis. [Abstract THLB106.] 18th International AIDS Conference (IAC). July 18-23, 2010; Vienna, Austria.


