REVIEW ARTICLE

CURRENT CONCEPTS

Tuberculosis

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Despite the availability of a cheap and effective treatment, tuberculosis still accounts for millions of cases of active disease and deaths worldwide. The disease disproportionately affects the poorest persons in both high-income and developing countries.[1] However, recent advances in diagnostics, drugs, and vaccines and enhanced implementation of existing interventions have increased the prospects for improved clinical care and global tuberculosis control.

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EPIDEMIOLOGY

In 2011, there were 8.7 million new cases of active tuberculosis worldwide (13% of which involved coinfection with the human immunodeficiency virus [HIV]) and 1.4 million deaths, including 430,000 deaths among HIV-infected patients[1] representing a slight decrease from peak numbers in the mid-2000s (Fig. 1). It has been estimated that there were 310,000 incident cases of multidrug-resistant tuberculosis, caused by organisms resistant to at least isoniazid and rifampin, among patients who were reported to have tuberculosis in 2011 (Fig. 2). More than 60% of these patients were in China, India, the Russian Federation, Pakistan, and South Africa.[1,2] A total of 84 countries have reported cases of extensively drug-resistant tuberculosis, a subset of multidrug-resistant tuberculosis with added resistance to all fluoroquinolones plus any of the three injectable antituberculosis drugs, kanamycin, amikacin, and capreomycin.[1-3] Sub-Saharan Africa has the highest rates of active tuberculosis per capita, driven primarily by the HIV epidemic.[1] The absolute number of cases is highest in Asia, with India and China having the greatest burden of disease globally.[1] In the United States and most Western European countries, the majority of cases occur in foreign-born residents and recent immigrants from countries in which tuberculosis is endemic.[4-6]

PATHOGENESIS

Patients with active pulmonary tuberculosis are the source of *Mycobacterium tuberculosis*. In more than 90% of persons infected with *M. tuberculosis*, the pathogen is contained as asymptomatic latent infection. Recent studies raise the possibility that some persons acquire and eliminate acute infection with *M. tuberculosis*.[7] The risk of active disease is estimated to be approximately 5% in the 18 months after initial infection and then approximately 5% for the remaining lifetime.[8] An estimated 2 billion persons worldwide have latent infection and are at risk for reactivation.[1] Contained latent infection reduces the risk of reinfection on repeated exposure, whereas active tuberculosis is associated with an increased risk of a second episode of tuberculosis on reexposure (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[8-10]

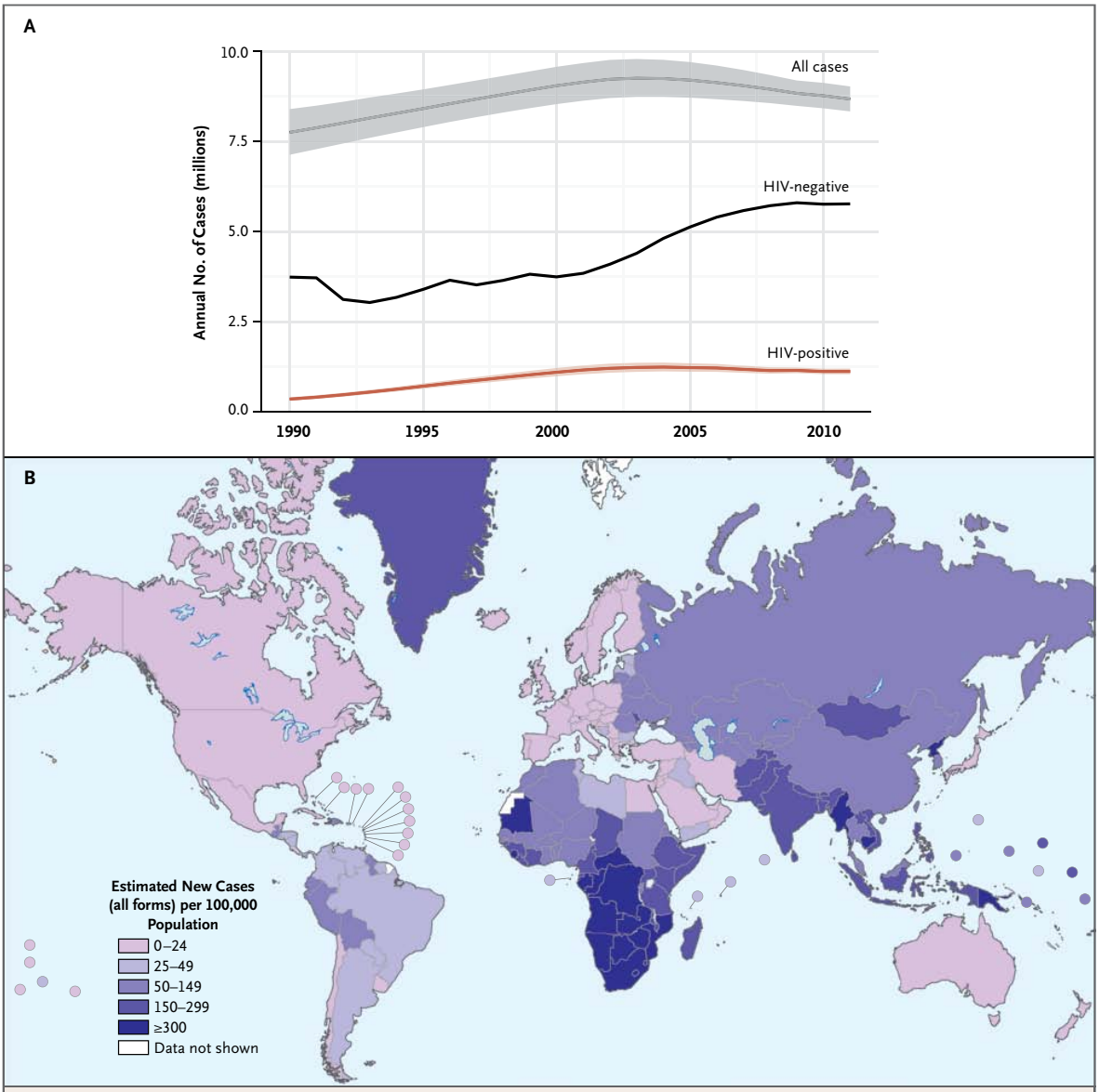

Figure 1. Global Incidence of Tuberculosis.

Panel A shows global trends in the estimated incidence of tuberculosis from 1990 through 2011 among all patients, those with human immunodeficiency virus (HIV) coinfection, and without HIV coinfection. The shading around the data curves indicates uncertainty intervals on the basis of available data. Panel B shows the estimated global incidence of tuberculosis in 2011.

Drug-resistant strains of *M. tuberculosis* arise from spontaneous chromosomal mutations at a predictable low frequency. Selection pressure that is caused by misuse of antituberculosis drugs, such as monotherapy or the addition of single drugs to failing regimens, results in the emergence of resistant mutants (acquired resistance). Transmission of such resistant strains to another person may result in infection and eventually disease (primary resistance). Outbreaks of highly fatal drug-resistant infection have been documented in several settings, especially those in which the prevalence of HIV infection is high.[11-13] Recent reports describing totally drug-resistant tuberculosis require confirmation.[14,15] The failure to detect drug resistance results in the pre-

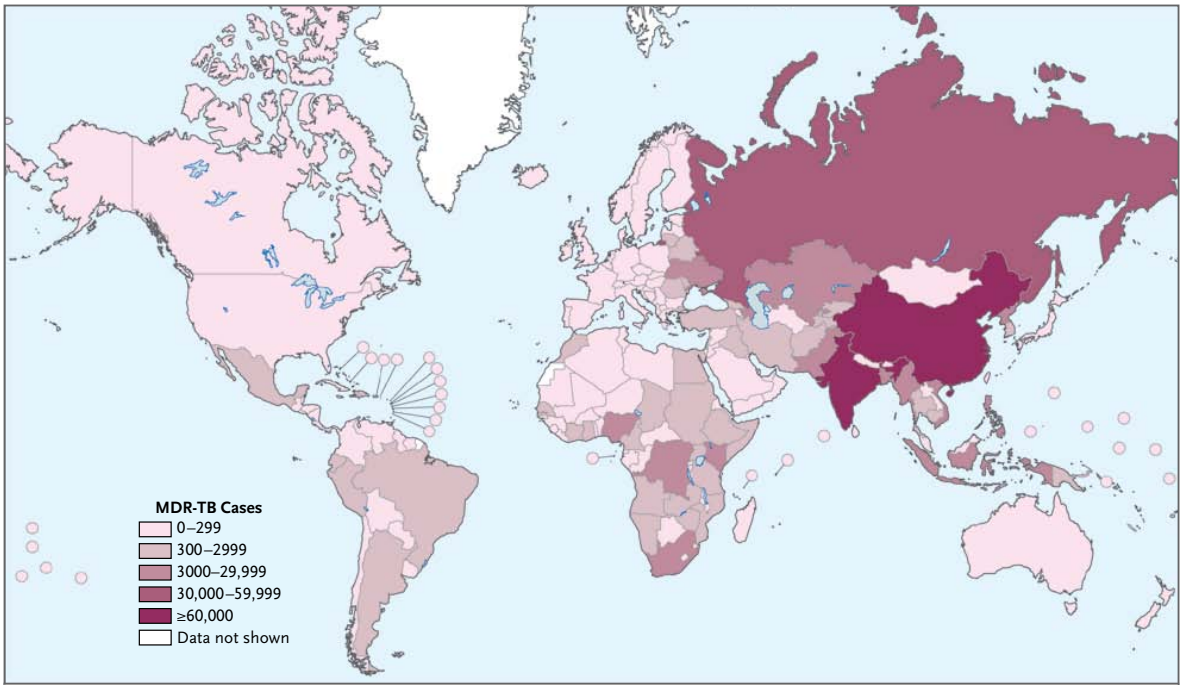

Figure 2. Global Numbers of Cases of Multidrug-Resistant Tuberculosis.
Shown are the estimated numbers of cases of multidrug-resistant disease (including extensively drug-resistant disease) among cases of pulmonary tuberculosis that were officially reported in 2011.

scription of inappropriate regimens, treatment failure, increased mortality, and further transmission of drug-resistant tuberculosis.[16]

CLINICAL FEATURES

The classic clinical features of pulmonary tuberculosis include chronic cough, sputum production, appetite loss, weight loss, fever, night sweats, and hemoptysis.[17] Extrapulmonary tuberculosis occurs in 10 to 42% of patients, depending on race or ethnic background, age, presence or absence of underlying disease, genotype of the *M. tuberculosis* strain, and immune status.[18] Extrapulmonary tuberculosis can affect any organ in the body, has varied and protean clinical manifestations, and therefore requires a high index of clinical suspicion.

HIV coinfection poses special challenges to clinical management in patients with active tuberculosis. The risk of active tuberculosis increases soon after infection with HIV,[19] and the manifestations of pulmonary tuberculosis at this stage are similar to those in HIV-negative persons. At CD4 counts of less than 200 per cubic millimeter, the presentation of tuberculosis may be atypical, with subtle infiltrates, pleural effusions, hilar lymphadenopathy, and other forms of extrapulmonary tuberculosis in as many as 50% of patients. At CD4 counts of less than 75 per cubic millimeter, pulmonary findings may be absent, and disseminated tuberculosis, manifested as a nonspecific, chronic febrile illness with widespread organ involvement and mycobacteremia, is more frequent, with high early mortality; polyclonal disease has also been described.[20] Such cases may be mistakenly diagnosed as other infectious diseases and are often identified only on autopsy.[21]

Asymptomatic, subclinical tuberculosis, with negative findings on a sputum smear and chest radiography and positive culture results, is a common feature of HIV-associated tuberculosis and may account for 10% of cases in regions in which tuberculosis is endemic.[17,22,23] Up to 25% of patients presenting for HIV care in such regions have undiagnosed active tuberculosis.[1] Therefore, screening for tuberculosis is recommended for all patients with HIV infection to identify patients with active disease and before

instituting isoniazid preventive therapy in the remainder. The presence of any one of four symptoms (cough, fever, night sweats, or weight loss) has been shown to have sensitivity in the range of 80% for identifying patients in whom further diagnostic evaluation is warranted, even in resource-constrained regions.[24] Proactive screening for tuberculosis is recommended in areas where the disease is highly endemic, since subclinical tuberculosis in patients with HIV infection or noncommunicable diseases (e.g., diabetes mellitus and tobacco-related chronic lung disease) may otherwise be missed.[24,25]

DIAGNOSIS

LATENT INFECTION

Screening and treatment for latent *M. tuberculosis* infection are indicated for groups in which the prevalence of latent infection is high (e.g., foreign-born persons from regions in which tuberculosis is endemic), those in whom the risk of reactivated disease is high (e.g., patients with HIV infection or diabetes and patients receiving immunosuppressive therapy), and those with both factors (e.g., recent contacts of patients with tuberculosis).[26,27] Latent infection can be diagnosed with either a tuberculin skin test (Fig. S2 in the Supplementary Appendix) or an interferon-gamma release assay. Specific guidelines from the Centers for Disease Control and Prevention in the United States,[28] the National Institute for Health and Clinical Excellence in the United Kingdom,[29] and the European Centre for Disease Prevention and Control[30] recommend the use of the interferon-gamma release assay and tuberculin skin test for screening for latent *M. tuberculosis* infection in various age and risk groups. The tuberculin skin test is less expensive and is therefore preferred in low-income regions. It is as sensitive as the interferon-gamma release assay but less specific.[31]

ACTIVE TUBERCULOSIS

Sputum microscopy and culture in liquid medium with subsequent drug-susceptibility testing are currently recommended as standard methods for diagnosing active tuberculosis. The use of solid culture medium is more cost-effective in resource-poor countries. Interferon-gamma release assays and tuberculin skin tests have no role in the diagnosis of active disease.[28-33] Nucleic acid amplification tests, imaging, and histopathological examination of biopsy samples supplement these evaluations. In resource-constrained settings with a high prevalence of tuberculosis and HIV infection, an estimated 30% of all patients with tuberculosis and more than 90% of those with multidrug-resistant and extensively drug-resistant tuberculosis do not receive a diagnosis.[1-3]

A new molecular diagnostic test called Xpert MTB/RIF assay detects *M. tuberculosis* complex within 2 hours, with an assay sensitivity that is much higher than that of smear microscopy.[34] In HIV-infected patients, the test has a rate of case detection that is increased by 45%, as compared with smear microscopy.[35] This molecular assay has the potential to improve the performance of national tuberculosis programs and is currently being implemented in district-level laboratories in 67 countries with a high prevalence of tuberculosis.[1] It is available in Europe and is being examined for approval in the United States.

DRUG-RESISTANT TUBERCULOSIS

The current standard for first-line drug-susceptibility testing is an automated liquid culture system, which requires 4 to 13 days for results. Commercial molecular line-probe assays can yield results in 24 hours, once they have been validated against automated liquid culture.[36-38] Within 2 hours, the Xpert MTB/RIF assay concurrently gives results on rifampin resistance, a proxy of multidrug-resistant tuberculosis in settings in which there is a high prevalence of drug resistance, since rifampin resistance in the absence of isoniazid resistance is uncommon. Assay modifications have been introduced to reduce false positive results with respect to rifampin resistance.[39] The World Health Organization (WHO) recommends that standard drug-susceptibility testing be performed at the same time that the Xpert MTB/RIF assay is performed to confirm rifampin resistance and the susceptibility of the *M. tuberculosis* isolate to other drugs.[40] Other screening tests for drug resistance include the microscopic-observation drug-susceptibility (MODS) assay, the nitrate reductase assay, and colorimetric reductase methods. The MODS assay simultaneously detects *M. tuberculosis* bacilli, on the basis of cording formation, and isoniazid and rifampin resistance.[41] Since most of these methods are not currently available in countries in which tuberculosis is highly endemic, it is estimated that only 10% of cases of multidrug-resistant tuberculosis are currently diagnosed worldwide and only half of them receive appropriate treatment.[1-3]

Table 1. Current Recommendations for Tuberculosis Treatment.

Type of Infection	Recommended Regimen	Comments
Active disease		
Newly diagnosed cases that are not multidrug-resistant	Isoniazid, rifampin, ethambutol, and pyrazinamide for 2 mo (intensive phase), followed by isoniazid and rifampin for 4 mo (continuation phase)	Pyridoxine supplementation recommended to prevent isoniazid-induced neuropathy
Multidrug-resistant disease	Four second-line antituberculosis drugs (as well as pyrazinamide), including a fluoroquinolone, a parenteral agent, ethionamide or prothionamide, and either cycloserine or para-aminosalicylic acid if cycloserine cannot be used	Initial treatment based on local disease patterns and pending drug-susceptibility results; later-generation fluoroquinolones (e.g., moxifloxacin or levofloxacin) preferred
Latent infection	Isoniazid at a dose of 300 mg daily for at least 6 mo and preferably for 9 mo	Recommended for 9 mo or more in HIV-infected persons; daily administration for 6 mo also an option but with lower efficacy; extension to 36 mo further reduces risk among HIV-positive patients in regions in which tuberculosis is endemic
	Isoniazid at a dose of 900 mg plus rifapentine at a dose of 900 mg weekly for 3 mo (directly observed therapy)	Studied with directly observed therapy in predominantly HIV-uninfected persons; higher completion rates and equal efficacy, as compared with isoniazid for 9 mo
	Rifampin at a dose of 600 mg daily for 4 mo	Shown to be effective in persons with silicosis
	Isoniazid at a dose of 300 mg plus rifampin at a dose of 600 mg daily for 3 mo	Effective alternative for HIV-infected persons
	Isoniazid at a dose of 900 mg plus rifampin at a dose of 600 mg twice weekly for 3 mo	Another effective alternative for HIV-infected persons

TREATMENT

LATENT INFECTION

Persons with latent *M. tuberculosis* infection who are at increased risk for active tuberculosis require preventive treatment.[28,42] The preferred regimen is isoniazid alone for 9 months or for a longer duration in HIV-infected persons in areas with a high prevalence of tuberculosis.[43,44] Recently, directly observed weekly administration of isoniazid and rifapentine for 12 weeks has been shown to be as effective as isoniazid alone in adults without HIV infection in countries with a low burden of tuberculosis. This regimen was associated with fewer serious adverse events than 9 months of isoniazid alone, although treatment discontinuation because of an adverse event was more common (Table 1).[45] The trial is continuing to assess safety and effectiveness in children and HIV-infected persons.

Current WHO guidelines[44] recommend that all HIV-infected persons with positive or unknown results on the tuberculin skin test and without active tuberculosis who are living in resource-constrained, high-burden countries receive preventive therapy with isoniazid for at least 6 months. Three regimens are effective for the prevention of active tuberculosis in HIV-infected persons: daily isoniazid for 6 to 9 months, daily rifampin and isoniazid for 3 months, and rifampin and isoniazid twice weekly for 3 months.[43,44] Rifampin-containing regimens have higher rates of drug toxicity than those that do not include rifampin.[44-46] The difficulty of diagnosing active tuberculosis in patients with HIV coinfection accounts in part for the slow adoption of isoniazid preventive therapy in clinical practice. Only patients with a positive tuberculin skin test who are receiving preventive therapy with isoniazid have decreased rates of active tuberculosis and death,[46] and protection against tuberculosis wanes within a few months after cessation of isoniazid therapy. A trial in Botswana recently showed that 36 months of preventive therapy with isoniazid, as compared with 6 months of therapy, reduced the subsequent rate of tuberculosis by 43%.[47] However, compliance with such a long-term regimen may be poor.[44] A daily regimen of rifapentine

Table 2. Status of Selected Trials of Tuberculosis Treatments.*

Trial or Investigational Drug	Description	Comments
Treatment of drug-sensitive active disease		
REMox	Standard 6-mo regimen vs. two 4-mo regimens including moxifloxacin	Results in 2014 have potential to shorten standard therapy to 4 mo
OFLOTUB III	Standard 6-mo regimen vs. 4-mo regimen including gatifloxacin	Results by mid-2013 have potential to shorten standard therapy to 4 mo
RIFAQUIN	Two experimental groups in which moxifloxacin is substituted for ethambutol for 2 mo, followed by moxifloxacin plus rifapentine twice weekly for 2 mo or moxifloxacin plus rifapentine weekly for 4 mo	Results expected by mid-2013
Multiple trials	Increased doses of rifampin and rifapentine	Higher doses of rifamycins may permit shorter regimens with standard drugs
Treatment of drug-resistant active disease		
Bedaquiline (TMC207)	Background therapy for multidrug-resistant disease plus bedaquiline	Mycobacterial ATP synthase inhibitor shown to improve sputum conversion at 8 wk; also to be studied in new regimens for drug-sensitive tuberculosis
Delamanid (OPC-67683)	Background therapy for multidrug-resistant disease plus delamanid	A nitroimidazole with activity against replicating bacilli through inhibition of mycolic acid synthesis; active against nonreplicating bacilli through generation of reactive nitrogen intermediates; shown to improve sputum-culture conversion at 8 wk
PA-824	PA-824 combined with moxifloxacin and pyrazinamide is being studied in a phase 2b trial (8 wk) for treatment of drug-sensitive and drug-resistant disease	A nitroimidazole with the same mechanism of action as delamanid; when combined with moxifloxacin and pyrazinamide, has high bactericidal activity at 14 days, suggesting promise for treatment of sensitive and resistant disease
Linezolid	Background therapy plus linezolid added immediately or 2 mo later in patients with extensively drug-resistant disease	A marketed oxazolidinone that improved sputum-culture conversion at 4 mo in a group receiving immediate versus delayed linezolid; for both linezolid regimens, 89% of patients had sputum-culture conversion on solid medium by 6 mo; high rate of peripheral neuropathy, including some cases of optic neuropathy
Sutezolid	Dose-ranging phase 2a trial completed	Analogue of linezolid that may have improved activity
AZD 5847	Phase 2a trial under way	More highly modified oxazolidinone
SQ109	Phase 2a trial completed; phase 2b combination trials to begin early in 2013	An ethylenediamine-based compound that is structurally related to ethambutol but has an entirely different mechanism of action

Empirical treatment of active disease		
PROMPT	Empirical therapy provided within 2 wk after start of antiretroviral therapy in patients with CD4+ cell count of <50/mm^3 and body-mass index of <18.5	Designed to reduce mortality from undiagnosed tuberculosis in HIV-infected patients
REMEMBER	Empirical therapy provided within 7 days after start of antiretroviral therapy in patients with CD4+ cell count of <50/mm^3	Designed to reduce mortality from undiagnosed tuberculosis in HIV-infected patients
Prevention of active disease in patients with latent infection		
ACTG 5279	Daily rifapentine plus isoniazid for 4 wk vs. daily isoniazid for 9 mo	Designed to determine whether shorter treatment is effective in HIV-positive patients

* A full listing of all trial references or clinical trial numbers is provided in the Supplementary Appendix at NEJM.org. ACTG 5279 denotes Ultra-Short-Course Rifapentine/Isoniazid for the Prevention of Active Tuberculosis in HIV-Infected Individuals with Latent Tuberculosis Infection, OFLOTUB Randomized, Open-Label, Controlled Trial of a 4-Month Gatifloxacin-Containing Regimen versus Standard Regimen for the treatment of Adult Patients with Pulmonary Tuberculosis, PROMPT Prevention of Early Mortality by Presumptive Tuberculosis Treatment, REMEMBER Reducing Early Mortality and Morbidity by Empiric Tuberculosis Treatment, REMox Rapid Evaluation of Moxifloxacin in Tuberculosis, and RIFAQUIN International Multicenter Trial to Evaluate High-Dose Rifapentine and a Quinolone in the Treatment of Pulmonary Tuberculosis.

and isoniazid for 1 month is also being studied (Table 2). Studies have been suggested to investigate targeted use of preventive therapy with isoniazid on a continuous or recurring basis in persons with HIV infection who have a positive tuberculin skin test.[48]

DRUG-SENSITIVE ACTIVE TUBERCULOSIS

Effective tuberculosis treatment requires accurate and early diagnosis, screening for drug resistance and HIV, the administration of effective regimens under supervision, and the provision of support to patients for compliance throughout the course of treatment. The current standard four-drug treatment regimen of first-line drugs (isoniazid, rifampin, pyrazinamide, and ethambutol) achieves cure rates of more than 95% in trial conditions and more than 90% in treatment under the oversight of tuberculosis-control programs.[1,49] Treatment requires a minimum of 6 months in two phases: 2 months of all four drugs in the intensive phase and 4 months of isoniazid and rifampin in the continuation stage (Table 1). Risk factors for relapse include cavitation, extensive disease, immunosuppression, and a sputum culture that remains positive at 8 weeks. If any of these risk factors is present, therapy may be extended for up to 9 months. Challenges with current therapy include inconsistent drug quality, the need to ensure that drug administration is directly observed and that other support is provided to patients, treatment interruptions and changes in regimen because of side effects, toxic effects, pharmacokinetic interactions (particularly with antiretroviral therapy in patients with HIV coinfection),[50] and compliance issues owing to the lengthy treatment period. Several trials in progress are adding or substituting fluoroquinolones or testing higher doses of rifamycins in an attempt to shorten standard therapy to 4 months (Table 2).

TUBERCULOSIS AND HIV COINFECTION

Tuberculosis leads to an increase in HIV replication and accelerates progression of HIV infection, with attendant high mortality. Early initiation of antiretroviral therapy results in a reduction in mortality; among patients with tuberculosis who do not receive antiretroviral therapy, those with very low numbers of CD4+ cells have a high short-term risk of death.[50-52] WHO recommends that antiretroviral therapy be started within the

first 8 weeks after the initiation of tuberculosis treatment and that patients with a CD4+ cell count of less than 50 per cubic millimeter receive antiretroviral therapy within the first 2 weeks.[42] One exception is patients with tuberculous meningitis, in whom the early initiation of antiretroviral therapy does not improve outcomes and results in an increased risk of adverse events.[42]

The immune reconstitution inflammatory syndrome (IRIS) occurs in at least 10% of HIV-infected patients who start antiretroviral therapy during tuberculosis treatment. These cases of IRIS include both new cases of active tuberculosis detected after the initiation of antiretroviral therapy (called unmasking IRIS) and clinical worsening during tuberculosis treatment after the initiation of antiretroviral therapy (called paradoxical IRIS).[53] The most common manifestations of IRIS are new-onset or worsening respiratory symptoms and increased lymphadenopathy. IRIS is more common in patients who have a reduced number of CD4+ cells and those in whom antiretroviral therapy was initiated early in the course of tuberculosis treatment, with rates approaching 50% among patients with a CD4+ cell count of less than 50 per cubic millimeter who started to receive antiretroviral therapy within 4 weeks after the start of tuberculosis treatment.[53] For antiretroviral therapy in patients with active tuberculosis, regimens with non-nucleoside reverse transcriptase inhibitors are preferred, and efavirenz is the drug of first choice.[54]

The use of rifampin significantly reduces serum concentrations of protease inhibitors.[55] Studies of the substitution of rifabutin for rifampin and increased doses of boosted protease inhibitors to avoid this reduction are under way.[55] Patients with HIV-associated tuberculosis should also receive prophylaxis with trimethoprim–sulfamethoxazole. In two clinical trials — the Prevention of Early Mortality by Presumptive Tuberculosis Treatment (PROMPT) study[56] and the Reducing Early Mortality and Morbidity by Empiric Tuberculosis Treatment (REMEMBER) study[57] — investigators are evaluating the use of early empirical tuberculosis therapy to reduce the high rate of death among patients living in tuberculosis-endemic countries who have a CD4+ cell count of less than 50 per cubic millimeter but who do not have probable or confirmed tuberculosis (Table 2).

MULTIDRUG-RESISTANT TUBERCULOSIS

The treatment of multidrug-resistant tuberculosis is based on expert opinion and requires the creation of combination drug regimens chosen from five hierarchical groups of first-line and second-line drugs[58,59] (Table S1 in the Supplementary Appendix). Such therapy is associated with a high risk of intolerance and serious toxic effects. Regimens may be chosen on a standardized or empirical basis and then switched to individualized therapy after data regarding drug-susceptibility testing become available. However, reliable drug-susceptibility testing is not widely available in regions in which tuberculosis is endemic, particularly for second-line drugs. WHO treatment guidelines for multidrug-resistant tuberculosis recommend that the intensive phase of therapy be administered for at least 8 months.[58,59] A fluoroquinolone and an injectable agent should routinely be included to provide a regimen with at least four second-line drugs that will have certain or nearly certain effectiveness, as well as pyrazinamide.

Such therapy should be administered for at least 20 months in patients who have not received previous treatment for multidrug-resistant tuberculosis and for up to 30 months in those who have received previous treatment. An observational study showed that a shorter regimen, with treatment given for 9 to 12 months (the so-called Bangladesh regimen), had acceptable efficacy with fewer adverse reactions[60] in a population with no previous exposure to second-line drugs. This regimen is being more widely evaluated in the ongoing Standardized Treatment Regimen of Antituberculosis Drugs for Patients with Multidrug-Resistant Tuberculosis (STREAM) trial.[61] Since most of the recommended drugs have serious side effects that render treatment particularly difficult, expert consultation is always advised for the treatment of multidrug-resistant tuberculosis (Table S2 in the Supplementary Appendix).

Extensively drug-resistant tuberculosis is extremely difficult to diagnose and treat in countries in which the disease is endemic. The condition has been associated with death rates as high

as 98% among HIV-infected persons.[12,13,62,63] Several new drugs with activity against multidrug-resistant and extensively drug-resistant tuberculosis have shown promise in early trials and are being investigated further (Table S3 in the Supplementary Appendix).

NEW DRUGS

Five classes of new drugs are being investigated in trials. Of these drugs, two classes (nitroimidazoles and oxazolidinones) and two drugs (bedaquiline and SQ-109) have new mechanisms of action for tuberculosis (Table S3 in the Supplementary Appendix). Phase 2 trials of bedaquiline or delamanid added to background therapy for multidrug-resistant tuberculosis have shown a significant increase in the rate of sputum-culture conversion at 8 weeks of treatment (Table 2).[64,65] Phase 3 trials of each drug are being initiated, and each manufacturer has applied for accelerated marketing approvals by regulatory agencies. Accelerated approval was recently granted by the Food and Drug Administration for the use of bedaquiline in multidrug-resistant tuberculosis.

Several studies of combination drugs are being conducted or are being planned, although these trials face barriers that include pharmacokinetic interactions, the reliance on clinical rather than surrogate end points, and the relatively low financial incentive for drug companies to perform such trials. The efficient evaluation of new drug combinations will require close cooperation among the drug companies and nonprofit sponsors of clinical trials. The three-drug combination of moxifloxacin, pyrazinamide, and PA-824 has 14-day bactericidal activity similar to that of standard four-drug therapy.[66] Linezolid has recently been shown to achieve sputum-culture conversion in patients with extensively drug-resistant tuberculosis, and further evaluations are under way.[67]

BCG AND NEW VACCINES

M. bovis bacilli Calmette–Guérin (BCG) vaccine continues to be administered in infants at birth in most regions where tuberculosis is endemic. On the basis of a meta-analysis of controlled clinical trials, the vaccine has an estimated overall efficacy of approximately 50% for the prevention of tuberculosis.[68] Since the BCG vaccine can cause fatal disseminated infection in immunosuppressed patients, it should not be administered in HIV-infected newborns. Although the BCG vaccine has never been routinely used in the United States, it is increasingly being considered for use in tuberculin-negative adults who are planning to travel to areas with a high prevalence of multidrug-resistant tuberculosis in order to provide medical care.

Through a major international effort, a range of vaccines, both as primary immunogens to replace BCG and as boosters for BCG, are being studied, with more than 30 vaccines in development. Twelve vaccines have entered clinical trials (Fig. S3 in the Supplementary Appendix).[69] A polyantigenic inactivated whole-cell vaccine showed 39% efficacy in a phase 3 trial for the prevention of tuberculosis among HIV-infected adults who had received previous BCG immunization.[70]

CONCLUSIONS

Tuberculosis remains a major cause of death worldwide. The rise and spread of drug resistance and synergistic interaction with the HIV epidemic are posing difficult challenges and threatening global efforts at tuberculosis control. New molecular diagnostics have made earlier and improved diagnosis of active disease possible. Laboratory expertise and resources are required for these tests to become available throughout the developing world. Newer antituberculosis drugs offer the promise of shortened treatment regimens for drug-sensitive disease and more effective treatment for drug-resistant disease and latent infection. New vaccines against tuberculosis in advanced clinical trials offer hope for future tuberculosis control. Although these scientific developments are promising, the global economic crises continue to hinder tuberculosis-control programs. Strong political and financial commitments[71] will be required to achieve global control of tuberculosis and avert millions of unnecessary deaths.

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