HIV-Associated Tuberculosis: Clinical Update

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The human immunodeficiency virus (HIV) epidemic has led to an increase in the incidence of tuberculosis globally, particularly in sub-Saharan Africa. Coinfection with HIV leads to difficulties in both the diagnosis and treatment of tuberculosis. Because of the poor performance of sputum smear microscopy in HIV-infected patients, more sensitive tests—such as liquid culture systems, nucleic acid amplification assays, and detection of mycobacterial products in various body fluids—are being investigated. The treatment of coinfected patients requires antituberculosis and antiretroviral drugs to be administered concomitantly; challenges include pill burden and patient compliance, drug interactions, overlapping toxic effects, and immune reconstitution syndrome. Both multidrug-resistant and extensively drug-resistant tuberculosis can spread rapidly among an immunocompromised population, with resulting high mortality rates. Current guidelines recommend starting antiretroviral treatment within a few weeks of antituberculosis therapy for patients with CD4 cell counts <350 cells/μL; however, important questions about the drug regimens and timing of antiretroviral therapy remain. Ongoing trials may answer many of these unresolved questions.

Globally, an estimated 33.2 million (30.6 million to 36.1 million) people were living with human immunodeficiency virus (HIV) infection in 2008. Southern Africa continued to bear a disproportionate share of the global burden of HIV: 35% of HIV infections and 38% of AIDS deaths in 2007 occurred in this subregion. At least one-third of HIV-infected persons worldwide are infected with *Mycobacterium tuberculosis*, and 8% to 10% of them develop clinical disease every year [1]. The World Health Organization (WHO) reported that among the 9.27 million incident cases of tuberculosis in 2007, an estimated 1.37 million (14.8%) occurred in HIV-positive patients, with 456,000 deaths from tuberculosis among HIV-infected patients. The African region accounted for most HIV-positive tuberculosis cases (79%), followed by the Southeast Asia region (mainly India), which had 11% of total cases (Figure 1) [2]. Although the prevalence of HIV infection among patients with tuberculosis ranges from 50% to 80% in many settings in sub-Saharan Africa, in other parts of the world it varies from 2% to 15% [2].

It is clear that the annual incidence of and mortality due to tuberculosis globally would be decreasing if it were not for the HIV epidemic. With the expansion and convergence of the HIV and tuberculosis epidemics worldwide, clinicians will increasingly be called on to manage and treat coinfected patients. This review aims to help clinicians who work in a variety of settings to approach the patient with dual infection in a pragmatic way. New approaches to diagnosis and treatment are described, bearing in mind that many of these may not be available in health care facilities in low-income countries, which are disproportionately affected by this coepidemic.

ISSUES IN THE DIAGNOSIS OF TUBERCULOSIS

Tuberculosis can occur at any stage of HIV disease, and its manifestations depend largely on the level of immunosuppression. Early during HIV disease, symptoms and signs are similar to those in HIV-uninfected persons: the lungs are most commonly affected, with cough, fever, and respiratory signs along with radiographic lesions, often with cavitation. On the other hand, extrapulmonary sites are more often involved among patients with immunosuppression, and pulmonary tuberculosis resembles primary disease (lymph node enlargement, miliary disease, and minimal parenchymal lesions). Common extrapulmonary sites include lymph nodes (superficial) and pleura; less commonly, the brain, pericardium, meninges, and abdomen are affected. In general, pulmonary tuberculosis in HIV-infected patients bears many similarities to childhood tu-

Received 27 May 2008; accepted 20 January 2010; electronically published 13 April 2010.
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Clinical Infectious Diseases 2010; 50(10):1377–1386

1058-4838/2010/5010-0009$15.00
DOI: 10.1086/652147

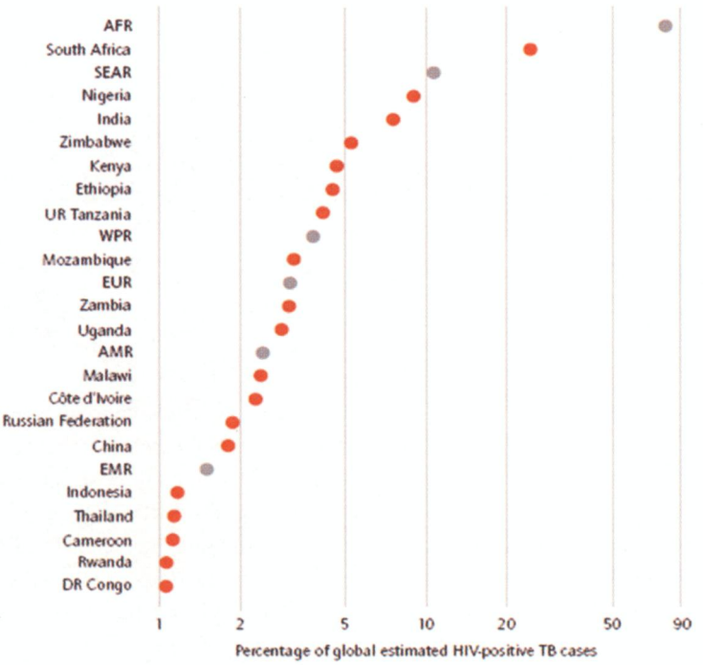

Figure 1. Geographic distribution of the estimated number of human immunodeficiency virus (HIV)–positive tuberculosis cases. For each country (*red circles*) and World Health Organization region (*gray circles*), the number of incident tuberculosis cases arising in people infected with HIV is shown as a percentage of the global total of such cases. Data are from the World Health Organization [2]. AFR, African region; AMR, American region; DR Congo, Democratic Republic of the Congo; EMR, Eastern Mediterranean region; EUR, European region; SEAR, Southeast Asian region; TB, tuberculosis; UR Tanzania, United Republic of Tanzania; WPR, Western Pacific region.

berculosis; both are paucibacillary, involve hilar and mediastinal lymph nodes, lack cavitation, and are smear negative. Diagnostic tests for tuberculosis in this population therefore need to be not only more sensitive but also applicable to sites other than pulmonary sites. Furthermore, physicians caring for HIV-infected patients need to consider tuberculosis in the differential diagnosis of many different symptom complexes and also screen for tuberculosis regularly. In fact, active case finding gives high yields when implemented in clinics that treat HIV-infected persons, including antenatal women [3–7]. Clinical algorithms often have high sensitivity but poor specificity, and the WHO has recommended using an algorithm that emphasizes the use of chest x-ray examination and sputum culture early in the evaluation [8, 9]. Nonresponse to a course of broad-spectrum antibiotics, such as amoxicillin or the combination of sulfamethoxazole and trimethoprim, could be used as supportive evidence, but this is often complicated because partial response of cough or fever is common even with underlying tuberculosis. Efforts should be made to confirm the diagnosis. The following investigations may be performed depending on indication, cost, and availability.

Microscopic detection. Since Koch's discovery of tuberculosis bacilli in 1882, microscopic detection of the acid-fast bacilli in clinical specimens has remained the cornerstone of tuberculosis diagnosis. Microscopy has the advantage of being inexpensive, relatively rapid to perform, and specific in most settings. However, to be considered smear positive a specimen needs to contain ~10^5 mycobacteria per milliliter; the sensitivity of sputum microscopy in HIV infection ranges from 43% to 51% [10]. Methods that improve speed or sensitivity include fluorescence microscopy [11] and alternative specimen processing methods, such as concentration and bleach sedimentation. Any procedure for digestion or liquefaction followed by centrifugation, prolonged gravity sedimentation, or filtration increases sensitivity by 13% to 33% over direct microscopy when culture is used as the reference standard [12].

Equipment costs limit the wider use of fluorescence microscopes in resource-limited settings. Alternative technologies using light-emitting diode bulbs allow fluorescence microscopes at a much lower cost; field-level evaluation has shown promising results [13, 14]. Furthermore, it has been demonstrated that 2 specimens collected on the same day (so-called front loading) give results equivalent to the traditional 3 specimens (including 1 overnight collection), increasing convenience for the patient and potentially increasing the proportion of patients treated appropriately [13, 15].

Growth-based detection. Culture on selective media remains the most sensitive method for detecting *Mycobacterium*

tuberculosis in clinical specimens and allows subsequent strain characterization and drug-sensitivity tests. Automated liquid culture systems have been developed as alternatives to conventional solid media culture. These systems detect bacterial carbon dioxide production or oxygen consumption with radiometric sensors (BACTEC 460 TB; Becton Dickinson Diagnostic Instruments Systems), fluorescent sensors (BACTEC Mycobacteria Growth Indicator Tube [MGIT] 960; Becton Dickinson Diagnostic Instruments Systems), colorimetric sensors (MB/BacT system; Organon Teknika), pressure sensors (ESP culture system II; Difco Laboratories), or redox reagents, such as Alamar blue. These techniques allow continuous monitoring of growth, obviating the need for mature colony formation and roughly halve the time to detection, compared with Lowenstein-Jensen culture [16–19]. Low-cost noncommercial methods have also been developed using liquid culture media (Middlebrook 7H11 agar) in plates and detection of microcolonies and cord formation by inverted microscopy. By adding antituberculosis drugs to adjacent wells and examining for comparative growth, this latter technique (termed *microscopic-observation drug susceptibility assay*) has been applied for early detection of drug resistance [20]. Liquid culture systems pose certain challenges: disposal of radioactive media, technical expertise, and higher contamination rates. Although these systems play an important role in centralized laboratories handling large specimen volumes, the cost-effectiveness, feasibility, and utility in resource-limited settings need further study. Attempts have been made to use the ability of mycobacteriophages to infect and replicate in viable *Mycobacterium tuberculosis* for diagnostic assays (FASTPlaqueTB; Biotech Laboratories), but its sensitivity in persons with tuberculosis and HIV coinfection is low, and the risk of contamination high [21].

Rapid species identification of culture isolates can be accomplished by molecular probes or high-performance liquid chromatography [22]. This is especially important in areas where HIV infection is prevalent, because nontuberculosis mycobacterial species often cause disease that mimics tuberculosis. Patients with these infections have a poor response to standard antituberculosis therapy (ATT) regimens and may raise suspicions of multidrug-resistant tuberculosis among care providers. Species identification is not routinely performed in most low-income tuberculosis-endemic countries, where >99% of mycobacterial disease is caused by *M. tuberculosis* species. However, *Mycobacterium avium* has been detected in pulmonary and disseminated tuberculosis, and *Mycobacterium kansasii* and *Mycobacterium fortuitum* have been detected in pulmonary forms of the disease; these infections are probably underdiagnosed in developing countries [23].

Antigen detection. Attempts have been made to detect *M. tuberculosis* MPB-64 (TAUNS) antigens in peripheral blood to diagnose extrapulmonary disease with good results [24]. The detection of early secreted antigenic target 6 in the cerebrospinal fluid of patients with tuberculosis and meningitis by indirect enzyme-linked immunosorbent assay (ELISA) is being used to develop an immunodiagnostic assay with increased sensitivity and specificity [25]. ELISA–based commercial assays have been developed to detect another cell wall antigen, lipoarabinomannan, in the urine to diagnosis tuberculosis. This test seems to perform better in HIV-infected patients, with a sensitivity of 52% compared with 21% in HIV-negative patients with tuberculosis [26]. The combination of urine lipoarabinomannan testing and sputum smear microscopy needs further evaluation for use in settings with a high HIV burden [27].

Molecular detection. Nucleic acid amplification testing provides a reliable way of increasing the specificity of diagnosis (ruling in disease), but sensitivity is variable, especially in paucibacillary disease. Despite the clear advantages of nucleic acid amplification tests over existing tests, their use in diagnosis is limited in tuberculosis-endemic settings, primarily because of their cost and complexity [28]. However, a molecular line probe assay is being scaled up by tuberculosis programs for rapid detection of rifampicin and isoniazid resistance and, in combination with liquid culture, is expected to provide timely results that confirm tuberculosis and the presence of drug resistance [29]. The test can be applied directly to smear-positive specimens, reducing the delay in the diagnosis of drug resistance considerably. Because of the high early mortality rates among patients with HIV and tuberculosis and the possibility that some of this is due to drug resistance, there is some justification for screening all coinfected patients for drug resistance.

Antibody detection. Antibodies to *M. tuberculosis* antigens can be detected in most immunocompetent patients with active tuberculosis. However, none of the existing commercial serological tests show adequate sensitivity and specificity to be recommended for diagnostic use. Moreover, no data are available to determine the accuracy of these tests in children or in patients with HIV infection [30].

Interferon γ release assay. HIV-related immunosuppression is the most significant risk factor for reactivation of tuberculosis in individuals with latent tuberculosis. There are 2 promising new in vitro tests to detect latent tuberculosis: QuantiFERON-TB Gold (Cellestis) uses a whole-blood assay to measure interferon γ (IFN-γ) production from sensitized T cells, whereas the T SPOT-TB test (Oxford Immunotec) uses an enzyme-linked immunospot assay to quantify the number of peripheral blood mononuclear cells producing IFN-γ in response to tuberculosis-specific antigen stimulation (early secreted antigenic target 6 and culture filtrate protein 10). Both of these assays give objective results, with sensitivity (as measured in patients with active tuberculosis) comparable to that of the tuberculin skin test, but are significantly more expensive [31]. IFN-γ assays do not differentiate between latent and active tuberculosis or

between immune reconstitution inflammatory syndrome (IRIS) and failure, and data regarding its predictive power are lacking. At this point, there is no evidence that IFN-γ assays offer significant advantages over tuberculin skin testing in HIV-infected patients to be cost-effective in developing countries. The tuberculin skin test itself performs poorly (due to anergy) and underestimates the prevalence of latent tuberculosis in countries of endemicity; it requires trained health care staff to correctly perform the tests and accurately read the results, and it requires a second patient visit [32]. For these reasons, the WHO recommends treatment of latent tuberculosis or isoniazid chemoprophylaxis for all HIV-infected patients in tuberculosis-endemic countries after active tuberculosis has been excluded.

Newer approaches to the diagnosis of tuberculosis—such as sensing volatile organic compounds from tuberculosis bacteria in exhaled air or headspace gas over sputum or bacterial cultures, measured using sensors or gas chromatography–mass spectroscopy [19]—need further research in patients with tuberculosis and HIV coinfection.

TREATMENT OF HIV-ASSOCIATED TUBERCULOSIS

The principles of tuberculosis treatment in HIV-infected individuals are the same as those in HIV-negative individuals. However, specific issues include regimen length and schedule of administration of antituberculosis drugs, timing and drug combinations of antiretroviral drugs, overlapping toxic effects, drug interactions, and occurrence of immune reconstitution.

ATT. The standard recommendation for the treatment of tuberculosis is a 6-month regimen of isoniazid, rifampicin, pyrazinamide, and ethambutol, irrespective of HIV status. However, the Centers for Disease Control and Prevention/Infectious Diseases Society of America guidelines recommend extending treatment beyond 6 months in HIV-infected patients, especially when there is delayed sputum conversion or evidence of dissemination and low CD4 cell count [33]. Many studies have shown lower cure rates and higher mortality and recurrence rates after standard ATT in coinfected patients [34]. Recurrences can result from endogenous reactivation or exogenous reinfection, with the relative proportions depending on the background incidence of tuberculosis, the level of immune suppression, the length of rifampicin-containing ATT, and adherence to treatment [34, 35]. Baseline isoniazid resistance has been identified as a risk factor for failure and the development of acquired rifampicin resistance, a phenomenon observed among HIV-infected patients treated with intermittent (once-, twice-, or thrice-weekly) regimens [36–38]. Table 1 summarizes the response to ATT among HIV-infected tuberculosis patients in various studies. In light of the clinical trials recently conducted, it is clear that rifampicin plays a key role in the treatment of HIV-associated tuberculosis: recurrence rates were 2–3 times higher when rifampicin was not included in the continuation phase [46, 47]. The addition of quinolones in the induction phase did not increase the cure rate any further [42]. Among antiretroviral therapy (ART)–naive patients, extending treatment to 9 months reduced recurrences but did not change mortality or the acquisition of rifampicin resistance, compared with a 6-month thrice-weekly regimen [37]. Acquired rifamycin resistance is a unique feature of HIV-associated tuberculosis, being rarely seen in HIV-uninfected patients. In a cohort of 1435 seronegative patients with drug-susceptible tuberculosis enrolled in 2 trials at the Tuberculosis Research Centre, Chennai, India, only 4 developed rifampicin resistance [48]. Suboptimal drug concentrations due to malabsorption coupled with increased tissue bacillary load and defective clearance apparently lead to the selection of genomic mutants resistant to rifampicin [49, 50]. Although no trials have directly compared daily and thrice-weekly treatment among coinfected patients, the current recommendation is to use daily treatment at least in the intensive phase for patients with CD4 cell counts <100 cells/μL [33, 51].

ART. Timely access to ART minimizes immune deterioration and improves tuberculosis outcomes [52, 53]. The first-line ART regimens that are most widely available and that are recommended by the WHO for the treatment of HIV disease include combinations of 3 drugs: 2 nucleoside reverse-transcriptase inhibitors (NRTIs) and 1 nonnucleoside reverse-transcriptase inhibitor (NNRTI) [52]. Although rifampicin, through its induction of the cytochrome enzyme system, lowers levels of both the NNRTIs—efavirenz and nevirapine—the former is less affected. Efavirenz is therefore the NNRTI of choice for patients with tuberculosis and HIV coinfection at the recommended dose of 600 mg [53, 54], which achieves adequate blood levels and is associated with good outcomes, despite high intraindividual and interindividual variability. Although the efavirenz dose (600 vs 800 mg) and concurrent rifampicin administration have less impact, a polymorphism in the *CYP2B6* gene (G-to-T mutation) results in significantly higher blood levels of the drug and may be associated with an increased risk of neurotoxicity [55]. Use of nevirapine (available as a generic fixed-drug combination) is not recommended routinely with rifampicin, unless there is a contraindication to efavirenz, such as pregnancy or psychiatric illness. However, some studies suggest that virological outcomes with nevirapine are comparable to those with efavirenz when used with rifampicin; if used, the lead-in phase is not required and full-dose nevirapine may be used from the start [56, 57]. Triple NRTI regimens containing abacavir or tenofovir can be used alternatively but have been associated with worse outcomes in patients with a high viral load [58]. Stavudine use should be discouraged because of its high rates of long-term metabolic toxic effects and its additive effect with isoniazid on producing or exacerbating peripheral

Table 1. Studies of the Effect of Human Immunodeficiency Virus (HIV) Coinfection on the Outcome of Tuberculosis Treatment

Author, year	Regimen(s) used[a]	No. of patients	Median CD4 cell count, cells/μL	No. of patients receiving ART during treatment	Cure rate, %	Follow-up, months	Relapse, %	Overall deaths, %	Salient findings
Perriens et al [39], 1995	2 $EHRZ_7/4\ HR_2$	123	338	0	78	24	9	23	Extending tuberculosis treatment reduced relapse but not survival
	2 $EHRZ_7/10\ HR_2$	124	413	0	78	24	2	31	
Kassim et al [40], 1995	2 $HRZ_7/4\ HR_7$	553	NS	0	59	18	4.5	22	Lower cure rate and higher mortality in HIV-positive compared with HIV-negative patients
Chaisson et al [41], 1996	2 $EHRZ_3/4\ HR_3$	177	475	0	69	28	5	34	Use of drugs other than isoniazid and rifampicin after 2 months was not useful. HIV-positive patients had higher failure rate and mortality than did HIV-negative patients
El Sadr et al [42], 1998	0.5 EHRZ ± $levo_7$/1.5 EHRZ ± $levo_3/4\ HR_3$	50	70	0	82	24	1	52	No significant impact at 8 weeks with the addition of levofloxacin. Intermittent regimens had high cure but high mortality rates in 6- and 9-month regimens
	0.5 EHRZ ± $levo_7$/1.5 EHRZ ± $levo_3/7\ HR_3$	51	…	0	74	24	2	49	
Vernon et al [43], 1999	2 $EHRZ_7/HRip_1$	36	118	0	83	20	20	…	Rifamycin monoresistance occurred among HIV-positive patients with tuberculosis treated with once-weekly rifapentine
	2 $EHRZ_7/HRip_2$	35	137	…	88	…	10	…	
Sterling et al [44], 1999	0.5 $EHRZ_7/1.5\ HR_2/4\ HR_2$	82	160	0	57	NS	6	27	Relapse rates were not statistically different in HIV-positive patients, but the mortality rate was higher
Driver et al [45], 2001	2 $EHRZ_7/4\ HR_7$	1413	NS	NS	NS	NS	5	NS	Relapse rates were low even in HIV-positive patients if regimen duration was longer
Burman et al [38], 2006	6/9 months of daily or intermittent therapy (rifabutin based)	169	90	137	91	24	4.5	13	Failure was associated with acquired rifampicin resistance if once- or twice-weekly therapy was used
Nahid et al [35], 2007	Daily or intermittent therapy for 6 months	33	157[b]	32	73	12	23	38	Duration of <6 months and intermittent dosing predicted relapse. ART during treatment decreased mortality and increased sputum conversion
	Daily or intermittent therapy for >6 months	163	…	…	…	12	7	31	
Swaminathan et al [37], 2009	2 $EHRZ_3/4\ HR_3$	167	152	0	83	36	15	36	Favorable outcomes at the end of treatment and death rates were similar, but culture-confirmed recurrences were fewer among patients in the 9-month arm, among ART-naive patients
	2 $EHRZ_3/7\ HR_3$	160	167	0	76	36	7	35	

NOTE. ART, antiretroviral therapy; NS, not specified.

[a] Numbers preceding regimens indicate the duration of treatment in months; subscript numbers at the end of regimens indicate the frequency of treatment in days per week. E, ethambutol; H, isoniazid; levo, levofloxacin; R, rifampicin; rip, rifapentine; Z, pyrazinamide.

[b] Mean.

Table 2. Studies of the Timing of Antiretroviral Therapy (ART) in Human Immunodeficiency Virus (HIV)–Infected Patients with Tuberculosis Undergoing Antituberculosis Therapy

Name of study, PI, country	Primary objective	Secondary objectives	Type of tuberculosis in cohort	ART regimen used with ATT	Treatment arms	Follow-up, months	Sample size	Status	Provisional completion date
Anti-HIV Drugs for Ugandan Patients with HIV and Tuberculosis, C. C. Whalen, Uganda [59]	CD4 cell count decline and progression to AIDS	Immune reconstitution, safety, response to ATT, HIV drug resistance	Smear- or culture-positive pulmonary tuberculosis	Abacavir, lamivudine, and zidovudine	Arm 1: ATT plus ART as soon as possible Arm 2: Delay ART until CD4 cell count <250 cells/μL	24	350	Recruiting	NA
CAMELIA study, F. X. Blanc, Cambodia [60]	Survival rate	Safety, IRIS, occurrence of opportunistic infections, tuberculosis and ART outcomes, adherence, pharmacokinetics of efavirenz	Positive on smear (sputum, lymph node, CSF, pleural fluid, stool)	Stavudine, lamivudine, and efavirenz	Arm 1: Early ART within 2 weeks Arm 2: Late ART after 2 months	12	660	Active but not recruiting	October 2010
ACTG 5221, D. Havlir, multinational [61]	Survival without progression to AIDS	NA	Confirmed or probable tuberculosis	Efavirenz, emtricitabine, and tenofovir	Arm 1: Early ART within 2 weeks Arm 2: Late ART after 2 months	12	800	Ongoing but not recruiting	2013
THIRST, N. M. Thielman, Tanzania [62]	Feasibility and safety of FDC of ART with ATT	IRIS	Probable tuberculosis	Zidovudine, lamivudine, and abacavir	Arm 1: Early ART within 2 weeks Arm 2: Late ART 8 weeks after commencing ATT	15	70	Completed	...
SAPIT trial, S. A. Karim, South Africa [63]	Incidence of progression to AIDS-defining illness and mortality	CD4 cell count, viral load, opportunistic infections	Smear-positive pulmonary tuberculosis	Didanosine, lamivudine, and efavirenz	Arm 1: Early ART within 2 weeks of ATT Arm 2: At the end of the intensive phase Arm 3: 6–8 months after ATT completed	18	700	Arm 3 terminated, arms 1 and 2 ongoing but not recruiting	February 2010
TB-HAART, P. Onyebujoh, multicentric (TDR/WHO)	Effect of early HAART on tuberculosis treatment failure, relapse, or death	Safety, opportunistic infections, all-cause mortality, sputum conversion rate, CD4 cell count trends	Smear- and culture-positive pulmonary tuberculosis	Zidovudine, lamivudine, and efavirenz	Arm 1: ATT plus ART as soon as possible (2 weeks) Arm 2: ATT plus placebo for 6 months followed by ART	24	1800	Recruiting	March 2011

NOTE. ACTG, AIDS Clinical Trials Group; ATT, antituberculosis therapy; CAMELIA, Early versus Late Introduction of Antiretroviral Therapy in Treatment-Naive HIV-Infected Patients with Tuberculosis in Cambodia; CSF, cerebrospinal fluid; FDC, fixed drug concentration; HAART, highly active ART; IRIS, immune reconstitution inflammatory syndrome; NA, not available; PI, principal investigator; SAPIT, Starting Antiretrovirals at Three Points in Tuberculosis Therapy; TDR/WHO, Special Program for Research and Training in Tropical Diseases, World Health Organization; THIRST, Tuberculosis and HIV Immune Reconstitution Syndrome Trial.

Table 3. Incidence of Tuberculosis Immune Reconstitution Inflammatory Syndrome (IRIS) in Human Immunodeficiency Virus (HIV)–Tuberculosis Coinfection

Study no.	Study, year	Years studied	Incidence of tuberculosis IRIS among HIV-positive patients with tuberculosis, proportion (%)	Median baseline parameters			Median time, days	
				Age of patients, years	CD4 cell count, cells/μL	Viral load, $\log_{10}$ copies/mL	From tuberculosis diagnosis and treatment to IRIS	From start of ART to IRIS
1	Narita et al [82], 1998	1996–1997	12/33 (36)	40[a]	51[a]	5.8	109[a]	15[a]
2	Breton et al [83], 2004	1996–2001	16/37 (43)	35	100	5.36	48	12
3	Breen et al [84], 2004	1997–2002	14/50 (28)	36	NA	NA	33	11
4	Kumarasamy et al [85], 2004	2000–2003	11/144 (8)	29	123	NA	42	22
5	Lawn et al [80], 2007	2002–2005	19/160 (12)	35	68	4.84	105	14

NOTE. ART, antiretroviral therapy; NA, not available.

[a] Mean.

neuropathy. All patients with tuberculosis and HIV coinfection should receive pyridoxine along with ATT and sulfamethoxazole-trimoxazole prophylaxis.

Uncertainty remains with respect to the optimal timing of ART in tuberculosis and HIV coinfection (Table 2). Early initiation reduces mortality and morbidity due to HIV and tuberculosis with faster sputum conversion [35]. The Starting Antiretrovirals at Three Points in Tuberculosis Therapy trial observed 50% lower mortality rates among patients who started ART during tuberculosis treatment, compared with those among patients who waited until ATT had been completed [64]. Reasons to delay the initiation of ART until after 2 months of ATT include drug interactions between rifampicin and NNRTIs, cumulative drug toxic effects (especially hepatotoxicity), pill burden, and IRIS [65]. Current WHO guidelines recommend that all HIV-infected individuals with active tuberculosis (regardless of CD4 cell count) receive ART as soon as tuberculosis treatment is tolerated, generally within 2–8 weeks [66, 67].

Many countries are now rolling out protease inhibitor–based second-line ART regimens for patients in whom first-line therapy fails. Rifampicin reduces levels of unboosted protease inhibitor by >70% and is not recommended with agents such as nelfinavir, indinavir, or atazanavir [65, 68]. Doses of ritonavir need to be much higher than those typically used, at the expense of increased hepatotoxicity [69, 70]. When progression of HIV disease is thought to be life-threatening, lopinavir-ritonavir (400 mg and 400 mg twice daily) or saquinavir-ritonavir (either 400 mg and 400 mg or 1000 mg and 100 mg) can be used with close monitoring for toxic effects. Alternatively, rifabutin, a weaker inducer of cytochrome enzymes, can be used with ritonavir-boosted protease inhibitor regimens with greater flexibility but requires dose adjustment [68]. The recommended dose of rifabutin given with protease inhibitors is 300 mg thrice weekly, except with ritonavir, for which 150 mg thrice weekly is used. Recent pharmacokinetic data raise questions regarding the adequacy of the lower dose [66, 71]. Rifabutin cannot be used in patients with leukopenia or thrombocytopenia, and higher doses are associated with uveitis. Clinicians should consider completing tuberculosis therapy before switching to second-line ART in patients who develop tuberculosis in the setting of first-line ART failure, until further data about the safety and efficacy of these drug combinations are available.

Adverse reactions occur more often among HIV-infected patients with tuberculosis who are taking concurrent medication than among the uninfected (serious adverse drug reactions, 27% vs 13%), mostly in the first 2 months of treatment [72–74]. Common metabolic pathways of antituberculosis and antiretroviral drugs, alcoholism, coinfection with hepatitis B and C virus, IRIS hepatitis, and obstruction by nodes at the porta hepatis all predispose patients to liver injury [75, 76]. Most patients present with transaminitis, which resolves when drugs are withheld. Nonhepatotoxic drugs, such as streptomycin, ethambutol, and a fluoroquinolone, should be substituted until liver functions return to normal, when all drugs can be reintroduced. Other adverse reactions include cutaneous and gastrointestinal symptoms and peripheral neuropathy, which can occasionally be disabling [37, 74].

TUBERCULOSIS IRIS

Transient worsening of symptoms and signs of tuberculosis or radiological deterioration after the initiation of antiretroviral treatment, despite a reduction in HIV load ($\geq$1 $\log_{10}$ copies/mL) and immunological recovery, is known as IRIS. Drug re-

sistance and other opportunistic infections need to be ruled out [65, 77–79]. There are 2 types of presentation: unmasking of undiagnosed tuberculosis and a paradoxical deterioration of existing tuberculosis lesions or appearance of new lesions after initial improvement [78]. Manifestations include fever, lymph node enlargement, worsening respiratory symptoms and signs, cold abscess, psoas abscesses, and central nervous system lesions (tuberculoma and meningitis) [80]. Hypercalcemia is a unique feature of tuberculosis IRIS [77]. Incident active tuberculosis occurs most often during the first 3 months after ART initiation and can be considerably reduced by efficient screening for tuberculosis before ART [77, 81]. The incidence of tuberculosis IRIS ranges from 8% to 43% (Table 3) and can be managed by anti-inflammatory drugs and steroids. Rarely, termination of ART is required [80]. Risk factors include lower CD4 cell count, higher viral load at start of treatment, rapidity of viral load decline [86, 87], bacillary and antigen load (disseminated tuberculosis) at initiation, starting highly active ART closer to starting ATT [65, 86], and genetic predisposition (HLA B-44) [88]. Although the pathophysiology of IRIS is incompletely understood, it is associated with an exuberant production of cytokines, such as IFN-γ [89].

MULTIDRUG-RESISTANT AND EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS

Data from HIV-endemic countries show that the prevalence of multidrug-resistant tuberculosis in HIV is similar to that in the general population; however, localized miniepidemics tend to occur in settings where there is close congregation of HIV-infected persons. It was estimated that 489,139 (95% confidence interval, 455,093–614,215) cases emerged in 2006, with the largest numbers in India, Russia, and China [90]. Although multidrug-resistant tuberculosis appears not to cause infection or disease more readily than drug-susceptible tuberculosis in HIV-infected persons, delayed diagnosis, inadequate initial treatment, and prolonged infectiousness contribute to increased attack rates among contacts and high case fatality rates among patients [91].

At least 4 effective drugs—including a fluoroquinolone, an injectable agent (capreomycin, kanamycin, or amikacin), and at least 2 agents from the remaining second-line anti-tuberculosis drug classes (cycloserine, thioamides [ethionamide or prothionamide], and p-aminosalicyclic acid)—along with pyrazinamide and ethambutol, if still sensitive, should be used. Therapy may be individualized on the basis of drug susceptibility test results; however, many countries use standardized regimens that are based on surveillance of antituberculosis drug resistance in the community [92].

Extremely drug-resistant tuberculosis is defined as multidrug-resistant tuberculosis plus resistance to any fluoroquinolone and 1 of the second-line antituberculosis injectable agents (kanamycin, amikacin, or capreomycin). Treatment options are extremely limited and challenging, with high frequencies of adverse events and death [91].

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

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