REVIEW ARTICLE

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HIV-Associated Tuberculosis

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Untreated human immunodeficiency virus (HIV) infection markedly increases the risk of tuberculosis, which remains the most common cause of hospitalization and death globally among people with HIV infection in the era of antiretroviral therapy (ART). Challenges related to diagnosing tuberculosis in people with HIV infection can result in diagnostic delays. Drug–drug interactions and immune reconstitution inflammatory syndrome (IRIS) complicate cotreatment of tuberculosis and HIV infection. Short regimens of rifapentine-based preventive therapy are effective, but access to these regimens is limited. This review covers recent advances in research and international guidelines, with a focus on clinical issues in adults living in countries where the HIV and tuberculosis disease burden is high.

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CME

EPIDEMIOLOGY

The relative risk of tuberculosis among people with HIV infection increases exponentially as CD4+ T-lymphocyte counts decline. The risk is increased by a factor of more than 25 when the CD4+ T-lymphocyte count is less than 200 per microliter, as compared with a count of 1000 per microliter.[1] The HIV pandemic resulted in sharp increases in the incidence of tuberculosis and associated deaths. Southern Africa and East Africa were the worst affected; in South Africa, the incidence increased by a factor of more than 3 during the 1990s and early 2000s (Fig. 1). The use of ART has been associated with a reduction in the incidence of tuberculosis among people with HIV infection by 67 to 84%.[3] Globally, there was a 60% reduction in the incidence of tuberculosis and a 72% reduction in deaths due to tuberculosis from 2000 through 2021 among people with HIV infection.[4]

Tuberculosis is the leading cause of death and hospitalization worldwide among adults with HIV infection (accounting for 40% of deaths and 18% of admissions).[5,6] The World Health Organization (WHO) estimates that tuberculosis developed in 10.6 million people in 2021, 6.7% of whom were HIV-positive. The prevalence of HIV infection among patients with tuberculosis is highest in Africa, exceeding 50% in southern Africa. The WHO estimated that 187,000 deaths were caused by HIV-associated tuberculosis in 2021, which accounted for 11.8% of deaths from tuberculosis globally.[4] Tuberculosis-related mortality is higher among people with HIV infection than among those without HIV infection for two key reasons. First, tuberculosis progresses more rapidly as immunosuppression worsens. Second, it is more difficult to diagnose tuberculosis in people with HIV infection, which can result in a delayed or missed diagnosis.

The most recently measured CD4+ T-lymphocyte count is the strongest predictor of the risk of tuberculosis in people who are receiving ART.[7] However, in a South African study, the incidence of tuberculosis was still 4 times as high among people receiving ART who had a CD4+ T-lymphocyte count exceeding 700 per microliter as among people living in the same community who did not have HIV infection, although ascertainment bias may have contributed to this finding.[8] In the

KEY POINTS

HIV-ASSOCIATED TUBERCULOSIS

- Almost half of inpatients with human immunodeficiency virus (HIV)–associated tuberculosis in countries with a high disease burden of HIV and tuberculosis have mycobacteremia, and features of sepsis are commonly present.
- Tuberculosis can be diagnosed rapidly with the use of molecular tests (e.g., the Xpert MTB/RIF assay) in sputum and a LAM assay in urine, which together detect more than two thirds of cases in unselected inpatients with HIV infection. Empirical tuberculosis treatment based on clinical and radiographic features is often needed in cases of severe illness, pending the results of mycobacterial cultures.
- Initiation of antiretroviral therapy in patients being treated for tuberculosis can cause the paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome, manifested as new, recurrent, or worsening symptoms and signs of tuberculosis. The syndrome can be managed or prevented with glucocorticoids.
- Isoniazid therapy and newer regimens (including rifapentine and isoniazid) are similarly effective in preventing tuberculosis in people with HIV infection, but the shorter rifamycin-based regimens are associated with fewer hepatotoxic effects and are more likely to be completed than the isoniazid-based regimens.

PopART trial, the risk of tuberculosis was 73% lower among people starting ART with a CD4+ T-lymphocyte count of more than 500 per microliter than those starting ART when the CD4+ T-lymphocyte count was 500 or less per microliter. This finding underlines the importance of early ART initiation for the prevention of tuberculosis.[9]

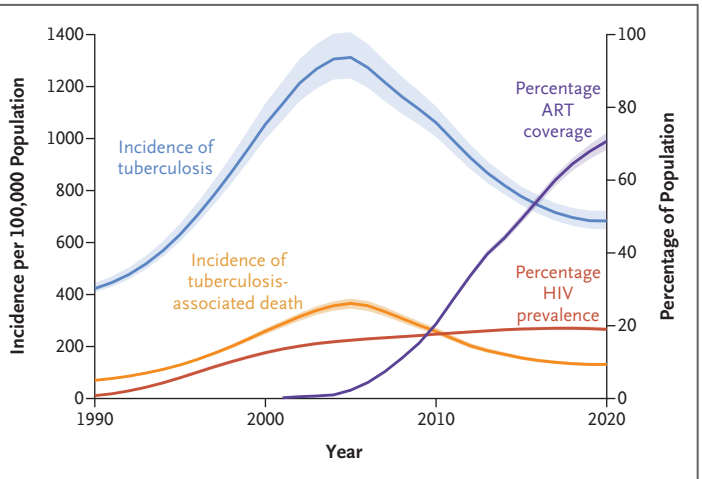

Figure 1. Temporal Trends in HIV Prevalence, Antiretroviral Therapy Coverage, Incidence of Tuberculosis, and Deaths from Tuberculosis in South Africa, 1990–2020.

The data, which are estimates derived from the Thembisa model,[2] show how the prevalence of human immunodeficiency virus (HIV) infection among persons 15 to 49 years of age rose dramatically in South Africa during the 1990s, with a concurrent increase in the incidence of tuberculosis and tuberculosis-associated deaths among persons 15 years of age or older. With increasing antiretroviral therapy (ART) coverage for persons of all ages from 2004 onward, there was a decrease in the incidence of tuberculosis and tuberculosis-associated deaths, but they have not returned to their 1990 baseline levels. Shading indicates the 95% confidence interval.

IMMUNOLOGY

Progressive CD4+ T-lymphocyte depletion, which is characteristic of untreated HIV infection, is associated with impaired containment of *Mycobacterium tuberculosis*. CD4+ T lymphocytes that produce interferon-γ activate macrophages infected with *M. tuberculosis* and facilitate intracellular killing. Macrophage activation is a key step in granuloma formation, which is critical for limiting the growth and spread of *M. tuberculosis*. Granulomas in HIV-associated tuberculosis are characterized by reduced numbers of CD4+ T lymphocytes, alterations in macrophage activation and maturation (fewer epithelioid and Langhans giant cells), increased neutrophil infiltration and necrosis, and an increase in the viral load.[10-12] In patients with advanced HIV infection, granulomas are poorly organized, and there may be inflammation without granuloma formation, which facilitates dissemination (Fig. 2).

CD4+ lymphopenia is not the only mechanism through which HIV infection increases the risk of tuberculosis. The risk is doubled in the first year after HIV seroconversion, before peripheral-blood CD4+ T-lymphocyte counts are depleted.[15] HIV alters adaptive immune-cell populations and function in multiple ways, increasing susceptibility to tuberculosis. Preferential depletion of effector memory CCR5+ CD4+ T lymphocytes occurs at mucosal sites. Selective depletion of *M. tuberculosis*–

specific CD4+ T lymphocytes occurs during early HIV infection.[16] In a nonhuman primate model, simian immunodeficiency virus (SIV) coinfection resulted in a dramatic depletion of *M. tuberculosis*–specific CD4+ T lymphocytes in granulomas after only 2 weeks of SIV coinfection, before CD4+ T-lymphocyte depletion in blood.[17]

HIV-associated chronic immune activation results in activated and differentiated T-lymphocyte phenotypes with increased expression of exhaustion markers such as programmed cell death protein 1 (PD-1) and T-cell immunoglobulin and mucin domain 3 (Tim-3), which lead to impaired pathogen-specific responses.[18,19] Increased type 1 interferon signaling in response to HIV infection may inhibit protective immune responses directed against *M. tuberculosis*.[20] This inhibited response may explain the finding from epidemiologic studies that ongoing HIV replication is associated with an increased risk of tuberculosis, regardless of the CD4+ T-lymphocyte count.[8,21,22] Other T-cell functional alterations include reduced interleukin-2 production, which impairs proliferative capacity,[23,24] and impaired cytokine production by mycobacterium-specific T cells in the airways.[25] The effects of HIV infection on

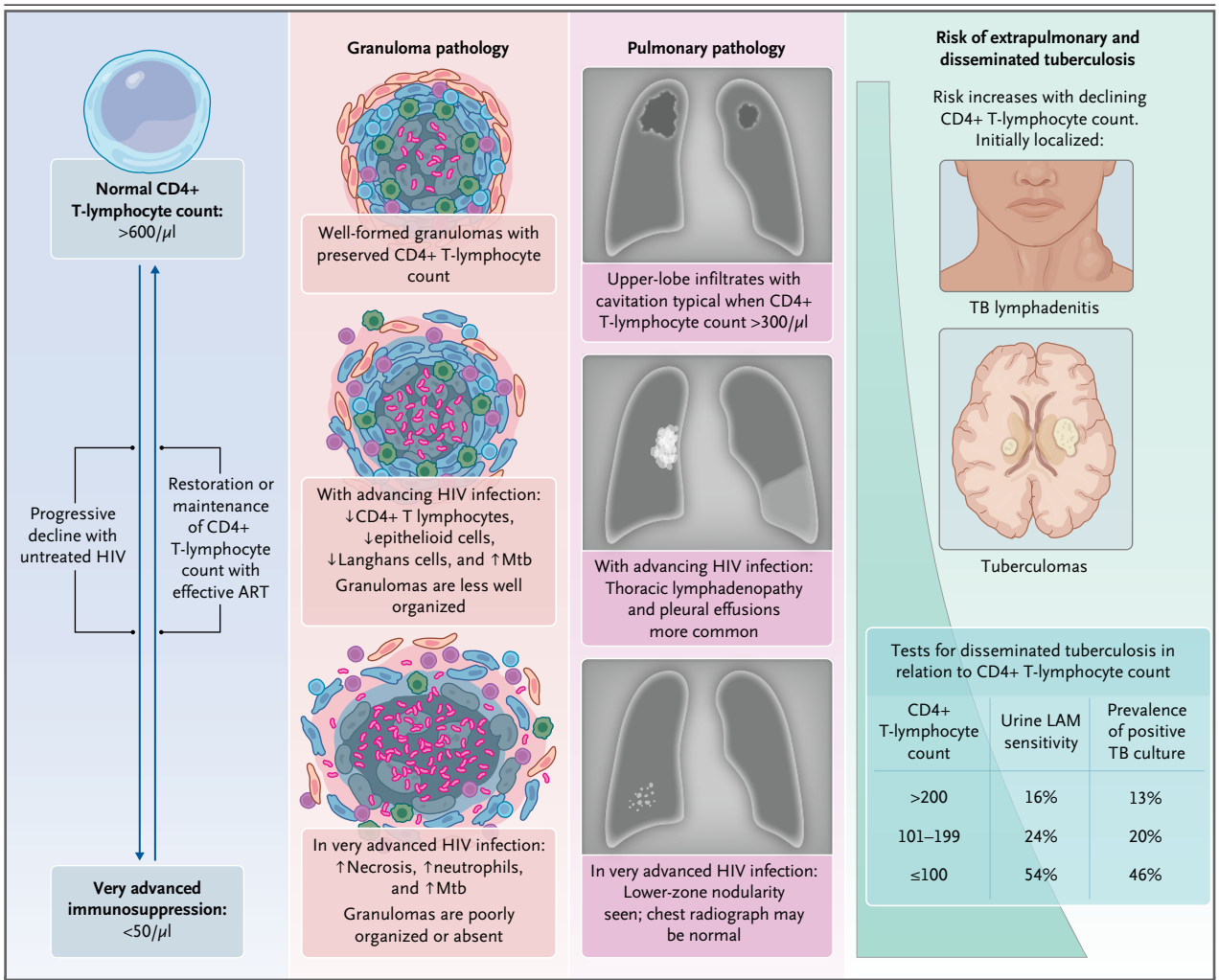

Figure 2. Relationship among the CD4+ T-Lymphocyte Count, the Pathological Features of Tuberculosis, Chest Radiology Features, and the Risks of Extrapulmonary and Disseminated Tuberculosis among People with HIV Infection.

In the table, data are shown for the sensitivity of the LAM assay (Alere)[13] and the prevalence of a positive tuberculosis (TB) blood culture[14] among patients with HIV-associated tuberculosis, stratified according to CD4+ T-lymphocyte count. LAM denotes lipoarabinomannan, and Mtb *Mycobacterium tuberculosis*.

innate immune-cell function may also increase the risk of tuberculosis by impairing macrophage phagocytosis and apoptosis, dendritic-cell processing and antigen presentation, and neutrophil microbial killing capacity.[12,26] ART increases CD4+ T-lymphocyte counts and reverses many of the immune deficits.

Tuberculin skin tests and interferon-γ release assays (IGRAs) reflect the presence of an adaptive memory response to mycobacterial antigens. These tests are used in the diagnosis of *M. tuberculosis* infection; however, the tests may be negative in people with advanced HIV infection.

CLINICAL FEATURES

Tuberculosis in people with HIV infection ranges from subclinical to life-threatening disease. Historically, tuberculosis has been viewed as a disease with dichotomous states: latent and active. With the availability of improved imaging techniques and the findings of screening studies, tuberculosis is now conceptualized as a continuous spectrum of disease stages from latent to subclinical to symptomatic, active disease.[27] Subclinical tuberculosis is defined by positive cultures for *M. tuberculosis* but with no symptoms.

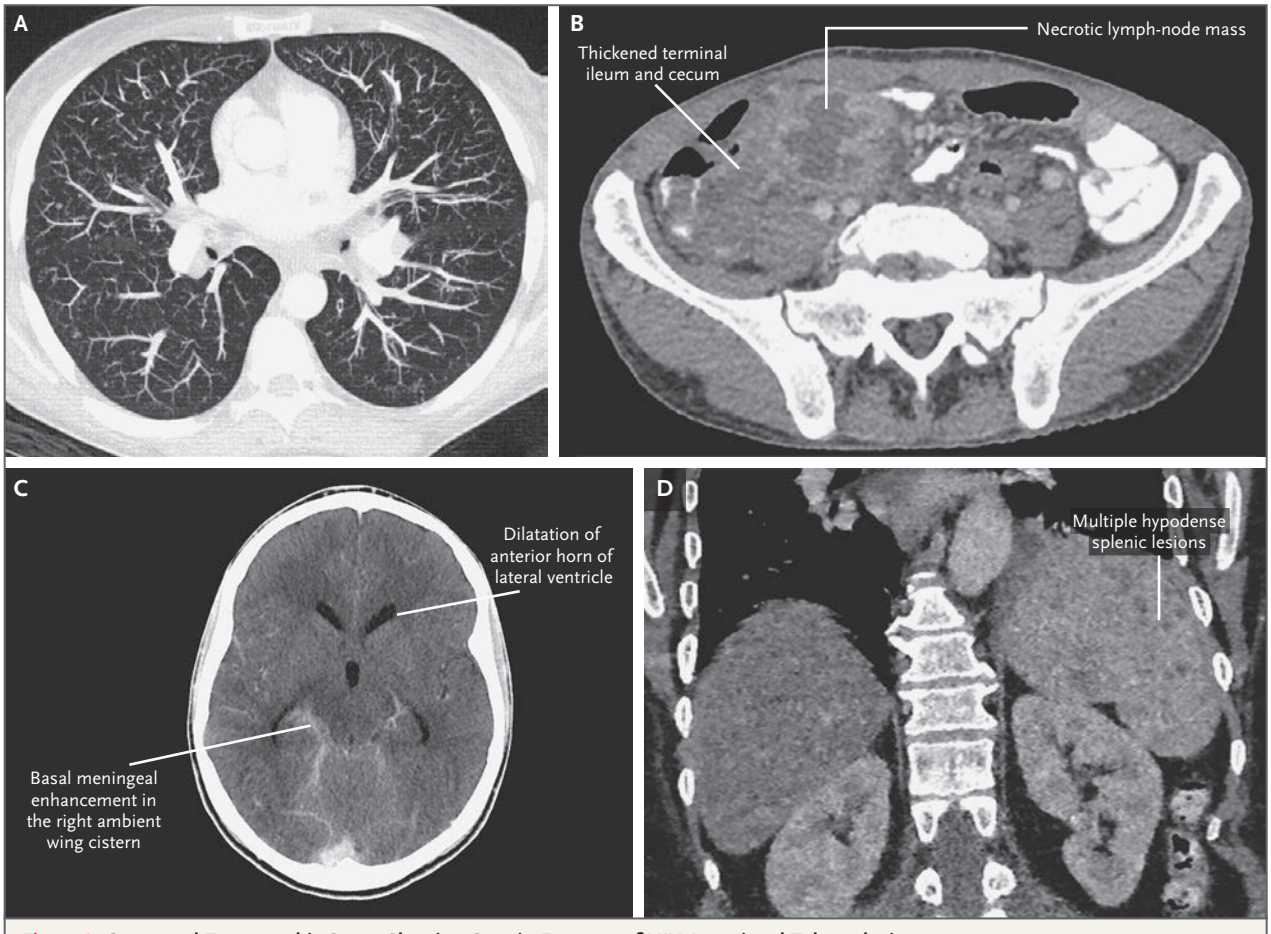

Figure 3. Computed Tomographic Scans Showing Certain Features of HIV-Associated Tuberculosis.

A computed tomographic (CT) scan of the chest (Panel A) shows a diffuse miliary infiltrate, with nodules that are 1 to 2 mm in diameter. An abdominal CT scan, obtained after the administration of contrast material (Panel B), shows a cluster of necrotic mesenteric nodes in the right iliac fossa, with rim enhancement and thickening of the terminal ileum and cecum. A head CT scan, obtained after the administration of contrast material (Panel C), shows basal meningeal enhancement, which is most prominent in the right ambient wing cistern, and dilatation of the anterior horns of the lateral ventricles, with diffuse sulcal effacement, findings suggestive of hydrocephalus. A portovenous-phase abdominal CT scan, obtained after the administration of contrast material (Panel D), shows an enlarged spleen containing multiple hypodense lesions that represent microabscesses.

The prevalence of subclinical tuberculosis among people with untreated HIV infection ranges between 7 and 52%.[28-30]

In people with HIV infection and mild immunosuppression, the features of tuberculosis are similar to those in people without HIV infection, who typically present with pulmonary tuberculosis. Extrapulmonary or disseminated tuberculosis occurs more often in people with HIV infection who have severe immunosuppression (CD4+ T-lymphocyte count, <200 per microliter). The most common sites of extrapulmonary tuberculosis are the lymph nodes, liver, spleen, serosal surfaces (causing effusions), and central nervous system (Fig. 3). Patients with severe immunosuppression have accelerated disease progression, which can mimic acute bacterial infections.

HIV infection alters the radiographic features of pulmonary tuberculosis, depending on the degree of immunosuppression. Upper-lobe disease, often with cavitation, is typical in the presence of mild immunosuppression, as it is in the absence of HIV infection. Typical features in patients with severe immunosuppression are lower-zone, noncavitating nodular opacities or consolidation, often with hilar or mediastinal adenopathy. In addition, 8 to 29% of patients with sputum cultures that are positive for *M. tuberculosis* have normal chest radiographs.[31-33]

Inpatients with HIV-associated tuberculosis in countries with a high burden of HIV infection and tuberculosis frequently present with sepsis and organ dysfunction.[34] A study conducted in Uganda showed that in 24% of patients with HIV infection who were admitted with severe sepsis, *M. tuberculosis* was cultured from blood.[35] In high-burden countries, almost half of inpatients with tuberculosis have mycobacteremia.[14] Bloodstream infection with *M. tuberculosis* can be associated with coagulopathy, elevated levels of markers of endothelial damage, and innate immune system activation and immune dysfunction.[34,36,37] Anemia is present in most inpatients with tuberculosis.[38] Postmortem studies have shown dissemination to multiple organs in approximately 90% of patients with HIV infection and tuberculosis.[5] Tuberculous meningitis is associated with very high mortality — approximately 40% — among people with HIV infection.[39]

DIAGNOSIS

Pulmonary tuberculosis is more difficult to diagnose in people with HIV infection who have a low CD4+ T-lymphocyte count than in those with a higher count because pulmonary cavities are usually absent in those with a low count,[31] and they have a lower bacterial load in sputum. A high proportion of inpatients with HIV infection are unable to produce a sputum sample.[40,41] Sputum induction with nebulized saline can improve the sputum yield.[42] Extrapulmonary and disseminated cases of tuberculosis are difficult to diagnose, irrespective of HIV status. Autopsy studies have shown that in almost 50% of patients with HIV infection, tuberculosis was undiagnosed at the time of death.[5] Earlier recognition, diagnosis, and treatment of tuberculosis could reduce these deaths.

Until 2010, microscopical examination of a sputum smear and culture were the main tests available for diagnosing tuberculosis. Microscopy has poor sensitivity in people with HIV infection (Table 1), and culture takes weeks to yield a positive result. The Xpert MTB/RIF test, a cartridge-based polymerase-chain-reaction (PCR) assay that simultaneously detects *M. tuberculosis* and rifampin resistance, which has a 2-hour turnaround time, was endorsed by the WHO in 2010. The second-generation assay, Xpert MTB/RIF Ultra, which has higher sensitivity but lower specificity than the original assay, was endorsed by the WHO in 2017. Xpert MTB/RIF and Xpert Ultra perform well relative to the reference standard of culture on extrapulmonary specimens. In disseminated tuberculosis, Xpert MTB/RIF and Xpert Ultra performed on concentrated urine specimens and lysed whole-blood specimens have a reasonable diagnostic yield.[41,50,51] Among inpatients with HIV infection, the reported diagnostic yield was 64% for Xpert MTB/RIF performed on urine specimens[41] and 37% for Xpert Ultra performed on blood specimens.[50]

Lipoarabinomannan (LAM) is a glycolipid in the cell wall of mycobacteria that may be detected in urine from patients with tuberculosis. An inexpensive, point-of-care, lateral-flow LAM assay (Alere) is available; the assay has a sensitivity of 52% among inpatients and 29% among outpatients. The sensitivity of the urinary LAM assay increases and the specificity decreases with

Table 1. Diagnostic Performance of Tests for HIV-Associated Tuberculosis.*

Test and Sample†	Sensitivity	Specificity	Comments
	percent		
Tests for pulmonary tuberculosis			
Sputum culture	Reference standard	Reference standard	Regarded as the reference standard; a single sputum culture may fail to reveal pulmonary tuberculosis because of the sample and other technical factors, and culture will be negative in patients with isolated extrapulmonary disease
Microscopy for acid-fast bacilli, sputum	22.0–43.0 for single smear[43]; 61.8 for multiple smears[44]	99.7[44]	False positive result may occur with nontuberculous mycobacterial infection or colonization[43,44]
MTB/RIF Xpert, sputum	74.9	99.7	Meta-analysis of 3 studies involving people with HIV infection[45]
MTB/RIF Xpert Ultra, sputum	87.6	92.8	Meta-analysis of 3 studies involving people with HIV infection[45]; sputum MTB/RIF Xpert Ultra results in more false positive results than does sputum MTB/RIF Xpert, particularly in patients treated previously for tuberculosis[46]
Tests for extrapulmonary tuberculosis			
MTB/RIF Xpert, CSF	71.1	96.9	Meta-analysis of 30 studies involving HIV-positive and HIV-negative patients, with reference standard of CSF tuberculosis culture, which is an imperfect reference standard, since many patients with tuberculosis-associated meningitis have a negative culture[47]
MTB/RIF Xpert Ultra, CSF	89.4	91.2	Meta-analysis of 6 studies involving HIV-positive and HIV-negative patients, with reference standard of CSF tuberculosis culture, which is an imperfect reference standard, as noted above[47]
MTB/RIF Xpert, pleural fluid	49.5	98.9	Meta-analysis of 25 studies involving HIV-positive and HIV-negative patients, with reference standard of pleural fluid tuberculosis culture, which is an imperfect reference standard, as noted above[47]
MTB/RIF Xpert Ultra, pleural fluid	75.0	87.0	Meta-analysis of 4 studies in HIV-positive and HIV-negative patients, with reference standard of pleural fluid tuberculosis culture, which is an imperfect reference standard, as noted above[47]
MTB/RIF Xpert, lymph-node aspirate	81.6	96.4	Meta-analysis of 4 studies involving HIV-positive and HIV-negative patients, with composite reference standard[47]
MTB/RIF Xpert Ultra, lymph-node aspirate	70.0	100	One study involving HIV-positive and HIV-negative patients, with composite reference standard[47]
Tests for disseminated tuberculosis			
Blood culture	Part of reference standard	Part of reference standard	Meta-analysis of 20 studies showed 45% predicted probability of positive tuberculosis blood culture among inpatients with HIV-associated tuberculosis, WHO danger signs, and a CD4+ T-lymphocyte count of 76/μl (median value for the cohort)[14]
Alere LAM, urine	42.0	91.0	Test performs best in inpatient settings and in patients with low CD4+ T-lymphocyte counts[13]; patients with disseminated nontuberculous mycobacteria infection may have false positive result; does not provide information on rifampin susceptibility

Table 1. (Continued.)

Test and Sample†	Sensitivity	Specificity	Comments
	percent		
FujiLAM, urine	70.7	90.9	Meta-analysis of 5 studies involving people with HIV infection and using microbiologic reference standard with biobanked samples;[48] recent study using real-time testing showed substantial lot variability in results[49]; test not currently available commercially

* CSF denotes cerebrospinal fluid, HIV human immunodeficiency virus, LAM lipoarabinomannan, and WHO World Health Organization.
† Of the nucleic acid amplification tests used for the diagnosis of tuberculosis, the cartridge-based Xpert MTB/RIF Ultra is the most widely used. Several other rapid molecular diagnostic assays not included in this table have been approved for use on sputum samples by the WHO for the diagnosis of tuberculosis in people with HIV infection: Truenat MTB; Truenat MTB Plus; moderate-complexity, automated nucleic acid amplification tests; and the TB-LAMP assay.

lower CD4+ T-lymphocyte counts.[13] Disseminated nontuberculous mycobacterial infection may cause false positive results.[52] Incorporating the urinary LAM assay in diagnostic algorithms for the detection of tuberculosis in inpatients with HIV infection has reduced mortality in randomized, controlled trials.[53] For countries with a high burden of HIV infection and tuberculosis, the WHO recommends the use of this assay in people with HIV infection if they have signs and symptoms of tuberculosis, are seriously ill, are inpatients with WHO clinical stage 3 or 4 disease, or have a CD4+ T-lymphocyte count of less than 200 per microliter (for inpatients) or less than 100 per microliter (for outpatients).[54]

The combination of the urinary LAM assay and sputum Xpert MTB/RIF testing in unselected inpatients with HIV infection had a diagnostic yield of 71% in countries with a high burden of HIV infection and tuberculosis.[55] Xpert Ultra testing of sputum and extrapulmonary samples may increase this diagnostic yield; however, if tests are negative or samples cannot be obtained, clinicians still often need to make a clinical and radiographic diagnosis of tuberculosis and start empirical treatment, especially in patients with low CD4+ T-lymphocyte counts. Chest radiographs showing features of pulmonary tuberculosis and abdominal ultrasonography showing features of disseminated or extrapulmonary tuberculosis have reasonable diagnostic performance and are widely available.[56,57]

Because tuberculosis is so common and difficult to diagnose in people with advanced HIV infection, several trials have tested initiating tuberculosis treatment with the use of a rule-based approach for patients starting ART who have low CD4+ T-lymphocyte counts and, in some studies, a low body-mass index and low hemoglobin levels.[58-60] None of these trials have shown reductions in mortality with this intervention, which suggests that the treatment of tuberculosis should be based on the individual clinical assessment and diagnostic testing.

TREATMENT

Drug-susceptible tuberculosis in people with HIV infection responds well to a 6-month rifampin-based regimen, which is standard care.[61] A trial of a new 4-month regimen (consisting of rifapentine, moxifloxacin, isoniazid, and pyrazinamide) showed that it was noninferior to standard care for the treatment of drug-susceptible tuberculosis.[62] However, only 8% of the trial participants were people with HIV infection, and those with a CD4+ T-lymphocyte count of less than 100 per microliter were excluded. The WHO has conditionally recommended this 4-month regimen for patients with drug-susceptible tuberculosis, including those with HIV infection, provided that the CD4+ T-lymphocyte count exceeds 100 per microliter.[63] Countries with a high burden of HIV infection and tuberculosis have not yet implemented this regimen because of the limited availability of rifapentine and because there is currently no coformulation in a fixed-dose combination tablet.

In 2022, the WHO recommended a 6-month regimen consisting of bedaquiline, pretomanid, linezolid, and moxifloxacin for the treatment of most patients with rifampin-resistant tuberculosis,

including those with HIV infection; moxifloxacin is omitted in patients who have tuberculosis that is also resistant to a fluoroquinolone.[64] The results of published trials that evaluated other regimens for the treatment of rifampin-resistant tuberculosis are shown in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. In general, the findings for people with HIV infection were similar to those for the overall trial population.

Adjunctive treatment with glucocorticoids has been shown to improve outcomes among patients with certain forms of tuberculosis. Current evidence does not support the use of adjunctive glucocorticoids in people with HIV-associated tuberculous meningitis, since a recent trial showed no reduction in mortality or neurologic disability,[65] or in those with tuberculous pericarditis, because of an increased risk of cancer.[66]

COMBINING TUBERCULOSIS TREATMENT AND ART

The use of ART in patients being treated for HIV-associated tuberculosis reduces mortality and the risk of relapse.[61] Delays in starting ART increase the risk of HIV-related morbidity and mortality. The WHO recommends that in patients not already receiving ART, it should be started within 2 weeks after the initiation of treatment for tuberculosis, regardless of the CD4+ T-lymphocyte count. In patients with tuberculous meningitis, a delay of 4 to 8 weeks is recommended.[67] Previous concerns about initiating ART in patients receiving treatment for tuberculosis included the high pill burden, shared toxicity, drug–drug interactions, and tuberculosis-associated IRIS. Most of these concerns have been allayed by the results of clinical trials and by advances in ART, including the development of single-tablet, fixed-dose combinations with substantially reduced toxicity.

Two forms of tuberculosis-associated IRIS are recognized. The unmasking form is characterized by the development of tuberculosis with marked inflammatory features in the first 3 months after the start of ART. The paradoxical form is manifested as inflammatory reactions after the initiation or reinitiation of ART in patients being treated for tuberculosis. Patients have new, recurrent, or worsening symptoms and signs of tuberculosis, which typically start 1 to 2 weeks after ART is initiated or reinitiated.[68]

In a meta-analysis, paradoxical tuberculosis-associated IRIS was reported in 18% of patients with HIV-associated tuberculosis starting ART.[69] The most common features were recurrent respiratory symptoms with worsening pulmonary infiltrates on imaging and enlarged lymph nodes, which frequently suppurated. Among the patients in the meta-analysis, 25% were hospitalized, and 2% died from tuberculosis-associated IRIS. Central nervous system involvement is the most life-threatening form of tuberculosis-associated IRIS. Prednisone treatment in patients with paradoxical tuberculosis-associated IRIS has been shown to reduce the duration of hospitalization and the need for therapeutic procedures.[70]

Factors that increase the risk of paradoxical tuberculosis-associated IRIS include a low CD4+ T-lymphocyte count, a high viral load, extrapulmonary tuberculosis, and a short interval between the start of tuberculosis treatment and the initiation of ART.[69] A meta-analysis of clinical trials that compared ART initiation at approximately 2 weeks after the start of tuberculosis treatment with ART initiation after 8 weeks showed that the risk of tuberculosis-associated IRIS was doubled among patients who started receiving ART earlier.[71] However, mortality was reduced by 29% with early ART initiation among patients who had a CD4+ T-lymphocyte count of less than 50 per microliter. Prophylactic prednisone (40 mg daily for 2 weeks, followed by 20 mg daily for 2 weeks) administered with ART reduced the incidence of paradoxical tuberculosis-associated IRIS by 30% among patients at high risk (defined by a CD4+ T-lymphocyte count of ≤100 cells per microliter and initiation of ART within 30 days after the start of tuberculosis treatment) who did not have contraindications to glucocorticoids.[72]

Rifampin and rifapentine are strong inducers of genes involved in the metabolism and efflux of many antiretroviral drugs.[73] Coadministration can result in subtherapeutic drug concentrations that lead to virologic failure and resistance. Three strategies are used to manage these drug–drug interactions: replacement of rifampin with rifabutin in the antituberculosis regimen, use of ART without clinically significant interactions, or an increase in the dose of an antiretroviral

drug that is affected. Rifabutin does not significantly reduce levels of exposure of currently recommended antiretroviral drugs, but access to rifabutin is limited in countries with a high HIV and tuberculosis disease burden. All currently preferred ART regimens include at least one antiretroviral drug that has a clinically significant interaction with rifampin and rifapentine. Efavirenz-based ART does not have clinically significant interactions, but efavirenz is no longer preferred because of its toxicity and low genetic barrier to resistance.

The dose of dolutegravir, which is the key antiretroviral drug in the first- and second-line ART regimens recommended by the WHO, can be doubled (50 mg twice daily) to overcome the effect of rifampin induction.[74] Provision of supplemental doses of dolutegravir to patients with tuberculosis can be challenging in areas with a high prevalence of HIV disease, where treatment for HIV infection and treatment for tuberculosis are often not coordinated and there is a risk of shortages of the single-tablet formulation. A study from Botswana[75] showed that double-dose dolutegravir was not given to almost half the patients with tuberculosis. However, virologic suppression was similar with standard and double doses of dolutegravir; this finding was also reported in a phase 2 randomized, controlled trial.[76] These findings suggest that a double dose of dolutegravir may not be necessary with rifampin coadministration, but a double dose is still recommended, pending further findings. Bictegravir is in the same antiretroviral class as dolutegravir but is more affected by rifampin induction. Double doses do not fully compensate for this effect; the current recommendation is not to coadminister with rifampin.[73] However, double dosing resulted in adequate virologic suppression in a phase 2 trial.[77]

SCREENING FOR HIV-ASSOCIATED TUBERCULOSIS

Early diagnosis of tuberculosis reduces morbidity, mortality, and transmission. In countries with a high HIV and tuberculosis disease burden, the aim of screening for tuberculosis in high-risk groups, such as people with HIV infection, is to identify both early symptomatic and subclinical tuberculosis. Screening tests should be affordable, have reasonable diagnostic performance (with an emphasis on high sensitivity), and ideally be available at the point of care. If a screening test is positive, then definitive diagnostic tests are performed. Symptom screening performs reasonably well in people who are not receiving ART, but the sensitivity in people receiving ART is suboptimal.[78] The C-reactive protein level has higher specificity than symptom screening in people who are not receiving ART, but the evidence in people who are receiving ART is limited. Measurement of C-reactive protein is available as a point-of-care test and is now recommended by the WHO.[57]

Chest radiography is widely used for screening, but its sensitivity is lower than that of symptom screening.[57,78] A parallel strategy of symptom screening and chest radiography (with definitive diagnostic testing if either is positive) has higher sensitivity than either screening test alone, but at the cost of lower specificity.[57,78] Expertise in interpreting chest radiographs is limited in areas with a high prevalence of HIV-associated tuberculosis. Computer-aided detection shows promise, but standardization and local calibration are needed before implementation can be recommended.[57] In addition, access to digital radiographic equipment is limited.

Targeted universal testing for tuberculosis is a strategy of testing sputum for tuberculosis with the use of definitive tests (rapid molecular diagnostic testing, culture, or both) in high-risk groups, such as people with HIV infection, regardless of the presence or absence of symptoms. Tuberculosis testing is usually performed when treatment for HIV infection is started or restarted, with annual testing thereafter. Trace positive results on the Xpert MTB/RIF Ultra assay (indicating detection of *M. tuberculosis* insertion sequences IS6110 and IS1810 but not the *rpoB* gene) have reasonably high specificity in passive case finding.[79] However, false positive results were reported in 90% of participants in a study of targeted universal testing for tuberculosis in a large cohort of people seen at clinics in South Africa, 71% of whom had HIV infection.[80] This finding suggests that trace positive Xpert MTB/RIF Ultra results should be confirmed with tuberculosis culture in targeted universal testing for tuberculosis. A cluster-randomized trial of this strategy showed a modest, nonsignificant

Table 2. Regimens Currently Recommended for the Prevention of HIV-Associated Tuberculosis.

Regimen*	U.S. Guidelines[73]	WHO Guidelines[82]
Isoniazid (900 mg) with rifapentine (900 mg) weekly for 3 mo	Preferred	Strong recommendation
Isoniazid (300 mg) with rifampin (600 mg) daily for 3 mo	Preferred	Strong recommendation
Isoniazid (300 mg) daily for 6–9 mo	Alternative	Strong recommendation
Rifampin (600 mg) daily for 4 mo	Alternative	Conditional recommendation
Isoniazid (300 mg) with rifapentine (600 mg) daily for 1 mo	Alternative	Conditional recommendation
Isoniazid (300 mg) daily for ≥36 mo	Not recommended	Conditional recommendation in settings with high tuberculosis transmission

* Doses shown are for adults with a body weight of more than 50 kg.

increase in the primary outcome of tuberculosis detection in intervention clinics as compared with control clinics.[81] There is a need for further research on this strategy in different settings, but it has already been implemented in many areas where the disease burden of HIV and tuberculosis is high.

PREVENTIVE THERAPY

There is a strong evidence base showing that many different regimens of preventive therapy reduce incident tuberculosis among people with HIV infection, including those receiving ART. Regimens currently recommended in the United States[73] and by the WHO[82] are listed in Table 2. A network meta-analysis[83] showed that these regimens were similarly effective in preventing tuberculosis, but the shorter rifamycin-based regimens were associated with a lower risk of hepatotoxic effects and a lower risk of death and were more likely to be completed than isoniazid-based regimens. Despite these advantages of the rifamycin-based regimens, widespread implementation has been hampered by the limited availability of rifapentine and because of clinically significant drug–drug interactions between many antiretroviral drugs and both rifampin and rifapentine, especially when these drugs are taken daily.

Therapy for the prevention of tuberculosis has a limited duration of benefit in high-transmission settings. A meta-analysis showed that isoniazid given indefinitely reduced the risk of tuberculosis by 38% as compared with isoniazid given for 6 months.[84] A repeat course of rifapentine plus isoniazid, given weekly for 3 months after a 1-year interval between the initial course of rifapentine–isoniazid and the repeat course, was no better than a single course in a randomized trial involving people with HIV infection who were receiving ART.[85]

A limitation of most of the clinical trials of preventive therapy is that the trial participants were not receiving ART. A meta-analysis of three trials of isoniazid preventive therapy[86] in people who were receiving ART (initiated before or at the time of enrollment) showed a relative risk of tuberculosis that was similar to the relative risk in studies performed before the ART era.[87] In this meta-analysis, the results of tuberculin skin testing or IGRA did not predict the benefit of preventive therapy in people receiving ART.[86] This was a surprising finding, since meta-analyses of studies from the era before ART showed that people with HIV infection and negative results of tuberculin skin tests did not benefit from preventive therapy.[87] The discrepancy between these findings remains unexplained. A positive tuberculin skin test or IGRA is an indication for preventive therapy in the U.S. guidelines, whereas these tests are optional in the WHO guidelines.

VACCINATION

The bacille Calmette–Guérin vaccine is partially protective against severe forms of tuberculosis in children but has no clear benefit in adults.

Several new vaccine candidates are currently in phase 2 and phase 3 trials, some of which include people with HIV infection.

In a phase 2 trial, the M72/AS01$_E$ vaccine reduced the incidence of tuberculosis by 50% among adults without HIV infection,[88] and the safety and immunogenicity of the vaccine has been shown in adults with HIV infection.[89] The M72/AS01$_E$ vaccine is composed of a fusion protein of two *M. tuberculosis* antigens with a potent adjuvant. A phase 3 trial evaluating the vaccine was begun in 2024 and includes people with HIV infection.

CONCLUSIONS

HIV-associated tuberculosis remains a global public health priority despite the reductions in incidence and mortality, which are largely attributable to the scale-up of ART. More widespread implementation of established screening strategies, diagnostics, and preventive therapy would have an effect on the dual epidemic, but new, improved diagnostic, treatment, and preventive tools are required.

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